Effective Health Care Program

Comparative Effectiveness Review
Number 153

Emerging Approaches to Diagnosis and Treatment of Non–Muscle-Invasive Bladder Cancer

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Comparative Effectiveness Review

Number 153

Emerging Approaches to Diagnosis and Treatment of Non–Muscle-Invasive Bladder Cancer

(with addendum)

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

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We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

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Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Emerging Approaches to Diagnosis and Treatment of Non–Muscle-Invasive Bladder Cancer

Structured Abstract

Objectives. Non–muscle-invasive bladder cancer (NMIBC) frequently recurs and can progress to muscle-invasive disease. This report reviews the current evidence on emerging approaches to diagnosing and treating bladder cancer.

Data sources. Electronic databases (Ovid MEDLINE®, January 1990–October 2014, Cochrane Central Register of Controlled Trials through September 2014, Cochrane Database of Systematic Reviews through September 2014, Health Technology Assessment through Third Quarter 2014, National Health Sciences Economic Evaluation Database through Third Quarter 2014, and Database of Abstracts of Reviews of Effects through Third Quarter 2014); reference lists; and clinical trials registries.

Review methods. Using predefined criteria, we selected studies on diagnostic accuracy of urinary biomarkers versus cystoscopy, and trials of fluorescent cystoscopy, intravesical therapy, and radiation therapy for NMIBC that evaluated bladder cancer recurrence, progression, mortality, or harms. The quality of included studies was assessed, data were extracted, and results were summarized qualitatively and using meta-analysis.

Results. Urinary biomarkers were associated with sensitivity for bladder cancer that ranged from 0.57 to 0.82 and specificity from 0.74 to 0.88, for positive likelihood ratios from 2.52 to 5.53 and negative likelihood ratios from 0.21 to 0.48 (strength of evidence [SOE]: moderate for quantitative nuclear matrix protein 22 [NMP22], qualitative bladder tumor antigen [BTA], fluorescence in situ hybridization [FISH], and ImmunoCyt™; low for other biomarkers). Sensitivity increased for higher stage and grade tumors. Studies that directly compared the accuracy of quantitative NMP22 and qualitative BTA found no differences in diagnostic accuracy (SOE: moderate).

Most trials found fluorescent cystoscopy to be associated with decreased risk of subsequent bladder recurrence versus white light cystoscopy, but results were inconsistent, and there was no difference in risk of progression or mortality (SOE: low).

Intravesical therapy was more effective than no intravesical therapy for reducing risk of bladder cancer recurrence (for bacillus Calmette-Guérin [BCG], relative risk [RR], 0.56; 95% confidence interval [CI]. 0.43 to 0.71; SOE: moderate; for mitomycin C [MMC], doxorubicin, and epirubicin, RR, 0.66 to 0.72; SOE: moderate). BCG was also associated with decreased risk of bladder cancer progression, but no intravesical agent was associated with decreased risk of all-cause or bladder cancer mortality. Intravesical therapy appeared to be effective across subgroups defined by tumor stage, grade, multiplicity, recurrence status, and size (SOE: low). Evidence was too limited to draw strong conclusions regarding effects of dose or duration of therapy on effectiveness. Compared with no intravesical therapy, BCG was associated with a higher rate of local and systemic adverse events (granulomatous cystitis or irritative symptoms in 27% to 84% of patients, macroscopic hematuria in 21% to 72%, and fever in 27% to 44%) (SOE: low). Compared with MMC, BCG was also associated with an increased risk of local adverse events

and fever (SOE: low). One randomized trial found no difference between radiation therapy and no radiation therapy in clinical outcomes in patients with T1G3 cancers.

Conclusions. Urinary biomarkers miss a substantial proportion of patients with bladder cancer, and additional research is needed to clarify advantages of fluorescent cystoscopy over white light cystoscopy. Intravesical therapy reduces risk of bladder cancer recurrence versus no intravesical therapy. BCG is the only intravesical therapy shown to be associated with decreased risk of bladder cancer progression, but it is associated with a high rate of adverse events. More research is needed to define optimal doses and regimens of intravesical therapy.

November 2016 update: An addendum is located at the end of the main report, before the appendixes.

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Executive Summary

Background

Bladder cancer is the 4th most commonly diagnosed cancer in men and the 10th most commonly diagnosed cancer in women in the United States.[1] The American Cancer Society estimated in 2014 that there would be 74,690 new cases of bladder cancer in the United States that year and about 15,580 deaths due to bladder cancer.[1] Bladder cancer occurs primarily in men age 60 and older, and roughly twice as frequently in white compared with black men.[2] Bladder cancer is an important health problem, with no improvement in associated mortality since 1975.[3] Economic analyses have shown bladder cancer to be the costliest cancer to treat on a per capita basis.[4] The most common risk factor for bladder cancer is cigarette smoking; other risk factors include occupational exposures and family history.

Bladder cancer is staged based on the extent of penetration or invasion into the bladder wall and adjacent structures.[5] Bladder cancers that have not invaded the bladder smooth muscle layer—stage classifications Tis (carcinoma in situ), Ta (noninvasive papillary carcinoma), and T1 (cancer that invades the subepithelial connective tissue) —are broadly grouped as non–muscle-invasive bladder cancer (NMIBC). Stage T2 cancers are muscle invasive, and higher stage cancers invade beyond the muscle layer into surrounding fat (stage classification T3 bladder cancer) or beyond the fat into nearby organs or structures (stage classification T4 bladder cancer). Approximately 75 percent of newly diagnosed bladder cancers are NMIBC.[6] Individuals with NMIBC generally have a good prognosis, with 5-year survival rates higher than 88 percent.[7] However, as many as 70 percent of NMIBC tumors recur after initial treatment, with a 10- to 20-percent risk of progression to invasive bladder cancer.[6] Prognosis is poorer for patients with muscle-invasive bladder cancers (5-year survival rates from 63% to 15%).[7]

A number of tests are available for screening, diagnosis, and staging of bladder cancer. Standard methods for identification of bladder cancer include urine dipstick and microscopic urinalysis (to detect hematuria) and urine cytology (to detect abnormal or cancerous cells in the urine), followed by imaging tests and cystoscopy.[8] Urine-based biomarkers have been developed as potential diagnostic alternatives or supplements to cytology, imaging, and cystoscopy.[9] A number of biomarkers have been evaluated in conjunction with cytology for diagnosis of bladder cancer, potentially reducing the need for cystoscopy. In addition to being performed for initial diagnosis and staging, diagnostic surveillance with cystoscopy and cytology is performed following treatment to identify patients with recurrence or progression of cancer. Urine-based biomarker tests may also be used to help identify recurrence and need for cystoscopy during surveillance.

The large number of available tests and testing strategies, and potential tradeoffs in diagnostic accuracy, risks, and patient preferences pose significant challenges in determining optimal testing and monitoring strategies. Tests with high false-positive rates could lead to unnecessary invasive procedures for further evaluation, and tests with high false-negative rates could lead to missed diagnoses.

Once bladder cancer has been diagnosed, a number of factors affect prognosis and treatment options. These include the stage of the cancer, tumor grade (higher grade tumors are more likely to recur and progress), whether the tumor is an initial tumor or a recurrence, number and size of tumors, and patient's age and general health. The main treatment for NMIBC is local resection with transurethral resection of the bladder tumor (TURBT), often with adjuvant intravesical therapy to destroy residual tumor cells using chemotherapeutic agents (e.g., mitomycin C

[MMC], apaziquone, paclitaxel, gemcitabine, thiotepa, valrubicin, doxorubicin, epirubicin), bacillus Calmette-Guérin (BCG), or interferon immunotherapy.[10] Clinical trials of electromotive drug administration to enhance the effectiveness of intravesical chemotherapy are underway in the United States.

The purpose of this report is to review the currently available evidence on the comparative effectiveness of diagnostic tests and treatments for NMIBC. Although updated guidelines for the treatment and followup of NMIBC from the European Association of Urology were published in 2013,[11] the literature continues to evolve, with much of the new evidence focusing on diagnostic techniques such as fluorescent cystoscopy or urine-based biomarkers and treatments with intravesical therapy alternatives to MMC and BCG. A systematic evidence review that includes recently published research may provide a better understanding of the comparative effectiveness of currently available approaches to diagnosis, treatment, and post-treatment surveillance for NMIBC. The systematic review may be used to update existing clinical recommendations that are several years old or may be out of date because of the development of new technologies and therapies.

Scope of Review and Key Questions

This topic was nominated for review by the American Urological Association and focuses on diagnosis of bladder cancer and treatment of NMIBC. The Key Questions and analytic framework used to guide this report are shown below. The analytic framework (Figure A) shows the scope of this review, including the target population, interventions, comparisons, and health outcomes we examined.

Key Question 1. What is the diagnostic accuracy of various urinary biomarkers compared with other urinary biomarkers or standard diagnostic methods (cystoscopy, cytology, and imaging) in (1) people with signs or symptoms warranting evaluation for possible bladder cancer or (2) people undergoing surveillance for previously treated bladder cancer?

a. Does the diagnostic accuracy differ according to patient characteristics (e.g., age, sex, race/ethnicity), or according to the nature of the presenting signs or symptoms?

Key Question 2. For patients with non–muscle-invasive bladder cancer, does the use of a formal risk-adapted assessment approach to treatment decisions (e.g., based on Guidelines of the European Association of Urology or on urinary biomarker tests) decrease mortality or improve other outcomes (e.g., recurrence, progression, need for cystectomy, quality of life) compared with treatment not guided by a formal assessed risk-adapted approach?

Key Question 3. For patients with non–muscle-invasive bladder cancer treated with transurethral resection of bladder tumor, what is the effectiveness of various intravesical chemotherapeutic or immunotherapeutic agents for decreasing mortality or improving other outcomes (e.g., recurrence, progression, need for cystectomy, quality of life) compared with TURBT alone?

a. What is the comparative effectiveness of various chemotherapeutic or immunotherapeutic agents, as monotherapy or in combination?
b. Does the comparative effectiveness differ according to tumor characteristics, such as stage, grade, size, multiplicity, whether the tumor is primary or recurrent, or molecular/genetic markers?
c. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, race/ethnicity, performance status, or medical comorbidities?
d. Does the comparative effectiveness of various chemotherapeutic or immunotherapeutic agents differ according to dosing frequency, duration of treatment, and/or the timing of administration relative to TURBT?

Key Question 4. For patients with high-risk non–muscle-invasive bladder cancer treated with TURBT, what is the effectiveness of external beam radiation therapy (either alone or with systemic chemotherapy/immunotherapy) for decreasing mortality or improving other outcomes compared with intravesical chemotherapy/immunotherapy alone or cystectomy?

Key Question 5. In surveillance of patients treated for non–muscle-invasive bladder cancer, what is the effectiveness of various urinary biomarkers to decrease mortality or improve other outcomes compared with other urinary biomarkers or standard diagnostic methods (cystoscopy, cytology, and imaging)?

a. Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?
b. Does the comparative effectiveness differ according to the treatment used (i.e., specific chemotherapeutic or immunotherapeutic agents and/or TURBT)?
c. Does the comparative effectiveness differ according to the length of surveillance intervals?

d. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, or race/ethnicity?

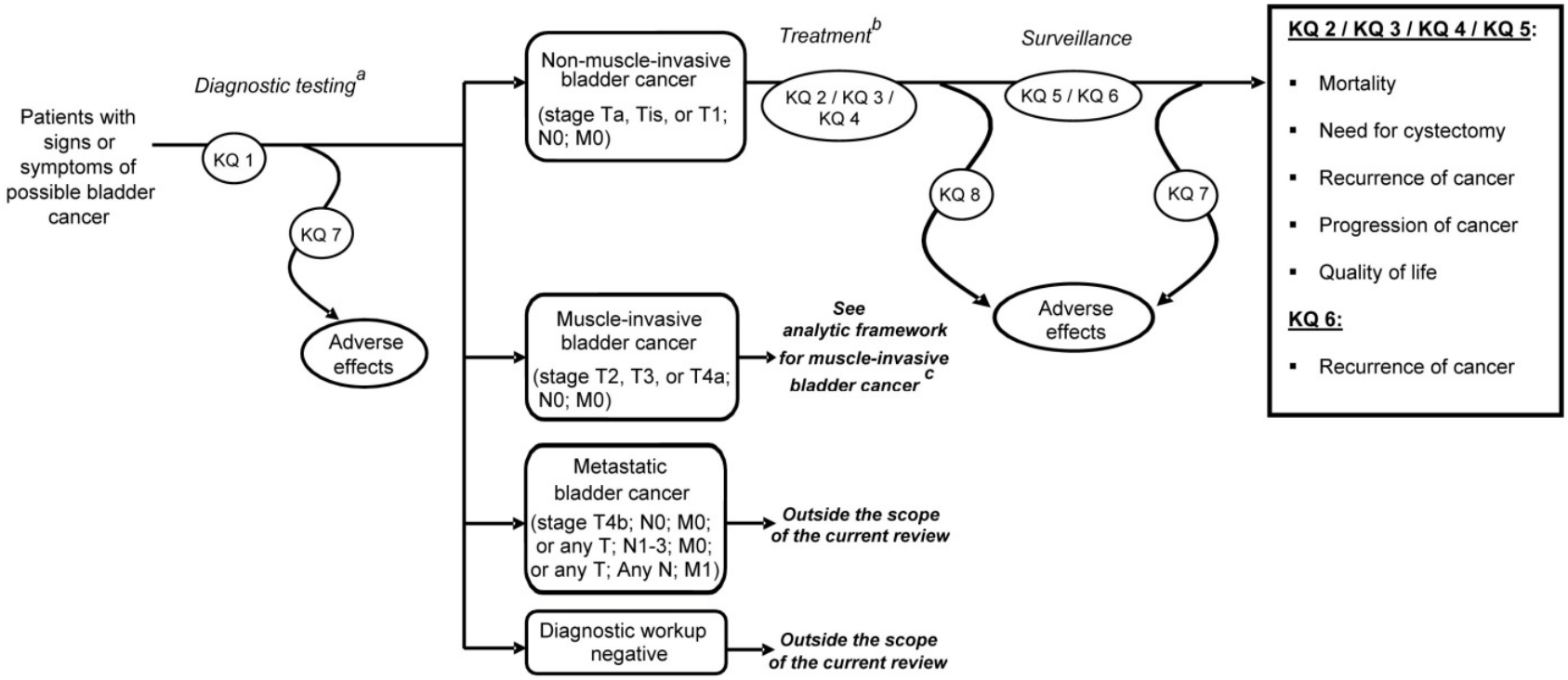
Key Question 6. For initial diagnosis or surveillance of patients treated for non–muscle-invasive bladder cancer, what is the effectiveness of blue light or other methods of augmented cystoscopy compared with standard cystoscopy for recurrence rates, progression of bladder cancer, mortality, or other clinical outcomes?

Key Question 7. What are the comparative adverse effects of various tests for diagnosis and post-treatment surveillance of bladder cancer, including urinary biomarkers, cytology, and cystoscopy?

Key Question 8. What are the comparative adverse effects of various treatments for non–muscle-invasive bladder cancer, including intravesical chemotherapeutic or immunotherapeutic agents and TURBT?

a. How do adverse effects of treatment vary by patient characteristics, such as age, sex, ethnicity, performance status, or medical comorbidities such as chronic kidney disease?

Figure A. Analytic framework



KQ = Key Question. Cancer stages shown are the TNM (tumor, node, metastasis) classification.

[a]Urinary biomarkers of interest are restricted to tests that are approved for diagnosis of bladder cancer by the U.S. Food and Drug Administration (BTAstat® [bladder tumor antigen], Alere NMP22®, BladderChek® [nuclear matrix protein 22], UroVysion® [fluorescence in situ hybridization], and ImmunoCyt™ [immunocytology]) or available in the United States and classified as a Laboratory Developed Test by the Food and Drug Administration (CxBladder™).

[b]Chemotherapeutic and immunotherapeutic agents of interest include mitomycin C, apaziquone, paclitaxel, gemcitabine, thiotepa, epirubicin, valrubicin, doxorubicin, bacillus Calmette-Guérin, and interferon.

[c]Muscle-Invasive Bladder Cancer Comparative Effectiveness Review: Chou R, Selph S, Buckley D, et al. Treatment of Nonmetastatic Muscle-Invasive Bladder Cancer. Comparative Effectiveness Review No. 152. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2012-00014-1.) AHRQ Publication No. 15-EHC015-EF. Rockville, MD: Agency for Healthcare Research and Quality; June 2015. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Methods

This Comparative Effectiveness Review (CER) follows the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (AHRQ Methods Guide)[12] and the AHRQ "Methods Guide for Medical Test Reviews."[13] All methods were determined a priori.

Searching for the Evidence

A research librarian experienced in conducting literature searches for CERs searched in Ovid MEDLINE® (January 1990–October 2014), Cochrane Central Register of Controlled Trials (through September 2014), Cochrane Database of Systematic Reviews (through September 2014), Health Technology Assessment (through Third Quarter 2014), National Health Sciences Economic Evaluation Database (through Third Quarter 2014), and Database of Abstracts of Reviews of Effects (through Third Quarter 2014) to capture both published and gray literature. We searched for unpublished studies in clinical trial registries (ClinicalTrials.gov, Current Controlled Trials, ClinicalStudyResults.org, and the World Health Organization International Clinical Trials Registry Platform) and regulatory documents (Drugs@FDA.gov and U.S. Food and Drug Administration (FDA) Medical Devices Registration and Listing). Reference lists of relevant studies and previous systematic reviews were hand-searched for additional studies. Scientific information packets were solicited from drug and device manufacturers, and a notice published in the *Federal Register* invited interested parties to submit relevant published and unpublished studies.

Study Selection

We developed criteria for inclusion and exclusion of studies based on the Key Questions and the defined population, interventions, comparators, outcomes, timing, and settings (PICOTS) and study designs. Inclusion and exclusion criteria are summarized below. Abstracts were reviewed by two investigators, and all citations deemed appropriate for inclusion by at least one of the reviewers were retrieved. Two investigators independently reviewed all full-text articles for inclusion. Discrepancies were resolved by discussion and consensus.

Population and Condition of Interest

For Key Questions related to diagnosis, we included studies of adults with signs or symptoms of possible bladder cancer (e.g., macroscopic or microscopic hematuria, irritative voiding symptoms) or undergoing surveillance following treatment for bladder cancer. For Key Questions related to treatment, we included adults with NMIBC who were undergoing treatment.

Interventions, Comparisons, and Study Designs of Interest

We included studies of urinary biomarkers for the diagnosis of bladder cancer approved by the FDA or available in the United States and classified as a Laboratory Developed Test by the FDA (CxBladder™). We excluded studies of diagnostic accuracy of other biomarkers and studies of included biomarkers that did not evaluate diagnostic accuracy of biomarkers against standard diagnostic methods (cystoscopy and histopathology). For cystoscopic methods, we included studies of fluorescent cystoscopy following intravesical instillation of a photosensitizing agent and other methods of augmented cystoscopy (e.g., narrow band imaging)

for the initial diagnosis or surveillance of bladder cancer compared with standard (white light) cystoscopy.

For treatments, we included studies of intravesical therapies (MMC, apaziquone, paclitaxel, gemcitabine, thiotepa, valrubicin, doxorubicin, epirubicin, BCG, and interferon) and external beam radiation therapy with or without systemic chemotherapy or immunotherapy versus TURBT, other intravesical therapies, or cystectomy. We included studies that compared different dosing regimens, different surveillance intervals, and risk-adapted approaches versus other approaches. We also included studies on the effects of patient and tumor characteristics on estimates of effectiveness.

For all Key Questions, we included randomized trials and, when randomized trials were not available, cohort studies with concurrent controls. For diagnostic accuracy, we also included cross-sectional studies. We excluded uncontrolled observational studies, case-control studies, case series, and case reports, as these studies are less informative than studies with a control group.

Outcomes of Interest

For diagnostic accuracy of urinary biomarkers, we evaluated sensitivity, specificity, predictive values, and likelihood ratios, using cystoscopy with biopsy as the reference standard. Clinical outcomes for trials of diagnostic methods and treatments were mortality, need for cystectomy, progression to muscle-invasive bladder cancer, bladder cancer recurrence, and quality of life. We also evaluated adverse effects of diagnostic testing (e.g., false-positives, labeling, anxiety, complications of cystoscopy) and adverse effects of treatment (e.g., cystitis, urinary urgency, urinary frequency, incontinence, hematuria, pain, urosepsis, myelosuppression).

Timing and Settings of Interest

For all Key Questions, we included studies conducted in inpatient or outpatient settings with any duration of followup.

Data Extraction and Data Management

For treatment studies, we extracted the following information into evidence tables: study design; setting; inclusion and exclusion criteria; dose and duration of treatment for experimental and control groups; duration of followup; number of subjects screened, eligible, and enrolled; population characteristics (including age, race/ethnicity, sex, stage of disease, and functional status); results; adverse events; withdrawals due to adverse events; and sources of funding. We calculated relative risks (RRs) and associated 95% confidence intervals (CIs) based on the information provided (sample sizes and incidence of outcomes in each intervention group). We noted discrepancies between calculated and reported results when present.

For diagnostic accuracy studies, we abstracted the following information: setting, screening test or tests, method of data collection, reference standard, inclusion criteria, population characteristics (including age, sex, race/ethnicity, smoking status, signs or symptoms, and prior bladder cancer stage or grade), proportion of individuals with bladder cancer, bladder cancer stage and grade, definition of a positive screening exam, proportion of individuals unexaminable by the screening test, proportion who did not undergo reference standard test, results, and sources of funding. We attempted to create two-by-two tables from information provided (sample size, prevalence, sensitivity, and specificity) and compared calculated measures of diagnostic accuracy based on the two-by-two tables with reported results. We noted

discrepancies between calculated and reported results when present. When reported, we also recorded the area under the receiver operating characteristic curve.[14,15]

Data extraction for each study was completed by one investigator and independently reviewed for accuracy and completeness by a second investigator.

Assessment of the Risk of Bias of Individual Studies

We assessed the risk of bias for randomized trials and observational studies using criteria adapted from those developed by the U.S. Preventive Services Task Force.[16] Studies of diagnostic accuracy were rated using criteria adapted from QUADAS-2, a revised tool for Quality Assessment of Diagnostic Accuracy Studies.[17] These criteria were applied in conjunction with the approaches recommended for medical interventions in the AHRQ Methods Guide[12] and in the AHRQ "Methods Guide for Medical Test Reviews."[13]

Two investigators independently assessed the risk of bias of each study. Discrepancies were resolved through discussion and consensus. Each study was rated as low, medium, or high risk of bias.[12]

Studies rated low risk of bias were considered to have no more than very minor methodological shortcomings, and their results are likely to be valid. Studies rated moderate risk of bias have some methodological shortcomings, but no flaw or combination of flaws judged likely to cause major bias. The category of moderate risk of bias is broad, and studies with this rating vary in their strengths and weaknesses; the results of some studies assessed to have moderate risk of bias are likely to be valid, while others may be only possibly valid. Studies rated high risk of bias have significant flaws that may invalidate the results. They have a serious or "fatal" flaw or combination of flaws in design, analysis, or reporting; large amounts of missing information; or serious discrepancies in reporting. We did not exclude studies rated as having high risk of bias a priori, but they were considered the least reliable when synthesizing the evidence, particularly when discrepancies between studies were present.

Assessing Applicability

We recorded factors important for understanding the applicability of studies, such as whether the publication adequately described the study sample, the country in which the study was conducted, the characteristics of the patient sample (e.g., age, sex, race/ethnicity, risk factors for bladder cancer, presenting symptoms, and medical comorbidities), tumor characteristics (e.g., stage and grade, primary or recurrent, unifocal or multifocal lesions), the characteristics of the diagnostic tests (e.g., specific test evaluated and cutoffs used) and interventions (e.g., treatment dose, duration, and interval) used, and the magnitude of effects on clinical outcomes.[12] There is no generally accepted universal rating system for applicability, which depends in part on context. Therefore, a rating of applicability (such as high or low) was not assigned because applicability may differ based on the user of this report.

Data Synthesis

For studies on diagnostic accuracy of urinary biomarkers, we performed meta-analyses to help summarize data and obtain more precise estimates.[18] We used a bivariate logistic mixed-effects model[19] to analyze sensitivity and specificity, incorporating the correlation between sensitivity and specificity. We assumed random effects across studies with a bivariate normal distribution for sensitivity and specificity, and heterogeneity among the studies was measured

based on the random-effect variance (τ^2). When few studies were available for an analysis, we used the moment estimates of correlation between sensitivity and specificity in the bivariate model. We calculated positive likelihood ratio and negative likelihood ratio using the summarized sensitivity and specificity.[20,21] For head-to-head comparisons, we used the same bivariate logistic mixed-effects model as described above but added an indicator variable for imaging modalities (equivalent to a meta-regression approach).

All quantitative analyses were conducted using SAS® 10.0 (SAS Institute Inc., Cary, NC).[22] We assessed the presence of statistical heterogeneity among the studies using the standard Cochran's chi-square test, and the magnitude of heterogeneity by using the I^2 statistic.[23] When statistical heterogeneity was present, we performed sensitivity analyses by conducting meta-analysis using the profile likelihood method.[24] We also performed sensitivity and subgroup analyses based on ratings for risk of bias, dose of intravesical therapy, inclusion of high-risk patients, and duration of followup. We stratified trials according to the type of instillation regimen, classified as single instillation, induction therapy (treatment for 4 to 8 weeks), maintenance therapy (treatment for longer than 8 weeks), or other. We calculated pooled RRs for the dichotomous outcomes for bladder cancer recurrence, bladder cancer progression, all-cause mortality, bladder cancer mortality, and local and systemic adverse events. Similar analyses were performed for trials of augmented cystoscopy (fluorescent light or narrow band imaging) versus white light cystoscopy.

Grading the Strength of Evidence for Each Key Question

We assessed the strength of evidence (SOE) for each Key Question and outcome using the approach described in the AHRQ Methods Guide,[12] based on the overall quality of each body of evidence; the risk of bias (graded low, moderate, or high); the consistency of results across studies (graded consistent, inconsistent, or unable to determine when only 1 study was available); the directness of the evidence linking the intervention and health outcomes (graded direct or indirect); the precision of the estimate of effect, based on the number and size of studies and CIs for the estimates (graded precise or imprecise); and reporting bias (suspected or undetected)

Assessments of reporting bias were based on whether studies defined and reported primary outcomes, identification of relevant unpublished studies, and when available, by comparing published results with results reported in trial registries.

We graded the SOE for each Key Question using the four categories recommended in the AHRQ Methods Guide.[12] A high grade indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect. A moderate grade indicates moderate confidence that the evidence reflects the true effect; further research may change our confidence in the estimate of effect and may change the estimate. A low grade indicates low confidence that the evidence reflects the true effect; further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. A grade of insufficient indicates that evidence either is unavailable or is too limited to permit any conclusion because of the availability of only poor-quality studies, extreme inconsistency, or extreme imprecision.

Results

Database searches resulted in 4,071 potentially relevant articles. After dual review of abstracts and titles, 643 articles were selected for full-text dual review, and 149 studies (in 192 publications) were determined to meet inclusion criteria and were included in this review.

Key Question 1. Diagnostic Accuracy: Comparison of Urinary Biomarkers

For this Key Question, we included 57 studies (in 60 publications) that evaluated the diagnostic accuracy of urinary biomarkers for diagnosis of bladder cancer.

- Quantitative nuclear matrix protein 22 (NMP22): Sensitivity was 0.69 (95% CI, 0.62 to 0.75) and specificity 0.77 (95% CI, 0.70 to 0.83), based on 19 studies, for a positive likelihood ratio of 3.05 (95% CI, 2.28 to 4.10) and negative likelihood ratio of 0.40 (95% CI, 0.32 to 0.50) (SOE: moderate)
  - For evaluation of symptoms: Sensitivity was 0.67 (95% CI, 0.55 to 0.77; 9 studies) and specificity 0.84 (95% CI, 0.75 to 0.90; 7 studies).
  - For surveillance: Sensitivity was 0.61 (95% CI, 0.49 to 0.71; 10 studies) and specificity 0.71 (95% CI, 0.60 to 0.81; 8 studies).
- Qualitative NMP22: Sensitivity was 0.58 (95% CI, 0.39 to 0.75) and specificity 0.88 (95% CI, 0.78 to 0.94), based on four studies, for a positive likelihood ratio of 4.89 (95% CI, 3.23 to 7.40) and negative likelihood ratio of 0.48 (95% CI, 0.33 to 0.71) (SOE: low).
  - For evaluation of symptoms: Sensitivity was 0.47 (95% CI, 0.33 to 0.61) and specificity 0.93 (95% CI, 0.81 to 0.97), based on two studies.
  - For surveillance: Sensitivity was 0.70 (95% CI, 0.40 to 0.89) and specificity 0.83 (95% CI, 0.75 to 0.89), based on two studies.
- Qualitative bladder tumor antigen (BTA): Sensitivity was 0.64 (95% CI, 0.58 to 0.69; 22 studies) and specificity 0.77 (95% CI, 0.73 to 0.81; 21 studies), for a positive likelihood ratio of 2.80 (95% CI, 2.31 to 3.39) and negative likelihood ratio of 0.47 (95% CI, 0.30 to 0.55) (SOE: moderate).
  - For evaluation of symptoms: Sensitivity was 0.76 (95% CI, 0.67 to 0.83; 8 studies), and specificity 0.78 (95% CI, 0.66 to 0.87; 6 studies).
  - For surveillance: Sensitivity was 0.60 (95% CI, 0.55 to 0.65; 11 studies) and specificity 0.76 (95% CI, 0.69 to 0.83; 8 studies).
- Quantitative BTA: Sensitivity was 0.65 (95% CI, 0.54 to 0.75) and specificity 0.74 (95% CI, 0.64 to 0.82), based on four studies, for a positive likelihood ratio of 2.52 (95% CI, 1.86 to 3.41) and negative likelihood ratio of 0.47 (95% CI, 0.37 to 0.61) (SOE: low).
  - For evaluation of symptoms: Sensitivity was 0.76 (95% CI, 0.61 to 0.87) and specificity 0.53 (95% CI, 0.38 to 0.68), based on one study.
  - For surveillance: Sensitivity was 0.58 (95% CI, 0.46 to 0.69) and specificity 0.79 (95% CI, 0.72 to 0.85), based on two studies.
- Fluorescence in situ hybridization (FISH): Sensitivity was 0.63 (95% CI, 0.50 to 0.75) and specificity 0.87 (95% CI, 0.79 to 0.93), based on 11 studies, for a positive likelihood ratio of 5.02 (95% CI, 2.93 to 8.60) and negative likelihood ratio of 0.42 (95% CI, 0.30 to 0.59) (SOE: moderate).
  - For evaluation of symptoms: Sensitivity was 0.73 (95% CI, 0.50 to 0.88) and specificity 0.95 (95% CI, 0.87 to 0.98), based on two studies, for a positive likelihood

ratio of 14.2 (95% CI, 5.2 to 39) and negative likelihood ratio of 0.29 (95% CI, 0.14 to 0.60).
    - For surveillance: Sensitivity was 0.55 (95% CI, 0.36 to 0.72; 7 studies) and specificity was 0.80 (95% CI, 0.66 to 0.89; 6 studies).
- ImmunoCyt™: Sensitivity was 0.78 (95% CI, 0.68 to 0.85) and specificity 0.78 (95% CI, 0.72 to 0.82), based on 14 studies, for a positive likelihood ratio of 3.49 (95% CI, 2.82 to 4.32) and negative likelihood ratio of 0.29 (95% CI, 0.20 to 0.41) (SOE: moderate).
    - For evaluation of symptoms: Sensitivity was 0.85 (95% CI, 0.78 to 0.90; 6 studies) and specificity 0.83 (95% CI, 0.77 to 0.87; 7 studies).
    - For surveillance: Sensitivity was 0.75 (95% CI, 0.64 to 0.83; 7 studies) and specificity 0.76 (95% CI, 0.70 to 0.81; 8 studies).
- CxBladder: Sensitivity was 0.82 (95% CI, 0.70 to 0.90) and specificity 0.85 (95% CI, 0.81 to 0.88) for evaluation of symptoms, based on one study, for a positive likelihood ratio of 5.53 (95% CI, 4.28 to 7.15) and negative likelihood ratio of 0.21 (95% CI, 0.13 to 0.36) (SOE: low).
- Direct (within-study) comparisons:
    - There was no difference between quantitative NMP22 (cutoff >10 U/mL) versus qualitative BTA in sensitivity (0.69 [95% CI, 0.62 to 0.76] vs. 0.66 [95% CI, 0.59 to 0.73], for a difference of 0.03 [95% CI, -0.04 to 0.10]) or specificity (0.73 [95% CI, 0.62 to 0.82] vs. 0.76 [95% CI, 0.66 to 0.84], for a difference of 0.03 [95% CI, -0.08 to 0.01]), based on seven studies (SOE: moderate).
    - ImmunoCyt was associated with higher sensitivity than FISH (0.71 [95% CI, 0.54 to 0.84] vs. 0.61 [95% CI, 0.43 to 0.76], for a difference of 0.11 [95% CI, 0.001 to 0.21]) but lower specificity (0.71 [95% CI, 0.62 to 0.79] vs. 0.79 [95% CI, 0.71 to 0.85], for a difference of -0.08 [95% CI, -0.15 to -0.001]), based on three studies (SOE: low).
    - Evidence for other head-to-head comparisons of urinary biomarkers was based on small numbers of studies with imprecise estimates and methodological shortcomings, precluding reliable conclusions regarding comparative test performance (SOE: insufficient).
    - Sixteen studies found sensitivity of various urinary biomarkers plus cytology to be associated with higher sensitivity than the urinary biomarker alone (0.8 [95% CI, 0.75 to 0.86] vs. 0.69 [95% CI, 0.61 to 0.76], for a difference of 0.13 [95% CI, 0.08 to 0.17]), with no difference in specificity (SOE: moderate).

Key Question 1a. Diagnostic Accuracy: Patient Characteristics or Presenting Signs or Symptoms

For this Key Question, we included 42 studies that evaluated diagnostic accuracy according to patient characteristics or the nature of the presenting signs or symptoms.

- Effects of tumor stage: Across urinary biomarkers, sensitivity increased with higher tumor stage. Evidence was most robust for quantitative NMP22 (11 studies), qualitative BTA (18 studies), and FISH (8 studies); the association between higher tumor stage and increased sensitivity was least pronounced for ImmunoCyt (10 studies). Sensitivity for carcinoma in situ (CIS) tumors was generally similar to or slightly lower than for T1 tumors (SOE: high).

- Effects of tumor grade: Across urinary biomarkers, sensitivity increased with higher tumor grade. Evidence was most robust for quantitative NMP22 (12 studies), ImmunoCyt (10 studies), qualitative BTA (18 studies), and FISH (9 studies) (SOE: high).
- Effects of tumor size: Two studies found that sensitivity was higher for larger (>1 cm or >2 cm) versus smaller tumors (SOE: low).
- Evidence on the effects of patient characteristics, such as age, sex, smoking status, and presence of other clinical conditions, on diagnostic accuracy of urinary biomarkers was limited and did not clearly or consistently indicate effects on sensitivity or specificity (SOE: low).

Key Question 2. Use of Formal Risk-Adapted Assessment Approach

This Key Question addresses the issue of whether use of a formal risk-adapted assessment approach to treatment decisions decreases mortality or improves other outcomes compared with treatment not guided by a formal risk-adapted assessment approach.

- No study compared clinical outcomes associated with use of a formal risk-adapted approach to guide treatment of NMIBC versus treatment not guided by a risk-adapted approach (SOE: insufficient).

Key Question 3. Effect of TURBT Plus Intravesical Therapy Versus TURBT Alone

This Key Question addresses the issue of whether the use of various intravesical chemotherapeutic or immunotherapeutic agents in addition to TURBT decreases mortality or improves other outcomes compared with TURBT alone. We included 37 studies (in 46 publications) that evaluated intravesical therapy versus no intravesical therapy.

- **BCG** was associated with decreased risk of bladder cancer recurrence (3 trials; RR, 0.56; 95% CI, 0.43 to 0.71; $I^2 = 0\%$) and progression (4 trials; RR, 0.39; 95% CI, 0.24 to 0.64; $I^2 = 40\%$) versus no intravesical therapy. No trial evaluated effects of BCG versus no intravesical therapy on risk of all-cause mortality. One trial found BCG to be associated with decreased risk of bladder cancer mortality, but the difference was not statistically significant (RR, 0.62; 95% CI, 0.32 to 1.19) (SOE: insufficient for all-cause and bladder cancer mortality; low for recurrence and progression).
- **MMC** was associated with decreased risk of bladder cancer recurrence versus no intravesical therapy (8 trials; RR, 0.71; 95% CI, 0.57 to 0.89; $I^2 = 72\%$), but there was no difference in risk of all cause-mortality (1 trial; hazard ratio [HR], 1.17; 95% CI, 0.89 to 1.53), and effects on bladder cancer mortality (1 trial; HR, 0.71; 95% CI, 0.34 to 1.46) and bladder cancer progression (5 trials; RR, 0.68; 95% CI, 0.39 to 1.20, $I^2 = 0\%$) were not statistically significant (SOE: moderate for recurrence; low for progression, all-cause mortality, and bladder cancer–specific mortality).
- **Doxorubicin** was associated with decreased risk of bladder cancer recurrence versus no intravesical therapy (10 trials; RR, 0.80; 95% CI, 0.72 to 0.88; $I^2 = 46\%$), no difference in risk of bladder cancer progression (5 trials; RR, 1.03; 95% CI, 0.72 to 1.46; $I^2 = 0\%$), and no clear effects on all-cause mortality (2 trials) or bladder cancer–specific mortality (1 trial) (SOE: moderate for recurrence; low for progression, all-cause mortality, and bladder cancer–specific mortality).

- **Epirubicin** was associated with decreased risk of bladder cancer recurrence (9 trials; RR, 0.63; 95% CI, 0.53 to 0.75; $I^2 = 64\%$) (SOE: moderate), but the effect on bladder cancer progression was not statistically significant (8 trials; RR, 0.79; 95% CI, 0.84 to 1.30; $I^2 = 27\%$) (SOE: low).
- **Gemcitabine** was examined in one trial that found no difference between single-instillation gemcitabine versus no intravesical therapy in risk of bladder cancer recurrence (RR, 0.98; 95% CI, 0.70 to 1.36); estimates for progression (RR, 3.00; 95% CI, 0.32 to 28.4), all-cause mortality (RR, 0.50; 95% CI, 0.13 to 2.00), and bladder cancer–specific mortality (RR, 1.00; 95% CI, 0.06 to 15.81) were very imprecise (SOE: low for bladder cancer recurrence; insufficient for all-cause and bladder cancer–specific mortality and progression).
- **Interferon alpha** was associated with decreased risk of bladder cancer recurrence versus no intravesical therapy that was not statistically significant (3 trials; RR, 0.75; 95% CI, 0.53 to 1.06; $I^2 = 50\%$), decreased risk of bladder cancer progression (2 trials; RR, 0.33; 95% CI, 0.14 to 0.76; $I^2 = 0\%$), and no difference in risk of bladder cancer–specific mortality (1 trial; RR, 1.00; 95% CI, 0.15 to 6.75) (SOE: low).
- **Interferon gamma** was associated with decreased risk of bladder cancer recurrence versus no intravesical therapy (1 trial; RR, 0.72; 95% CI, 0.51 to 1.01), with no difference in risk of bladder cancer progression (1 trial; RR, 1.08; 95% CI, 0.07 to 16.4) (SOE: low).
- **Thiotepa** was associated with decreased risk of bladder cancer recurrence versus no intravesical therapy that was not statistically significant (5 trials; RR, 0.78; 95% CI, 0.58 to 1.06; $I^2 = 69\%$), with insufficient evidence to determine effects on progression or mortality (SOE: low for recurrence, insufficient for all-cause and bladder cancer mortality and progression).

Key Question 3a. Comparative Effectiveness: Chemotherapeutic or Immunotherapeutic Agents as Monotherapy or in Combination

For this Key Question, we included 54 studies in 66 publications.

BCG Versus MMC

- There were no differences between BCG and MMC in risk of bladder cancer recurrence (10 trials; RR, 0.95; 95% CI, 0.81 to 1.11; $I^2 = 67\%$), but BCG was associated with decreased risk in the subgroup of trials that evaluated maintenance regimens (5 trials; RR, 0.79; 95% CI, 0.71 to 0.87; $I^2 = 0\%$). There was no difference in risk of all-cause (7 trials; RR, 0.94; 95% CI, 0.83 to 1.06; $I^2 = 0\%$) or bladder cancer–specific mortality (5 trials; RR, 0.77; 95% CI, 0.54 to 1.10; $I^2 = 0\%$) or progression (7 trials; RR, 0.88; 95% CI, 0.66 to 1.17; $I^2 = 18\%$) (SOE: moderate for all-cause mortality, bladder cancer–specific mortality, and progression; low for recurrence).
- There were no differences between BCG alone and BCG plus MMC given sequentially in risk of all-cause (1 trial; RR, 1.57; 95% CI, 0.67 to 3.71) or bladder cancer–specific mortality (2 trials; RR, 1.10; 95% CI, 0.50 to 2.38; $I^2 = 17\%$), bladder cancer recurrence (4 trials; RR, 1.03; 95% CI, 0.70 to 1.52; $I^2 = 75\%$), progression (3 trials; RR, 0.87; 95% CI, 0.40 to 1.91; $I^2 = 22\%$), or cystectomy (4 trials; RR, 0.87; 95% CI, 0.41 to 1.84; $I^2 = 0\%$) (SOE: low).

- There were no differences between BCG plus MMC administered sequentially and MMC alone in risk of all-cause (2 trials; RR, 1.53; 95% CI, 0.72 to 1.74 and RR 0.95; 95% CI, 0.71 to 1.30) or bladder cancer–specific mortality (2 trials; RR, 0.64; 95% CI, 0.22 to BCG 1.88 and RR, 0.95; 95% CI, 0.45 to 1.56), bladder cancer recurrence (2 trials; RR, 0.88; 95% CI, 0.75 to 1.03; $I^2 = 0\%$), or progression (2 trials; RR, 0.82; 95% CI, 0.40 to 1.68 and RR, 1.28; 95% CI, 0.35 to 4.61) (SOE: low).

BCG Versus Doxorubicin

- BCG was associated with decreased risk of bladder cancer recurrence versus doxorubicin (2 trials; RR, 0.31; 95% CI, 0.16 to 0.61 and RR, 0.75; 95% CI, 0.64 to 0.88), but there were no differences in risk of all-cause mortality (2 trials; RR, 0.40; 95% CI, 0.01 to 12 and RR, 1.00; 95% CI, 0.71 to 1.37) or bladder cancer progression (1 trial; RR, 0.20; 95% CI, 0.02 to 1.72) (SOE: low).

BCG Versus Epirubicin

- BCG was associated with reduced risk of bladder cancer recurrence versus epirubicin, but statistical heterogeneity was high (5 trials; RR, 0.54; 95% CI, 0.40 to 0.74; $I^2 = 76\%$). Estimates favored BCG for all-cause (3 trials; RR, 0.72; 95% CI, 0.44 to 1.19; $I^2 = 87\%$) and bladder cancer–specific mortality (3 trials; RR, 0.72; 95% CI, 0.25 to 2.08; $I^2 = 80\%$) and bladder cancer progression (5 trials; RR, 0.60; 95% CI, 0.36 to 1.01; $I^2 = 47\%$), but differences were not statistically significant (SOE: moderate for recurrence; low for all-cause mortality, bladder cancer–specific mortality, and progression).
- There was no difference between BCG alone and BCG plus epirubicin administered sequentially in risk of bladder cancer recurrence (3 trials; RR, 1.25; 95% CI, 0.92 to 1.69; $I^2 = 0\%$). BCG alone was associated with increased risk of bladder cancer progression (3 trials; RR, 1.92; 95% CI, 0.73 to 5.07; $I^2 = 0\%$), but the difference was not statistically significant (SOE: low).
- One trial found no differences between BCG alone and epirubicin plus interferon alpha-2b in risk of bladder cancer–specific mortality (RR, 0.79; 95% CI, 0.32 to 1.63) or progression-free survival, although BCG was associated with decreased risk of bladder cancer recurrence (RR, 0.66; 95% CI, 0.51 to 0.85) (SOE: low).

BCG Versus Gemcitabine

- There were no differences between BCG and gemcitabine in risk of all-cause mortality (1 trial; RR, 1.20; 95% CI, 0.04 to 34), progression (2 trials; RR, 1.11; 95% CI, 0.53 to 2.34 and RR, 0.52; 95% CI, 0.13 to 2.06), or quality of life (1 trial) (SOE: low).
- Evidence from three trials was insufficient to determine effects of BCG versus gemcitabine on risk of bladder cancer recurrence because of clinical heterogeneity and inconsistent findings (RR, 1.67 [95% CI, 1.21 to 2.29]; RR, 0.53 [95% CI, 0.28 to 1.01]; and RR, 0.76 [95% CI, 0.44 to 1.90]) (SOE: insufficient).
- There were no differences between BCG alone and BCG plus gemcitabine administered sequentially in risk of bladder cancer recurrence (1 trial; RR, 0.86; 95% CI, 0.49 to 1.51) or progression (1 trial; RR, 1.18; 95% CI, 0.30 to 4.61) (SOE: low).

BCG Versus Interferon

- BCG was associated with reduced risk of bladder cancer recurrence versus interferon alpha-2a (1 trial; RR, 0.57; 95% CI, 0.39 to 0.82), but the difference in risk of bladder cancer progression was not statistically significant (1 trial; RR, 0.69; 95% CI, 0.25 to 1.92) (SOE: low).
- In patients pretreated with MMC, BCG alone was associated with reduced risk of bladder cancer recurrence versus alternating BCG plus interferon alpha-2b (1 trial; RR, 0.42; 95% CI, 0.30 to 0.59) (SOE: low).
- Differences between BCG alone and coadministration of BCG and interferon alpha-2b in risk of bladder cancer recurrence (1 trial; RR, 0.88; 95% CI, 0.71 to 1.08) or progression (1 trial; RR, 0.76; 95% CI, 0.17 to 3.30) did not reach statistical significance (SOE: low).

BCG Versus Thiotepa

- Two trials found that, for maintenance therapy, BCG was associated with decreased risk of recurrence versus thiotepa (RR, 0.38 [95% CI, 0.19 to 0.76] and RR, 0.04 [95% CI, 0.00 to 0.63]), but estimates for other outcomes were too imprecise to evaluate effects (SOE: low for recurrence; insufficient for progression, death, and cystectomy).

MMC Versus Doxorubicin

- There was no difference between MMC and doxorubicin in risk of bladder cancer recurrence (6 trials; RR, 1.00; 95% CI, 0.82 to 1.22; $I^2 = 44\%$), but MMC was associated with a non–statistically significant trend toward decreased risk of bladder cancer progression (4 trials; RR, 0.63; 95% CI, 0.37 to 1.08; $I^2 = 21\%$) (SOE: low).

MMC Versus Epirubicin

- There was no difference between MMC and epirubicin in risk of bladder cancer recurrence in one trial (RR, 1.16; 95% CI, 0.52 to 2.58) (SOE: low).

MMC Versus Gemcitabine

- In one trial, MMC was associated with no difference in risk of bladder cancer progression compared with gemcitabine ($p = 0.29$). MMC was associated with increased risk of recurrence, but the difference was not statistically significant (RR, 1.64; 95% CI, 0.64 to 4.19) (SOE: low).

MMC Versus Interferon Alpha

- One trial found no difference between MMC and interferon alpha in risk of bladder cancer recurrence (RR, 0.77; 95% CI, 0.58 to 1.01) or bladder cancer progression (RR, 1.38; 95% CI, 0.49 to 3.88) (SOE: low).

MMC Versus Interferon Gamma

- MMC was associated with increased risk of bladder cancer recurrence versus interferon gamma in one trial (RR, 1.61; 95% CI, 0.97 to 2.67) (SOE: low).

MMC Versus Thiotepa

- Two trials found no difference between MMC and thiotepa in risk of recurrence (RR, 1.76 [95% CI, 0.36 to 8.70] and RR, 1.14 [95% CI, 0.60 to 2.16]) (SOE: low).

Doxorubicin Versus Epirubicin

- Doxorubicin was associated with increased risk of bladder cancer recurrence versus epirubicin (3 trials; RR, 1.56; 95% CI, 1.08 to 2.22; $I^2 = 0\%$); the difference in risk of progression was not statistically significant (1 trial; RR, 1.32; 95% CI, 0.50 to 3.47) (SOE: low).

Doxorubicin Versus Thiotepa

- There was no statistically significant difference between doxorubicin and thiotepa in risk of bladder cancer recurrence (RR, 1.22; 95% CI, 0.76 to 1.94). Estimates from one trial for progression (RR, 2.11; 95% CI, 0.40 to 11.06), noncancer mortality (RR, 0.35; 95% CI, 0.01 to 8.45), and cancer-specific mortality (RR, 3.17; 95% CI, 0.13 to 76.1) were very imprecise (SOE: low for recurrence; insufficient for progression, noncancer mortality, and cancer-specific mortality).

Epirubicin Versus Interferon Alpha

- Epirubicin was associated with decreased risk of bladder cancer recurrence versus interferon alpha in one trial (RR, 0.67; 95% CI, 0.49 to 0.91) (SOE: low).

Key Question 3b. Comparative Effectiveness: Tumor Characteristics

For this Key Question, we included 29 studies.

- There were no clear differences in estimates of effectiveness of intravesical therapies in subgroups defined by tumor stage, grade, size, multiplicity, recurrence status, or DNA ploidy (SOE: low).

Key Question 3c. Comparative Effectiveness: Patient Characteristics

- No trial evaluated how estimates of effectiveness of intravesical therapy vary in subgroups defined by patient characteristics, such as age, sex, race/ethnicity, performance status, and comorbidities (SOE: insufficient).
- In patients with recurrence or progression following prior BCG therapy, one trial found maintenance therapy with gemcitabine to be associated with decreased risk of recurrence versus repeat treatment with BCG, and one trial found MMC maintenance therapy to be associated with lower likelihood of disease-free survival than gemcitabine; estimates for progression were imprecise (SOE: low).

Key Question 3d. Comparative Effectiveness: Dosing Frequency, Treatment Duration, Timing

For this Key Question, we included 53 studies (in 57 publications) that compared different doses or instillation regimens of the same drug or different BCG strains.

BCG

- Six trials found no clear differences between standard and lower doses of BCG in risk of recurrence, progression, or bladder cancer–specific mortality, including in patients with higher risk NMIBC, although there was some inconsistency between trials. Standard therapy was associated with increased risk of local and systemic adverse events versus lower dose BCG in most trials (SOE: low).
- Three trials of responders to BCG induction therapy found no clear differences between maintenance therapy versus no maintenance therapy in risk of all-cause mortality (3 trials; RR, 0.90; 95% CI, 0.72 to 1.11) or bladder cancer–specific mortality (2 trials; RR, 1.14; 95% CI, 0.24 to 5.40), although maintenance therapy was associated with decreased risk of recurrence (RR, 0.76 [95% CI, 0.65 to 0.88] and RR, 0.16 [95% CI, 0.02 to 1.21]) (SOE: low).
- Two of three trials found that more prolonged courses of BCG were associated with decreased risk of bladder cancer recurrence versus induction therapy in patients with higher risk NMIBC, but increased risk of adverse events (SOE: low).
- One trial found OncoTICE® strain BCG to be associated with lower likelihood of 5-year recurrence-free survival than BCG Connaught (48% vs. 74%; p = 0.01), and one trial found OncoTICE strain BCG to be associated with lower likelihood of 5-year recurrence-free survival than RIVM strain BCG (36% vs. 54%; p = 0.07). Four trials that compared non-OncoTICE BCG strains found no differences (SOE: low).

MMC

- One trial of patients with NMIBC (not selected for being at higher risk) found no clear differences between MMC 40 mg single instillation and MMC 40 mg five instillations in risk of recurrence, progression, or mortality. The single instillation was associated with lower risk of local adverse events (SOE: low).
- One trial of patients with higher risk NMIBC found that MMC 20 mg induction therapy for 6 weeks was associated with higher risk of recurrence than maintenance therapy. There were no clear differences in risk of adverse events (SOE: low).
- Two trials of MMC maintenance regimens in patients with NMIBC not selected for being at higher risk found some evidence that a higher total number of instillations and increased frequency during initial therapy were associated with lower risk of recurrence and progression, and might be associated with lower risk of local adverse events (SOE: low).
- One trial found no difference between “optimized” (through alkalinization of urine) versus nonoptimized administration of intravesical MMC in risk of recurrence in patients with low-risk NMIBC, but one trial of patients with higher risk NMIBC found optimized administration to be associated with lower risk of recurrence and increased risk of local adverse events (SOE: low).

Doxorubicin

- Two trials of patients with NMIBC not selected for being at higher risk found no differences between doxorubicin 30 mg and 20 mg given as short (8 weeks) or long (2 years) regimens in risk of recurrence or progression, with no differences in adverse events (SOE: low).
- Two trials of patients with NMIBC not selected for being at higher risk found no clear differences between doxorubicin induction therapy alone and induction plus maintenance in risk of recurrence, progression, or mortality, with no differences in adverse events (SOE: low).
- Two trials of doxorubicin found no clear benefits associated with administration prior to TURBT or multiple instillations immediately after TURBT, with some evidence of increased adverse events with multiple immediate post-TURBT instillations (SOE: low).

Epirubicin

- Three trials of epirubicin found no clear evidence that higher doses are associated with reduced risk of recurrence or progression versus lower doses, with no differences in adverse events (SOE: moderate).
- Three trials found no clear difference between single-instillation epirubicin and multiple instillations in patients with low- or high-risk NMIBC in risk of recurrence, progression, or bladder cancer–specific mortality, with some evidence of lower risk of local adverse events with single instillation (SOE: moderate).
- Two trials, including one trial of patients with higher risk NMIBC, found no clear differences between epirubicin maintenance therapy and induction without maintenance in risk of recurrence or progression. There were no differences in risk of local adverse events (SOE: moderate).
- Five trials that evaluated different epirubicin regimens that included maintenance therapy found some evidence that more intensive therapy is associated with decreased risk of recurrence, but results were inconsistent. There was no difference in risk of adverse events (SOE: low).

Thiotepa

- Two trials found no clear differences between thiotepa 30 mg and 60 mg for maintenance or for treatment of incompletely resected NMIBC or CIS (SOE: low).

Interferon Alpha-2b

- Four trials found that higher doses of interferon alpha-2b were associated with improved outcomes related to recurrence, progression, or resolution of bladder cancer marker lesions versus lower doses, but most estimates were imprecise and did not reach statistical significance. There were no clear differences in risk of local or systemic adverse events (SOE: low).

Multiple Drugs

- One trial found no difference between initiation of intravesical therapy (9 instillations over 6 months) with MMC or doxorubicin 50 mg on the day of TURBT versus 1 to 2 weeks after TURBT in risk of recurrence, progression, or mortality, or between

maintenance beyond 6 months versus no additional maintenance therapy. There were no clear differences in local or systemic adverse events (SOE: low).

Key Question 4. For TURBT Patients, Effectiveness of Radiation Therapy Versus Intravesical Therapy or Cystectomy

This Key Question addressed the effectiveness of external beam radiation therapy for decreasing mortality or improving other outcomes compared with intravesical chemotherapy/immunotherapy alone or cystectomy in patients treated with TURBT. One randomized trial (rated moderate risk of bias) compared external beam radiation therapy with no radiation therapy in patients with NMIBC.

- One randomized trial of patients with T1 Grade (G) 3G3 bladder cancer found no effects of radiation therapy versus no radiotherapy (for unifocal disease and no CIS) or radiation therapy versus intravesical therapy (for multifocal disease or CIS) in recurrence-free survival (HR, 0.94; 95% CI, 0.67 to 1.30), progression-free interval (HR, 1.07; 95% CI, 0.65 to 1.74), progression-free survival (HR, 1.35; 95% CI, 0.92 to 1.98), or overall survival (HR, 1.32; 95% CI, 0.86 to 2.04) after 5 years (SOE: low).

Key Question 5. Effectiveness of Urinary Biomarkers Versus Other Urinary Biomarkers or Standard Diagnostic Methods for Surveillance

- No study evaluated the effectiveness of urinary biomarkers to decrease mortality or improve other outcomes compared with standard diagnostic methods or other urinary biomarkers in surveillance of patients treated for NMIBC.

Key Question 5a. Comparative Effectiveness: Tumor Characteristics

- No evidence was found (SOE: insufficient).

Key Question 5b. Comparative Effectiveness: Treatment Used

This Key Question addressed the issue of whether comparative effectiveness differs according to the treatment used (i.e., specific chemotherapeutic or immunotherapeutic agents and/or TURBT).

- No evidence was found (SOE: insufficient).

Key Question 5c. Comparative Effectiveness: Surveillance Intervals

- No evidence was found (SOE: insufficient).

Key Question 5d. Comparative Effectiveness: Patient Characteristics

- No evidence was found (SOE: insufficient).

Key Question 6. Effectiveness of Augmented Versus Standard Cystoscopy

This Key Question addresses the effectiveness of blue light or other methods of augmented cystoscopy compared with standard cystoscopy for recurrence rates, progression of bladder cancer, mortality, or other clinical outcomes in initial diagnosis or surveillance of patients treated for NMIBC. We included 14 trials (in 19 publications) that evaluated clinical outcomes of augmented (fluorescent or narrow band imaging) cystoscopy versus standard white light cystoscopy.

- There was no difference between fluorescent versus white light cystoscopy in risk of mortality (3 trials; RR, 1.28; 95% CI, 0.55 to 2.95; $I^2 = 41\%$) (SOE: low).
- Fluorescent cystoscopy with 5-aminolevulinic acid (5-ALA) or hexaminolevulinate (HAL) was associated with decreased risk of bladder cancer recurrence versus white light cystoscopy at short-term (<3 months; 9 trials; RR, 0.58; 95% CI, 0.36 to 0.94, $I^2 = 75\%$), intermediate-term (3 months to <1 year; 5 trials; RR, 0.67; 95% CI, 0.51 to 0.88; $I^2 = 35\%$), and long-term followup (≥1 year; 11 trials; RR, 0.81; 95% CI, 0.68 to 0.98; $I^2 = 64\%$), but findings were inconsistent and potentially susceptible to performance bias (because of failure to blind the initial cystoscopy) and publication bias (SOE: low).
- There was no difference between fluorescent and white light cystoscopy in risk of progression to muscle-invasive bladder cancer (9 trials; RR, 0.78; 95% CI, 0.55 to 1.12; $I^2 = 0\%$) (SOE: moderate).
- Narrow band imaging was associated with lower risk of bladder cancer recurrence at 3 months (3.9% vs. 17%; odds ratio [OR], 0.62; 95% CI, 0.41 to 0.92) and at 12 months (OR, 0.24; 95% CI, 0.07 to 0.81) compared with white light cystoscopy in one trial (SOE: low).

Key Question 7. Adverse Effects: Tests

We included seven studies that evaluated adverse effects of various tests for diagnosis and post-treatment surveillance of bladder cancer.

- Urinary biomarkers miss 23 to 42 percent of patients with bladder cancer and are incorrectly positive in 11 to 28 percent of patients without bladder cancer, but no study directly measured effects of inaccurate diagnosis on clinical outcomes (SOE: insufficient).
- There were no clear differences between fluorescent cystoscopy and white light cystoscopy in the risk of false-positives in two trials (SOE: low).
- There were no clear differences between fluorescent cystoscopy and white light cystoscopy in the risk of renal and genitourinary adverse events in two trials (SOE: low).

Key Question 8. Adverse Effects: Treatments

This Key Question addressed adverse effects of various treatments, including intravesical chemotherapeutic or immunotherapeutic agents and TURBT. We included 22 studies of intravesical therapies that reported harms.

Intravesical Therapy Versus No Intravesical Therapy

- Four trials of BCG versus no intravesical therapy reported granulomatous cystitis or irritative symptoms in 27 to 84 percent of patients treated with BCG, macroscopic hematuria in 21 to 72 percent, and fever in 27 to 44 percent. Harms were not reported in patients who did not receive intravesical therapy (SOE: low).
- Evidence on harms associated with non-BCG intravesical therapies versus no intravesical therapy was very limited, although some trials reported an increased risk of local adverse events with intravesical therapies. Evidence was insufficient to determine effects of non-BCG intravesical therapies versus no intravesical therapy on risk of systemic adverse events (SOE: low for local adverse events; insufficient for systemic adverse events).

BCG Versus MMC

- BCG was associated with increased risk of any local adverse event (2 trials; RR, 2.01; 95% CI, 1.59 to 2.54; $I^2 = 0\%$), granulomatous cystitis (5 trials; RR, 1.71; 95% CI, 1.22 to 2.41; $I^2 = 58\%$), dysuria (3 trials; 48% vs. 32%; RR, 1.23; 95% CI, 1.03 to 1.46; $I^2 = 34\%$), and hematuria (6 trials; RR, 1.78; 95% CI, 1.24 to 2.56; $I^2 = 62\%$) versus MMC (SOE: low for local adverse events and dysuria; moderate for granulomatous cystitis and hematuria).
- BCG was associated with increased risk of any systemic adverse event (2 trials; RR, 2.01; 95% CI, 1.59 to 2.54; $I^2 = 0\%$) and fever (4 trials; RR, 4.51; 95% CI, 2.31 to 8.82; $I^2 = 25\%$) versus MMC (SOE: low).
- There was no difference between BCG and MMC in risk of discontinuation of instillations (4 trials; RR, 1.26; 95% CI, 0.39 to 4.01; $I^2 = 70\%$) (SOE: low).
- BCG alone was associated with increased risk of discontinuation of instillations versus BCG plus MMC given sequentially (1 trial; RR, 4.06; 95% CI, 2.09 to 7.86) (SOE: low).

BCG Plus MMC Versus MMC

- There was no difference between sequentially administered BCG plus MMC and MMC alone in local adverse events (1 trial; RR, 1.36; 95% CI, 0.60 to 3.08) or risk of granulomatous cystitis (1 trial; RR, 1.30; 95% CI, 0.88 to 1.93) (SOE: low).
- There was no difference between BCG and MMC given sequentially and MMC used alone in systemic adverse events (1 trial; RR, 1.07; 95% CI, 0.63 to 1.84), but BCG plus MMC was associated with increased risk of fever (1 trial; 12% vs. 3%; RR, 3.75; 95% CI, 1.08 to 13) (SOE: low).
- There was no difference between alternating BCG plus MMC and MMC alone in risk of discontinuation of instillations in patients with CIS (1 trial; RR, 0.54; 95% CI, 0.16 to 1.84) or in patients with Ta or T1 tumors (1 trial; RR, 0.93; 95% CI, 0.52 to 1.65) (SOE: low).

BCG Versus Doxorubicin

- BCG was associated with increased risk of cystitis versus doxorubicin (1 trial; RR, 17; 95% CI, 1 to 289), but there was insufficient evidence to determine effects on dysuria (3 trials; data not pooled) and hematuria (2 trials; data not pooled) because of small numbers of trials with inconsistent results (SOE: low for cystitis; insufficient for dysuria and hematuria).

BCG Versus Epirubicin

- BCG was associated with increased risk of local side effects (1 trial; RR, 3.28; 95% CI, 1.26 to 8.53), granulomatous cystitis (4 trials; RR, 1.86; 95% CI, 1.35 to 2.56; $I^2 = 65\%$), dysuria (1 trial; RR, 2.43; 95% CI, 1.13 to 5.24), hematuria (4 trials; RR, 1.77; 95% CI, 1.41 to 2.22; $I^2 = 0\%$), and fever (2 trials; RR, 9.73; 95% CI, 2.72 to 35; $I^2 = 0\%$) versus epirubicin alone, but results were mixed for discontinuation of intravesical therapy (2 trials; data not pooled) (SOE: low for local side effects, dysuria, granulomatous cystitis, hematuria, and fever; insufficient for discontinuation of instillations).
- BCG alone was associated with increased risk of systemic adverse events (1 trial; RR, 5.97; 95% CI, 2.18 to 16), granulomatous cystitis (1 trial; RR, 2.28; 95% CI, 1.46 to 3.54), and discontinuation of instillations (1 trial; RR, 4.56; 95% CI, 1.35 to 15) versus sequentially administered BCG and epirubicin, but there was no difference in risk of dysuria (1 trial; RR, 1.22; 95% CI, 0.56 to 2.66), hematuria (2 trials; RR, 2.27; 95% CI, 0.86 to 6.00; $I^2 = 0\%$), or fever (2 trials; RR, 2.09; 95% CI, 0.48 to 9.02; $I^2 = 0\%$) (SOE: low).

BCG Versus Gemcitabine

- There were no differences between BCG and gemcitabine in risk of local adverse events requiring postponement or discontinuation of intravesical therapy (1 trial; RR, 1.33; 95% CI, 0.32 to 5.49), systemic adverse events (1 trial; RR, 0.50; 95% CI, 0.10 to 2.5), dysuria (2 trials; RR, 1.51; 95% CI, 0.92 to 2.50; $I^2 = 0\%$), or hematuria (2 trials; RR, 4.62; 95% CI, 0.78 to 27; $I^2 = 29\%$), but BCG was associated with increased risk of fever (2 trials; RR, 6.24; 95% CI, 1.03 to 38; $I^2 = 5\%$) (SOE: low).
- One trial found no difference between BCG alone and BCG plus gemcitabine given sequentially in risk of dysuria (RR, 0.92; 95% CI, 0.52 to 1.65) or hematuria (RR, 0.30; 95% CI, 0.08 to 1.09) (SOE: low).

BCG Versus Interferon

- BCG was associated with increased risk of dysuria versus interferon alpha-2a (1 trial; RR, 84; 95% CI, 5.29 to 1,319) but no difference in risk of fever (1 trial; RR, 4.82; 95% CI, 0.25 to 94) (SOE: low).
- BCG alone was associated with increased risk of constitutional symptoms (1 trial; RR, 1.63; 95% CI, 1.12 to 2.38) and fever (1 trial; RR, 2.26; 95% CI, 1.30 to 3.95) versus coadministration of BCG and interferon alpha-2b (SOE: low).

BCG Versus Thiotepa

- BCG was associated with increased risk of bladder irritability (1 trial; RR, 2.93; 95% CI, 1.45 to 5.90), cystitis (1 trial; RR, 18; 95% CI, 1.11 to 306), and fever (1 trial; RR, 8.36; 95% CI, 0.47 to 150) versus thiotepa (SOE).

MMC Versus Doxorubicin

- Evidence was insufficient to determine effects of MMC versus doxorubicin on risk of local adverse events, based on inconsistent results from six trials (SOE: insufficient).

MMC Versus Epirubicin

- One small trial found no difference between MMC and epirubicin 80 mg in risk of urinary symptoms (SOE: low).

MMC Versus Interferon Alpha

- One trial found MMC to be associated with greater risk of hematuria versus interferon alpha (RR, 2.00; 95% CI, 1.09 to 3.65), decreased risk of fever (RR, 0.13; 95% CI, 0.03 to 0.55), and no difference in risk of dysuria or urinary frequency (SOE: low).

MMC Versus Gemcitabine

- One trial found MMC to be associated with increased risk of chemical cystitis versus gemcitabine (RR, 3.93; 95% CI, 1.17 to 13.14), with no difference in risk of dysuria or hematuria (SOE: low).

Doxorubicin Versus Epirubicin

- Doxorubicin was associated with increased risk of chemical cystitis versus epirubicin (1 trial; RR, 1.85; 95% CI, 1.13 to 3.03), with no clear difference in risk of dysuria or urinary frequency (2 trials) or hematuria (3 trials; RR, 1.53; 95% CI, 0.50 to 4.66; I^2 = 0%) (SOE: low).

Doxorubicin Versus Thiotepa

- One trial found no difference between doxorubicin and thiotepa in risk of bladder irritability (RR, 0.92; 95% CI, 0.36 to 2.37) (SOE: low).

Epirubicin Versus Interferon Alpha

- One trial found no difference between epirubicin and interferon alpha in risk of dysuria or fever (SOE: low).

Key Question 8a. Adverse Effects of Treatments: Patient Characteristics

- No study evaluated how harms of treatment vary in subgroups defined by patient characteristic, such as age, sex, race/ethnicity, performance status, or medical comorbidities (SOE: insufficient).

Discussion

Key Findings and Strength of Evidence

The key findings of this review are described in the summary-of-evidence table (Table A).

Table A. Summary of the strength of evidence

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
Key Question 1. What is the diagnostic accuracy of various urinary biomarkers compared with other urinary biomarkers or standard diagnostic methods (cystoscopy, cytology, and imaging) in 1) people with signs or symptoms warranting evaluation for possible bladder cancer or 2) people undergoing surveillance for previously treated bladder cancer?	Quantitative NMP22: sensitivity and specificity	Moderate	Sensitivity was 0.69 (95% CI, 0.62 to 0.75) and specificity 0.77 (95% CI, 0.70 to 0.83), based on 19 studies, for a positive likelihood ratio of 3.05 (95% CI, 2.28 to 4.10) and negative likelihood ratio of 0.40 (95% CI, 0.32 to 0.50).
	Qualitative NMP22: sensitivity and specificity	Low	Sensitivity was 0.58 (95% CI, 0.39 to 0.75) and specificity 0.88 (95% CI, 0.78 to 0.94), based on 4 studies, for a positive likelihood ratio of 4.89 (95% CI, 3.23 to 7.40) and negative likelihood ratio of 0.48 (95% CI, 0.33 to 0.71).
	Qualitative BTA: sensitivity and specificity	Moderate	Sensitivity was 0.64 (95% CI, 0.58 to 0.69; 22 studies) and specificity 0.77 (95% CI, 0.73 to 0.81; 21 studies), for a positive likelihood ratio of 2.80 (95% CI, 2.31 to 3.39) and negative likelihood ratio of 0.47 (95% CI, 0.30 to 0.55).
	Quantitative BTA: sensitivity and specificity	Low	Sensitivity was 0.65 (95% CI, 0.54 to 0.75) and specificity 0.74 (95% CI, 0.64 to 0.82), based on 4 studies, for a positive likelihood ratio of 2.52 (95% CI, 1.86 to 3.41) and negative likelihood ratio of 0.47 (95% CI, 0.37 to 0.61).
	FISH: sensitivity and specificity	Moderate	Sensitivity was 0.63 (95% CI, 0.50 to 0.75) and specificity 0.87 (95% CI, 0.79 to 0.93), based on 11 studies, for a positive likelihood ratio of 5.02 (95% CI, 2.93 to 8.60) and negative likelihood ratio of 0.42 (95% CI, 0.30 to 0.59).
	ImmunoCyt™: sensitivity and specificity	Moderate	Sensitivity was 0.78 (95% CI, 0.68 to 0.85) and specificity 0.78 (95% CI, 0.72 to 0.82), based on 14 studies, for a positive likelihood ratio of 3.49 (95% CI, 2.82 to 4.32) and negative likelihood ratio of 0.29 (95% CI, 0.20 to 0.41).
	CxBladder™: sensitivity and specificity	Low	Sensitivity was 0.82 (95% CI, 0.70 to 0.90) and specificity 0.85 (95% CI, 0.81 to 0.88) for evaluation of symptoms, based on 1 study, for a positive likelihood ratio of 5.53 (95% CI, 4.28 to 7.15) and negative likelihood ratio of 0.21 (95% CI, 0.13 to 0.36).

Table A. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	Quantitative NMP22 versus qualitative BTA: sensitivity and specificity	Moderate	Based on 7 studies, there was no difference between quantitative NMP22 (cutoff >10 U/mL) and qualitative BTA in sensitivity (0.69; 95% CI, 0.62 to 0.76 vs. 0.66; 95% CI, 0.59 to 0.73, for a difference of 0.03; 95% CI, -0.04 to 0.10) or specificity (0.73; 95% CI, 0.62 to 0.82 vs. 0.76; 95% CI, 0.66 to 0.84, for a difference of 0.03; 95% CI, -0.08 to 0.01).
	ImmunoCyt versus FISH: sensitivity vs. specificity	Low	ImmunoCyt was associated with higher sensitivity than FISH (0.71; 95% CI, 0.54 to 0.84 vs. 0.61; 95% CI, 0.43 to 0.76, for a difference of 0.11; 95% CI, 0.001 to 0.21) but lower specificity (0.71; 95% CI, 0.62 to 0.79 vs. 0.79; 95% CI, 0.71 to 0.85, for a difference of -0.08; 95% CI, -0.15 to -0.001), based on 3 studies.
	Other head-to-head comparisons of urinary biomarkers	Insufficient	Evidence for other head-to-head comparisons of urinary biomarkers was based on small numbers of studies with imprecise estimates and methodological shortcomings, precluding reliable conclusions regarding comparative test performance.
	Various urinary biomarkers plus cytology vs. the urinary biomarker alone: sensitivity and specificity	Moderate	Sixteen studies found various urinary biomarkers plus cytology to be associated with higher sensitivity than the urinary biomarker alone (0.81; 95% CI, 0.75 to 0.86 vs. 0.69; 95% CI, 0.61 to 0.76, for a difference of 0.13; 95% CI, 0.08 to 0.17), with no difference in specificity.
Key Question 1a. Does the diagnostic accuracy differ according to patient characteristics (e.g., age, sex, race/ethnicity), or according to the nature of the presenting signs or symptoms?	Effects of tumor stage: sensitivity	High	Across urinary biomarkers, sensitivity increased with higher tumor stage. Evidence was most robust for quantitative NMP22 (11 studies), qualitative BTA (18 studies), and FISH (8 studies); the association between higher tumor stage and increased sensitivity was least pronounced for ImmunoCyt (10 studies). Sensitivity was generally similar to or slightly lower for CIS tumors than for T1 tumors.

Table A. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	Effects of tumor grade: sensitivity	High	Across urinary biomarkers, sensitivity increased with higher tumor grade. Evidence was most robust for quantitative NMP22 (12 studies), ImmunoCyt (10 studies), qualitative BTA (18 studies), and FISH (9 studies).
	Effects of tumor size: sensitivity	Low	Two studies found that sensitivity was higher for larger (>1 cm or >2 cm) vs. smaller tumors.
	Effects of patient characteristics (age, sex, smoking status, and presence of other clinical conditions): sensitivity and specificity	Low	Evidence on the effects of patient characteristics, such as age, sex, smoking status, and presence of other clinical conditions, on diagnostic accuracy of urinary biomarkers was limited but did not clearly or consistently indicate effects on sensitivity or specificity.
Key Question 2. For patients with non–muscle-invasive bladder cancer, does the use of a formal risk-adapted assessment approach to treatment decisions (e.g., Guidelines of the European Association of Urology or based on urinary biomarker tests) decrease mortality or improve other outcomes (e.g., recurrence, progression, need for cystectomy, quality of life) compared with treatment not guided by a formal assessed risk-adapted approach?	Mortality, recurrence, progression, need for cystectomy, quality of life	Insufficient	No studies.
Key Question 3. For patients with non–muscle-invasive bladder cancer treated with transurethral resection of bladder tumor (TURBT), what is the effectiveness of various intravesical chemotherapeutic or immunotherapeutic agents for decreasing mortality or improving other outcomes (e.g., recurrence, progression, need for cystectomy, quality of life) compared with TURBT alone?	*BCG vs. no intravesical therapy*: All-cause mortality	Insufficient	No trial evaluated effects of BCG vs. no intravesical therapy on risk of all-cause mortality.
	BCG vs. no intravesical therapy: Bladder cancer–specific mortality	Insufficient	One trial found BCG to be associated with decreased risk of bladder cancer–specific mortality vs. no intravesical therapy, but the difference was not statistically significant (RR, 0.62; 95% CI, 0.32 to 1.19).
	BCG vs. no intravesical therapy: Recurrence	Low	BCG was associated with decreased risk of bladder cancer recurrence vs. no intravesical therapy (3 trials; RR, 0.56; 95% CI, 0.43 to 0.71; $I^2 = 0\%$).
	BCG vs. no intravesical therapy: Progression	Low	BCG was associated with decreased risk of bladder cancer progression (4 trials; RR, 0.39; 95% CI, 0.24 to 0.64; $I^2 = 40\%$) vs. no intravesical therapy.

Table A. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	MMC vs. no intravesical therapy: All-cause mortality	Low	There was no difference in risk of all cause-mortality for MMC vs. no intravesical therapy (1 trial; HR, 1.17; 95% CI, 0.89 to 1.53).
	MMC vs. no intravesical therapy: Bladder cancer–specific mortality	Low	The effects on bladder cancer-specific mortality were not statistically significant for MMC vs. no intravesical therapy (1 trial; HR, 0.71; 95% CI, 0.34 to 1.46).
	MMC vs. no intravesical therapy: Recurrence	Moderate	MMC was associated with decreased risk of bladder cancer recurrence vs. no intravesical therapy (8 trials; RR, 0.71; 95% CI, 0.57 to 0.89; $I^2 = 72\%$).
	MMC vs. no intravesical therapy: Progression	Low	Effects of MMC on bladder cancer progression were not statistically significant (5 trials; RR, 0.68; 95% CI, 0.39 to 1.20; $I^2 = 0\%$) vs. no intravesical therapy.
	Doxorubicin vs. no intravesical therapy: All-cause mortality	Low	Doxorubicin was associated with no clear effects on all-cause mortality (2 trials) vs. no intravesical therapy.
	Doxorubicin vs. no intravesical therapy: Bladder cancer–specific mortality	Low	Doxorubicin was associated with no clear effects on bladder cancer–specific mortality (1 trial) vs. no intravesical therapy.
	Doxorubicin vs. no intravesical therapy: Recurrence	Moderate	Doxorubicin was associated with decreased risk of bladder cancer recurrence vs. no intravesical therapy (10 trials; RR, 0.80; 95% CI, 0.72 to 0.88; $I^2 = 46\%$).
	Doxorubicin vs. no intravesical therapy: Progression	Low	Doxorubicin was associated with no difference in risk of bladder cancer progression (5 trials; RR, 1.03; 95% CI, 0.72 to 1.46; $I^2 = 0.0\%$) vs. no intravesical therapy.
	Epirubicin vs. no intravesical therapy: Recurrence	Moderate	Epirubicin was associated with decreased risk of bladder cancer recurrence (9 trials; RR, 0.63; 95% CI, 0.53 to 0.75; $I^2 = 64\%$) vs. no intravesical therapy.
	Epirubicin vs. no intravesical therapy: Progression	Low	Epirubicin was associated with a non–statistically significant effect on bladder cancer progression (8 trials; RR, 0.79; 95% CI, 0.84 to 1.30; $I^2 = 27\%$).
	Gemcitabine vs. no intravesical therapy: All-cause mortality, bladder cancer–specific mortality, progression	Insufficient	Estimates for progression (RR, 3.00; 95% CI, 0.32 to 28.4), all-cause mortality (RR, 0.50; 95% CI, 0.13 to 2.00), and bladder cancer–specific mortality (RR, 1.00; 95% CI, 0.06 to 15.81) were very imprecise for gemcitabine vs. no intravesical therapy.

Table A. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	Gemcitabine vs. no intravesical therapy: Recurrence	Low	One trial found no difference between single-instillation gemcitabine vs. no intravesical therapy in risk of bladder cancer recurrence (RR, 0.98; 95% CI, 0.70 to 1.36).
	Interferon alpha vs. no intravesical therapy: Bladder cancer–specific mortality	Low	Interferon alpha was associated with no difference in risk of bladder cancer–specific mortality (1 trial; RR, 1.00; 95% CI, 0.15 to 6.75).
	Interferon alpha vs. no intravesical therapy: Recurrence	Low	Interferon alpha was associated with a non–statistically significant reduction in risk for bladder cancer recurrence vs. no intravesical therapy (3 trials; RR, 0.75; 95% CI, 0.53 to 1.06; I^2 = 50%).
	Interferon alpha vs. no intravesical therapy: Progression	Low	Interferon alpha was associated with decreased risk of bladder cancer progression vs. no intravesical therapy (2 trials; RR, 0.33; 95% CI, 0.14 to 0.76; I^2 = 0%).
	Interferon gamma vs. no intravesical therapy: Recurrence	Low	Interferon gamma was associated with decreased risk of bladder cancer recurrence vs. no intravesical therapy (1 trial; RR, 0.72; 95% CI, 0.51 to 1.01).
	Interferon gamma vs. no intravesical therapy: Progression	Low	Interferon gamma was associated with no difference in risk of bladder cancer progression vs. no intravesical therapy (1 trial; RR, 1.08; 95% CI, 0.07 to 16.4).
	Thiotepa vs. no intravesical therapy: Recurrence	Low	Thiotepa was associated with decreased risk of bladder cancer recurrence vs. no intravesical therapy in 5 trials (RR, 0.78; 95% CI, 0.58 to 1.06; I^2 = 69%).
Key Question 3a. What is the comparative effectiveness of various chemotherapeutic or immunotherapeutic agents, as monotherapy or in combination?	*BCG vs. MMC*: All-cause mortality	Moderate	There was no difference in risk of all-cause mortality between BCG and MMC (7 trials; RR, 0.94; 95% CI, 0.83 to 1.06; I^2 = 0%).
	BCG vs. MMC: Bladder cancer–specific mortality	Moderate	There was no difference between BCG and MMC in risk of bladder cancer–specific mortality (5 trials; RR, 0.77; 95% CI, 0.54 to 1.10; I^2 = 0%).
	BCG vs. MMC: Recurrence	Low	There were no differences between BCG and MMC in risk of bladder cancer recurrence (10 trials; RR, 0.95; 95% CI, 0.81 to 1.11; I^2 = 67%).
	BCG vs. MMC: Progression	Moderate	There was no difference in risk of progression (7 trials; RR, 0.88; 95% CI, 0.66 to 1.17; I^2 = 18%).

Table A. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	BCG alone vs. BCG plus MMC given sequentially: All-cause mortality, bladder cancer–specific mortality, recurrence, progression	Low	There were no differences sequentially in risk of all-cause (1 trial; RR, 1.57; 95% CI, 0.67 to 3.71) or bladder cancer–specific mortality (2 trials; RR, 1.10; 95% CI, 0.50 to 2.38; I^2 = 17%), bladder cancer recurrence (4 trials; RR, 1.03; 95% CI, 0.70 to 1.52; I^2 = 75%), progression (3 trials; RR, 0.87; 95% CI, 0.40 to 1.91; I^2 = 22%), or cystectomy (4 trials; RR, 0.87; 95% CI, 0.41 to 1.84; I^2 = 0%).
	BCG plus MMC given sequentially vs. MMC alone: All-cause mortality, bladder cancer–specific mortality, recurrence, progression	Low	There were no differences in risk of all-cause (2 trials; RR, 1.53; 95% CI, 0.72 to 1.74 and RR, 0.95; 95% CI, 0.71 to 1.30) or bladder cancer–specific mortality (2 trials; RR, 0.64; 95% CI, 0.22 to 1.88 and RR, 0.95; 95% CI, 0.45 to 1.56), bladder cancer recurrence (2 trials; RR, 0.88; 95% CI, 0.75 to 1.03; I^2 = 0%), or progression (2 trials; RR, 0.82; 95% CI, 0.40 to 1.68 and RR, 1.28; 95% CI, 0.35 to 4.61).
	BCG vs. doxorubicin: All-cause mortality, recurrence, progression	Low	BCG was associated with decreased risk of bladder cancer recurrence vs. doxorubicin (2 trials; RR, 0.31; 95% CI, 0.16 to 0.61 and RR, 0.75; 95% CI, 0.64 to 0.88), but there was no difference in risk of all-cause mortality (2 trials; RR, 0.40; 95% CI, 0.01 to 12 and RR, 1.00; 95% CI, 0.71 to 1.37) or bladder cancer progression (1 trial; RR, 0.20; 95% CI, 0.02 to 1.72).
	BCG vs. epirubicin: All-cause mortality	Low	Estimates favored BCG for all-cause mortality, but differences were not statistically significant (3 trials; RR, 0.72; 95% CI, 0.44 to 1.19; I^2 = 87%).
	BCG vs. epirubicin: Bladder cancer–specific mortality	Low	Estimates favored BCG for bladder cancer–specific mortality, but differences were not statistically significant (3 trials; RR, 0.72; 95% CI, 0.25 to 2.08; I^2 = 80%).
	BCG vs. epirubicin: Recurrence	Moderate	BCG was associated with reduced risk of bladder cancer recurrence, but statistical heterogeneity was high (5 trials; RR, 0.54; 95% CI, 0.40 to 0.74; I^2 = 76%).

Table A. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	BCG vs. epirubicin: Progression	Low	Estimates favored BCG for bladder cancer progression, but differences were not statistically significant (5 trials; RR, 0.60; 95% CI, 0.36 to 1.01; I^2 = 47%).
	BCG alone vs. BCG plus epirubicin given sequentially: Recurrence, progression	Low	There were no differences in risk of bladder cancer recurrence (3 trials; RR, 1.25; 95% CI, 0.92 to 1.69; I^2 = 0%). BCG was associated with increased risk of bladder cancer progression, but the difference was not statistically significant (3 trials; RR, 1.92; 95% CI, 0.73 to 5.07; I^2 = 0%).
	BCG vs. epirubicin plus interferon: Bladder cancer–specific mortality, progression	Low	One trial found no differences in risk of bladder cancer–specific mortality (RR, 0.79; 95% CI, 0.32 to 1.63) or progression-free survival, although BCG was associated with decreased risk of bladder cancer recurrence (RR, 0.66; 95% CI, 0.51 to 0.85).
	BCG vs. gemcitabine: All-cause mortality	Low	There were no differences in risk of all-cause mortality (1 trial; RR, 1.20; 95% CI, 0.04 to 34).
	BCG vs. gemcitabine: Recurrence	Insufficient	Evidence from 3 trials was insufficient to determine risk of bladder cancer recurrence because of clinical heterogeneity and inconsistent findings (RR, 1.67; 95% CI, 1.21 to 2.29; RR, 0.53; 95% CI, 0.28 to 1.01; and RR, 0.76; 95% CI, 0.44 to 1.90).
	BCG vs. gemcitabine: Progression	Low	There were no differences in risk of progression (2 trials; RR, 1.11; 95% CI, 0.53 to 2.34 and RR, 0.52; 95% CI, 0.13 to 2.06).
	BCG vs. gemcitabine: Quality of life	Low	There were no differences for BCG vs. gemcitabine in quality of life (1 trial).
	BCG alone vs. BCG plus gemcitabine given sequentially: Recurrence, progression	Low	There were no differences in risk of bladder cancer recurrence (1 trial; RR, 0.86; 95% CI, 0.49 to 1.51) or progression (1 trial; RR, 1.18; 95% CI, 0.30 to 4.61).
	BCG vs. interferon alpha-2a: Recurrence, progression	Low	BCG was associated with reduced risk of bladder cancer recurrence (1 trial; RR, 0.57; 95% CI, 0.39 to 0.82), but the difference in risk of bladder cancer progression was not statistically significant (1 trial; RR, 0.69; 95% CI, 0.25 to 1.92).

Table A. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	BCG alone vs. alternating BCG and interferon alpha-2b: Recurrence	Low	BCG alone was associated with reduced risk of bladder cancer recurrence (1 trial; RR, 0.42; 95% CI, 0.30 to 0.59).
	BCG alone vs. coadministration of BCG and interferon alpha-2b: Recurrence, progression	Low	Differences in risk of bladder cancer recurrence (1 trial; RR, 0.88; 95% CI, 0.71 to 1.08) or progression (1 trial; RR, 0.76; 95% CI, 0.17 to 3.30) did not reach statistical significance.
	BCG vs. thiotepa: Recurrence	Low	Two trials found maintenance therapy with BCG to be associated with decreased risk of recurrence vs. thiotepa (RR, 0.38; 95% CI, 0.19 to 0.76 and RR, 0.04; 95% CI, 0.00 to 0.63).
	BCG vs. thiotepa: Progression, mortality, and cystectomy	Insufficient	Estimates were too imprecise to evaluate effects.
	MMC vs. doxorubicin: Recurrence, progression	Low	There was no difference in risk of bladder cancer recurrence (6 trials; RR, 1.00; 95% CI, 0.82 to 1.22; $I^2 = 44\%$), but MMC was associated with a non–statistically significant trend toward decreased risk of bladder cancer progression (4 trials; RR, 0.63; 95% CI, 0.37 to 1.08; $I^2 = 21\%$).
	MMC vs. epirubicin: Recurrence	Low	There was no difference in risk of bladder cancer recurrence in 1 trial (RR, 1.16; 95% CI, 0.52 to 2.58).
	MMC vs. gemcitabine: Recurrence, progression	Low	In 1 trial, there was no difference in risk of bladder cancer progression (p = 0.29). MMC was associated with increased risk of recurrence, but the difference was not statistically significant (RR, 1.64; 95% CI, 0.64 to 4.19).
	MMC vs. interferon alpha: Recurrence, progression	Low	One trial found no difference between MMC and interferon alpha in risk of bladder cancer recurrence (RR, 0.77; 95% CI, 0.58 to 1.01) or bladder cancer progression (RR, 1.38; 95% CI, 0.49 to 3.88).
	MMC vs. interferon gamma: Recurrence	Low	MMC was associated with increased risk of bladder cancer recurrence in 1 trial (RR, 1.61; 95% CI, 0.97 to 2.67).
	MMC vs. thiotepa: Recurrence	Low	Two trials found no difference between MMC and thiotepa in risk of recurrence (RR, 1.76; 95% CI, 0.36 to 8.70 and RR, 1.14; 95% CI, 0.60 to 2.16).

Table A. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	Doxorubicin vs. epirubicin: Recurrence, progression	Low	Doxorubicin was associated with increased risk of bladder cancer recurrence (3 trials; RR, 1.56; 95% CI, 1.08 to 2.22; I^2 = 0%); the difference in risk of progression was not statistically significant (1 trial; RR, 1.32; 95% CI, 0.50 to 3.47).
	Doxorubicin vs. thiotepa: Recurrence	Low	There was no statistically significant difference in risk of bladder cancer recurrence (RR, 1.22; 95% CI, 0.76 to 1.94).
	Doxorubicin vs. thiotepa: Progression, noncancer mortality, cancer-specific mortality	Insufficient	Estimates from 1 trial for progression (RR, 2.11; 95% CI, 0.40 to 11.06), noncancer mortality (RR, 0.35; 95% CI, 0.01 to 8.45), and cancer-specific mortality (RR, 3.17; 95% CI, 0.13 to 76.1) were very imprecise.
	Epirubicin vs. interferon alpha: Recurrence	Low	Epirubicin was associated with decreased risk of bladder cancer recurrence in 1 trial (RR, 0.67; 95% CI, 0.49 to 0.91).
Key Question 3b. Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?	Stage, grade, tumor multiplicity, primary vs. recurrent	Low	There were no clear differences in estimates of effectiveness of intravesical therapies in subgroups defined by tumor stage, grade, size, multiplicity, recurrence status, or DNA ploidy.
Key Question 3c. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, race/ethnicity, performance status, or medical comorbidities?	Age, sex, race/ethnicity, performance status, comorbidities	Insufficient	No studies.
	Recurrence, disease-free survival	Low	In patients with recurrence or progression following prior BCG therapy, 1 trial found maintenance therapy with gemcitabine to be associated with decreased risk of recurrence vs. repeat treatment with BCG, and 1 trial found MMC maintenance therapy to be associated with lower likelihood of disease-free survival than gemcitabine; estimates for progression were imprecise.
Key Question 3d. Does the comparative effectiveness of various chemotherapeutic or immunotherapeutic agents differ according to dosing frequency, duration of treatment, and/or the timing of administration relative to TURBT?	Standard vs. lower dose BCG: recurrence, progression, mortality, adverse events	Low	Six trials found no clear differences in risk of recurrence, progression, or bladder cancer mortality, including in patients with higher risk NMIBC, although there was some inconsistency between trials. Standard therapy was associated with increased risk of local and systemic adverse events vs. lower dose BCG.

Table A. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	Maintenance vs. induction BCG: recurrence, progression, adverse events	Low	Two trials found more prolonged courses of BCG to be associated with decreased risk of bladder cancer recurrence vs. induction therapy in patients with higher risk NMIBC (RR, 0.54; 95% CI, 0.31 to 0.95) but increased risk of adverse events.
	BCG maintenance for 1 vs. 3 years: recurrence, progression, mortality, adverse events	Low	One trial of patients with solitary T1/G3 or multiple Ta–T1/G1–G3 tumors found no difference between 1 vs. 3 years of BCG maintenance therapy in risk of recurrence, progression, mortality, or adverse events.
	MMC single vs. 5 instillations: recurrence, progression, mortality, adverse events	Low	One trial of patients with NMIBC (not selected for being at higher risk) found no clear differences in risk of recurrence, progression, or mortality. The single instillation was associated with lower risk of local adverse events.
	MMC induction vs. maintenance: recurrence, adverse events	Low	One trial of patients with higher risk NMIBC found MMC 20 mg induction therapy for 6 weeks to be associated with higher risk of recurrence than maintenance therapy. There were no clear differences in risk of adverse events.
	MMC maintenance therapy with increased frequency and number of instillations vs. fewer instillations: recurrence, progression, adverse events	Low	Two trials of MMC maintenance regimens in patients with NMIBC not selected for being at higher risk found some evidence that a higher total number of instillations and increased frequency during initial therapy were associated with lower risk of recurrence and progression, and might be associated with lower risk of local adverse events.
	MMC optimized through alkalinization of urine vs. nonoptimized administration: recurrence, adverse events	Low	One trial found no difference between “optimized” versus nonoptimized administration of intravesical MMC in risk of recurrence in patients with low-risk NMIBC, but 1 other trial of patients with higher risk NMIBC found optimized administration to be associated with lower risk of recurrence and increased risk of local adverse events.

Table A. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	Doxorubicin 8 weeks vs. 2 years: recurrence, progression, adverse events	Low	Two trials of patients with NMIBC not selected for being at higher risk found no differences between doxorubicin 30 mg and 20 mg given as short (8 weeks) or long (2 years) regimens in risk of recurrence or progression, with no differences in adverse events.
	Doxorubicin induction vs. maintenance: recurrence, progression, mortality, adverse events	Low	Two trials of patients with NMIBC not selected for being at higher risk found no clear differences between doxorubicin induction therapy and induction plus maintenance in risk of recurrence, progression, or mortality, with no differences in adverse events.
	Doxorubicin prior to vs. after TURBT: recurrence, adverse events	Low	Two trials of doxorubicin found no clear benefits associated with administration prior to TURBT or multiple instillations immediately after TURBT, with some evidence of increased adverse events with multiple immediate post-TURBT instillations.
	Epirubicin higher vs. lower doses: recurrence, progression, adverse events	Moderate	Three trials of epirubicin found no clear evidence that higher doses are associated with reduced risk of recurrence or progression vs. lower doses, with no differences in adverse events.
	Epirubicin single vs. multiple instillations: recurrence, progression, bladder cancer mortality, adverse events	Moderate	Three trials found no clear difference between single-instillation epirubicin and multiple instillations in patients with low- or high-risk NMIBC in risk of recurrence, progression, or bladder cancer mortality, with some evidence of lower risk of local adverse events with single instillation.
	Epirubicin maintenance vs. induction without maintenance: recurrence, progression, adverse events	Moderate	Two trials found no clear differences between epirubicin maintenance therapy and induction without maintenance in risk of recurrence or progression, including 1 trial of patients with higher risk NMIBC. There were no differences in risk of local adverse events.

Table A. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	Epirubicin, more vs. less intensive therapy: recurrence, adverse events	Low	Five trials that evaluated different epirubicin regimens that included maintenance therapy found some evidence that more intensive therapy is associated with decreased risk of recurrence, but results were inconsistent. There was no difference in risk of adverse events.
	Thiotepa 30 vs. 60 mg: recurrence, adverse events	Low	Two trials found no clear differences between thiotepa 30 mg and 60 mg for maintenance or for treatment of incompletely resected NMIBC or CIS.
	Interferon alpha-2b, high vs. lower doses: recurrence, progression, resolution of bladder cancer marker lesions	Low	Three trials found higher doses of interferon alpha-2b to be associated with improved outcomes related to recurrence, progression, or resolution of bladder cancer marker lesions vs. lower doses, but most estimates were imprecise and did not reach statistical significance. There were no clear differences in risk of local or systemic adverse events.
	MMC or doxorubicin on day of TURBT vs. 1 to 2 weeks after TURBT: recurrence, progression, mortality, adverse events	Low	One trial found no difference between initiation of intravesical therapy (9 instillations over 6 months) with MMC or doxorubicin 50 mg on the day of TURBT versus 1 to 2 weeks after TURBT in risk of recurrence, progression, or mortality.
	MMC or doxorubicin maintenance vs. no maintenance: recurrence, progression, mortality, adverse events	Low	One trial found no difference between maintenance beyond 6 months vs. no additional maintenance therapy. There were no clear differences in local or systemic adverse events.
Key Question 4. For patients with high risk non–-muscle-invasive bladder cancer treated with TURBT, what is the effectiveness of external beam radiation therapy (either alone or with systemic chemotherapy/immunotherapy) for decreasing mortality or improving other outcomes compared with intravesical chemotherapy/immunotherapy alone or cystectomy?	Mortality, recurrence, progression	Low	One randomized trial of patients with T1G3 bladder cancer found no effects of radiation therapy vs. no radiotherapy (for unifocal disease and no CIS) or radiation therapy vs. intravesical therapy (for multifocal disease or CIS) in recurrence-free survival (HR, 0.94; 95% CI, 0.67 to 1.30), progression-free interval (HR, 1.07; 95% CI, 0.65 to 1.74), progression-free survival (HR, 1.35; 95% CI, 0.92 to 1.98), or overall survival (HR, 1.32; 95% CI, 0.86 to 2.04) after 5 years.

Table A. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
Key Question 5. In surveillance of patients treated for non–muscle-invasive bladder cancer, what is the effectiveness of various urinary biomarkers to decrease mortality or improve other outcomes compared with other urinary biomarkers or standard diagnostic methods (cystoscopy, cytology, and imaging)?	Mortality	Insufficient	No studies.
Key Question 5a. Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?		Insufficient	No studies.
Key Question 5b. Does the comparative effectiveness differ according to the treatment used (i.e., specific chemotherapeutic or immunotherapeutic agents and/or TURBT)?		Insufficient	No studies.
Key Question 5c. Does the comparative effectiveness differ according to the length of surveillance intervals?		Insufficient	No studies.
Key Question 5d. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, or race/ethnicity?		Insufficient	No studies.
Key Question 6. For initial diagnosis or surveillance of patients treated for non–muscle-invasive bladder cancer, what is the effectiveness of blue light or other methods of augmented cystoscopy compared with standard cystoscopy for recurrence rates, progression of bladder cancer, mortality, or other clinical outcomes?	*Fluorescent cystoscopy vs. white light cystoscopy:* Mortality	Low	There was no difference between fluorescent and white light cystoscopy in risk of mortality (3 trials; RR, 1.28; 95% CI, 0.55 to 2.95; $I^2 = 41\%$).

Table A. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	Fluorescent cystoscopy vs. white light cystoscopy: Recurrence	Low	Fluorescent cystoscopy with 5-ALA or HAL was associated with decreased risk of bladder cancer recurrence vs. white light cystoscopy at short-term (<3 months; 9 trials; RR, 0.58; 95% CI, 0.36 to 0.94; I^2=75%), intermediate-term (3 months to <1 year; 5 trials; RR, 0.67; 95% CI, 0.51 to 0.88; I^2=35%), and long-term followup (≥1 year; 11 trials; RR, 0.81; 95% CI, 0.68 to 0.98; I^2=64%), but findings were inconsistent and potentially susceptible to performance bias (because of failure to blind the initial cystoscopy) and publication bias.
	Fluorescent cystoscopy vs. white light cystoscopy: Progression	Moderate	There was no difference between fluorescent and white light cystoscopy in risk of progression to muscle-invasive bladder cancer (9 trials; RR, 0.78; 95% CI, 0.55 to 1.12; I^2 = 0%).
	Narrow band imaging vs. white light cystoscopy: Recurrence	Low	Narrow band imaging was associated with lower risk of bladder cancer recurrence at 3 months (3.9% vs. 17%; OR, 0.62; 95% CI, 0.41 to 0.92) and at 12 months (OR, 0.24; 95% CI, 0.07 to 0.81) in 1 trial.
Key Question 7. What are the comparative adverse effects of various tests for diagnosis and post-treatment surveillance of bladder cancer, including urinary biomarkers, cytology, and cystoscopy?	Urinary biomarkers: adverse clinical outcomes	Insufficient	Urinary biomarkers miss 23% to 42% of patients with bladder cancer and are incorrectly positive in 11% to 28% of patients without bladder cancer, but no study directly measured effects of inaccurate diagnosis on clinical outcomes.
	Fluorescent vs. white light cystoscopy: false-positives	Low	There were no clear differences between fluorescent cystoscopy and white light cystoscopy in risk of false-positives in 2 trials.
	Fluorescent vs. white light cystoscopy: renal and genitourinary adverse events	Low	There were no clear differences between fluorescent cystoscopy and white light cystoscopy in risk of renal and genitourinary adverse events in 2 trials.

Table A. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
Key Question 8. What are the comparative adverse effects of various treatments for non–-muscle-invasive bladder cancer, including intravesical chemotherapeutic or immunotherapeutic agents and TURBT?	BCG vs. no intravesical therapy: local and systemic adverse events	Low	Four trials reported granulomatous cystitis or irritative symptoms in 27% to 84% of patients, macroscopic hematuria in 21% to 72%, and fever in 27% to 44%. Harms were not reported in patients who did not receive intravesical therapy.
	Non-BCG intravesical therapies vs. no intravesical therapy: local and systemic adverse events	Low (local adverse events); insufficient (systemic adverse events)	Evidence on harms was very limited, although some trials reported an increased risk of local adverse events. Evidence was insufficient to determine effects of non-BCG intravesical therapies vs. no intravesical therapy on risk of systemic adverse events.
	BCG vs. MMC: Local adverse events	Low (moderate for cystitis and hematuria)	BCG was associated with increased risk of any local adverse event (2 trials; RR, 2.01; 95% CI, 1.59 to 2.54; I^2 = 0%), granulomatous cystitis (5 trials; RR, 1.71; 95% CI, 1.22 to 2.41; I^2 = 58%), dysuria (3 trials; 48% vs. 32%; RR, 1.23; 95% CI, 1.03 to 1.46; I^2 = 34%), and hematuria (6 trials; RR, 1.78; 95% CI, 1.24 to 2.56; I^2 = 62%) vs. MMC.
	BCG vs. MMC: Systemic adverse events	Low	BCG was associated with increased risk of any systemic adverse event (2 trials; RR, 2.01; 95% CI, 1.59 to 2.54; I^2 = 0%) and fever (4 trials; RR, 4.51; 95% CI, 2.31 to 8.82; I^2 = 25%) vs. MMC.
	BCG alone vs. BCG plus MMC given sequentially: Discontinuation of therapy	Low	BCG alone was associated with increased risk of discontinuation of instillations vs. BCG plus MMC given sequentially (1 trial; RR, 4.06; 95% CI, 2.09 to 7.86).
	BCG plus MMC given sequentially vs. MMC alone: Local adverse events	Low	There was no difference between sequentially administered BCG plus MMC and MMC alone in local adverse events (1 trial; RR, 1.36; 95% CI, 0.60 to 3.08) or risk of granulomatous cystitis (1 trial; RR, 1.30; 95% CI, 0.88 to 1.93).
	BCG plus MMC given sequentially vs. MMC alone: Systemic adverse events	Low	There was no difference between BCG and MMC given sequentially and MMC used alone in systemic adverse events (1 trial; RR, 1.07; 95% CI, 0.63 to 1.84), but BCG plus MMC was associated with increased risk of fever (1 trial; 12% vs. 3%; RR, 3.75; 95% CI, 1.08 to 13).

Table A. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	BCG plus MMC given sequentially vs. MMC alone: Discontinuation of therapy	Low	There was no difference between alternating BCG plus MMC and MMC alone in risk of discontinuation of instillations in patients with CIS (1 trial; RR, 0.54; 95% CI, 0.16 to 1.84) or in patients with Ta or T1 tumors (1 trial; RR, 0.93; 95% CI, 0.52 to 1.65).
	BCG vs. doxorubicin: Local adverse events	Low (cystitis); insufficient (dysuria and hematuria)	BCG was associated with increased risk of cystitis vs. doxorubicin (1 trial; RR, 17; 95% CI, 1 to 289), but there was insufficient evidence to determine effects on dysuria (3 trials; data not pooled) and hematuria (2 trials; data not pooled) because of small numbers of trials with inconsistent results.
	BCG vs. epirubicin: Local adverse events	Low	BCG was associated with increased risk of local side effects (1 trial; RR, 3.28; 95% CI, 1.26 to 8.53).
	BCG vs. epirubicin: Discontinuation of therapy	Insufficient	Results were mixed for discontinuation of intravesical therapy (2 trials; data not pooled).
	BCG vs. epirubicin: Systemic adverse events	Low	BCG was associated with increased risk of granulomatous cystitis (4 trials; RR, 1.86; 95% CI, 1.35 to 2.56; I^2 = 65%), dysuria (1 trial; RR, 2.43; 95% CI, 1.13 to 5.24), hematuria (4 trials; RR, 1.77; 95% CI, 1.41 to 2.22; I^2 = 0%), and fever (2 trials; RR, 9.73; 95% CI, 2.72 to 35; I^2 = 0%).
	BCG alone vs. BCG plus epirubicin given sequentially: Local adverse events	Low	There was no difference in risk of dysuria (1 trial; RR, 1.22; 95% CI, 0.56 to 2.66) or hematuria (2 trials; RR, 2.27; 95% CI, 0.86 to 6.00; I^2 = 0%).
	BCG alone vs. BCG plus epirubicin given sequentially: Systemic adverse events	Low	BCG was associated with increased risk of systemic adverse events (1 trial; RR, 5.97; 95% CI, 2.18 to 16) and granulomatous cystitis (1 trial; RR, 2.28; 95% CI, 1.46 to 3.54) but no difference in risk of fever (2 trials; RR, 2.09; 95% CI, 0.48 to 9.02; I^2 = 0%).
	BCG alone vs. BCG plus epirubicin given sequentially: Discontinuation of therapy	Low	BCG was associated with increased risk of discontinuation of instillations (1 trial; RR, 4.56; 95% CI, 1.35 to 15).

Table A. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	BCG vs. gemcitabine: Local adverse events	Low	There were no differences between BCG and gemcitabine in risk of local adverse events requiring postponement or discontinuation of intravesical therapy (1 trial; RR, 1.33; 95% CI, 0.32 to 5.49).
	BCG vs. gemcitabine: Systemic adverse events	Low	There were no differences in systemic adverse events (1 trial; RR, 0.50; 95% CI, 0.10 to 2.5), dysuria (2 trials; RR, 1.51; 95% CI, 0.92 to 2.50; $I^2 = 0\%$), or hematuria (2 trials; RR, 4.62; 95% CI, 0.78 to 27; $I^2 = 29\%$), but BCG was associated with increased risk of fever (2 trials; RR, 6.24; 95% CI, 1.03 to 38; $I^2 = 5\%$).
	BCG alone vs. BCG plus gemcitabine given sequentially: Local adverse events	Low	One trial found no difference in risk of dysuria (RR, 0.92; 95% CI, 0.52 to 1.65) or hematuria (RR, 0.30; 95% CI, 0.08 to 1.09).
	BCG vs. interferon alpha-2a: Local adverse events	Low	BCG was associated with increased risk of dysuria (1 trial; RR, 84; 95% CI, 5.29 to 1,319).
	BCG vs. interferon alpha-2a: Systemic adverse events	Low	There was no difference in risk of fever (1 trial; RR, 4.82; 95% CI, 0.25 to 94).
	BCG alone vs. coadministration of BCG and interferon alpha-2b: Systemic adverse events	Low	BCG was associated with increased risk of constitutional symptoms (1 trial; RR, 1.63; 95% CI, 1.12 to 2.38) and fever (1 trial; RR, 2.26; 95% CI, 1.30 to 3.95).
	BCG vs. thiotepa: Local adverse events	Low	BCG was associated with increased risk of bladder irritability (1 trial; RR, 2.93; 95% CI, 1.45 to 5.90) and cystitis (1 trial; RR, 18; 95% CI, 1.11 to 306).
	BCG vs. thiotepa: Systemic adverse events	Low	BCG was associated with increased risk of fever (1 trial; RR, 8.36; 95% CI, 0.47 to 150).
	MMC vs. doxorubicin: Local adverse events	Insufficient	Evidence was insufficient to determine effects of MMC vs. doxorubicin on risk of local adverse events, based on inconsistent results from 6 trials.
	MMC vs. epirubicin: Local adverse events	Low	One small trial found no difference between MMC and epirubicin 80 mg in risk of urinary symptoms.
	MMC vs. interferon alpha: Local adverse events	Low	One trial found MMC to be associated with greater risk of hematuria vs. interferon alpha (RR, 2.00; 95% CI, 1.09 to 3.65) and no difference in risk of dysuria or urinary frequency.

Table A. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	MMC vs. interferon alpha: Systemic adverse events	Low	One trial found MMC to be associated with decreased risk of fever (RR, 0.13; 95% CI, 0.03 to 0.55).
	MMC vs. gemcitabine: Local adverse events	Low	One trial found MMC to be associated with increased risk of chemical cystitis (RR, 3.93; 95% CI, 1.17 to 13.14), with no difference in risk of dysuria or hematuria.
	Doxorubicin vs. epirubicin: Local adverse events	Low	Doxorubicin was associated with increased risk of chemical cystitis (1 trial; RR, 1.85; 95% CI, 1.13 to 3.03), with no clear difference in risk of dysuria or urinary frequency (2 trials) or hematuria (3 trials; RR, 1.53; 95% CI, 0.50 to 4.66; I^2 = 0%).
	Doxorubicin vs. thiotepa: Local adverse events	Low	One trial found no difference in risk of bladder irritability (RR, 0.92; 95% CI, 0.36 to 2.37).
	Epirubicin vs. interferon alpha: Local adverse events	Low	One trial found no difference in risk of dysuria.
	Epirubicin vs. interferon alpha: Systemic adverse events	Low	One trial found no difference in risk of fever.
Key Question 8a. How do adverse effects of treatment vary by patient characteristics, such as age, sex, race/ethnicity, performance status, or medical comorbidities such as chronic kidney disease?	Adverse effects	Insufficient	No studies

5-ALA = 5-aminolevulinic acid; BCG = bacillus Calmette-Guérin; BTA = bladder tumor antigen; CI = confidence interval; CIS = carcinoma in situ; FISH = fluorescence in situ hybridization; G = grade; HAL = hexaminolevulinate; HR = hazard ratio; MMC = mitomycin C; NMIBC = non–muscle-invasive bladder cancer; NMP22 = nuclear matrix protein 22; OR = odds ratio; RR = relative risk; T = tumor; TURBT = transurethral resection of bladder tumor

Urinary biomarkers were associated with sensitivity for bladder cancer that ranged from 0.58 to 0.77 and specificity that ranged from 0.72 to 0.89, for positive likelihood ratios that ranged from 2.18 to 6.10 and negative likelihood ratios that ranged from 0.21 to 0.48. Findings were robust in sensitivity and stratified analyses, although evidence was strongest for quantitative NMP22 and qualitative BTA (SOE: moderate) and relatively sparse for other biomarkers (SOE: low). Across urinary biomarkers, sensitivity was greater for higher stage and higher grade tumors (SOE: high). For qualitative BTA, sensitivity was somewhat higher for evaluation of patients with signs or symptoms of bladder cancer than for surveillance of patients previously treated for bladder cancer, but for quantitative NMP22 there was no clear difference in diagnostic accuracy based on reason for testing. Studies that directly compared the accuracy of quantitative NMP22 and qualitative BTA found no differences in diagnostic accuracy (SOE: moderate). There were too few head-to-head comparisons of other urinary biomarkers to reach firm conclusions regarding comparative accuracy. Sensitivity was increased when urinary biomarkers were used

in conjunction with urine cytology (SOE: moderate). No study evaluated clinical outcomes associated with use of urinary biomarkers for diagnosis or surveillance of bladder cancer (SOE: insufficient). Urinary biomarkers miss 23 to 42 percent of patients with bladder cancer and are incorrectly positive in 11 to 28 percent of patients without bladder cancer, which could result in delayed diagnosis or unnecessary cystoscopies and other diagnostic procedures, but no study directly measured effects of inaccurate diagnosis on clinical outcomes (SOE: insufficient).

Most trials found that fluorescent cystoscopy was associated with decreased risk of subsequent bladder recurrence versus white light cystoscopy, but there was no difference in risk of progression or mortality, although data for these outcomes were relatively sparse (SOE: low). In addition, evidence on effects on risk of recurrence was inconsistent, and the only trial[25] designed to minimize performance bias (by blinding the cystoscopist to instillation of photosensitizer vs. placebo) found no difference in risk of bladder cancer recurrence.

Intravesical therapy was effective for reducing risk of bladder cancer recurrence versus no intravesical therapy. Compared with no intravesical therapy, BCG was associated with decreased risk of bladder cancer recurrence (RR, 0.63; 95% CI, 0.50 to 0.79) as well as progression (RR, 0.50; 95% CI, 0.32 to 0.77) (SOE: moderate). MMC, doxorubicin, and epirubicin were also associated with decreased risk of bladder cancer recurrence versus no intravesical therapy (RR, 0.66 to 0.80), but effects on bladder cancer progression were not statistically significant (MMC and epirubicin) or showed no effect (doxorubicin). Although trials varied with respect to doses, instillation regimens, and patient populations evaluated, findings were generally robust in sensitivity and subgroup analyses. No intravesical agent, including BCG, was associated with decreased risk of all-cause or bladder cancer–specific mortality versus no intravesical therapy. Evidence on gemcitabine, interferon alpha, and thiotepa was sparse, and we found no randomized trials of valrubicin, paclitaxel, or apaziquone.

Head-to-head trials of intravesical therapy using different drugs showed few clear differences. For BCG versus MMC, the most well-studied comparison, there was no difference on any outcome, including bladder cancer recurrence, progression, or mortality (SOE: moderate). However, BCG was associated with decreased risk of bladder cancer recurrence in the subgroup of trials that evaluated maintenance regimens (SOE: low). Other head-to-head comparisons were evaluated in fewer trials, and in general showed few differences. A possible exception was for BCG versus epirubicin, for which there was some evidence that BCG might be associated with decreased risk of bladder cancer recurrence and progression versus epirubicin (SOE: low). Although doxorubicin was associated with increased risk of bladder cancer recurrence versus epirubicin (RR, 1.56; 95% CI, 1.08 to 2.22), this finding was based on only three trials (SOE: low).[26-28] Evidence to determine the effects of tumor characteristics on estimates of effectiveness of intravesical therapies was limited but indicated no differences in risk estimates based on factors such as tumor stage, grade, multiplicity, recurrence status, and size (SOE: low). However, even if relative estimates of effectiveness are similar, absolute effects will vary depending on the underlying incidence of recurrence, progression, mortality, or other outcomes. Therefore, patients with higher stage, higher grade, multiple, recurrent, or larger tumors would be expected to experience greater absolute benefits. Evidence to determine the effects of patient characteristics, such as age, sex, race/ethnicity, performance status, or comorbidities, on estimates of effectiveness of intravesical therapies was not available.

Results from trials that compared effects of intravesical therapy using different doses or instillation regimens for the same agent were difficult to interpret because of variability in the patient populations, doses, instillation regimens, and other factors. For BCG, there were no clear

differences between standard and lower doses in risk of bladder cancer recurrence, progression, or mortality, including in patients with higher risk NMIBC, but there was some inconsistency between trials (SOE: low). Limited evidence suggested that BCG maintenance regimens (>6 weeks) are more effective than induction regimens (≤6 weeks) at reducing risk of bladder cancer recurrence in patients with higher risk tumors (SOE: low). Trials on the effects of dose and duration of other intravesical agents on outcomes reported inconsistent results and were clinically heterogeneous, making it difficult to draw strong conclusions (SOE: insufficient to low). However, there is no evidence that prolonging therapy for more than 1 year is more effective than shorter regimens.

Evidence on harms associated with intravesical therapies was more limited than evidence on benefits. Trials of BCG versus no intravesical therapy found that local and systemic adverse events were relatively common (chemical cystitis or irritative symptoms in 27% to 84% of patients, macroscopic hematuria in 21% to 72%, and fever in 27% to 44%) (SOE: low). BCG was also associated with an increased risk of local adverse events and fever versus MMC (SOE: low to moderate). Standard-dose BCG was associated with increased risk of local and systemic adverse events versus lower dose BCG. Few trials reported harms of intravesical agents other than BCG versus no intravesical therapy or versus another intravesical agent.

The only randomized trial of radiation therapy found no effects on recurrence, progression, or survival in patients with T1 Grade (G) 3 cancers when compared with no radiotherapy (for unifocal cancers and no CIS) or against intravesical therapy (for multifocal disease or CIS) (SOE: low).[29]

Findings in Relationship to What Is Already Known

Our findings on diagnostic accuracy were generally consistent with prior systematic reviews that found urinary biomarkers insufficiently accurate to replace cystoscopy.[30-32] Estimates for sensitivity and specificity were generally similar in our review and prior reviews, even though we excluded case-control studies and included more recently published studies. In addition, prior reviews did not evaluate potential differences in diagnostic accuracy for testing performed for evaluation of signs and symptoms of bladder cancer versus for surveillance.

Prior systematic reviews[33,34] found fluorescent cystoscopy to be associated with decreased risk of recurrent bladder cancer versus white light cystoscopy, but they were published prior to a recent trial that was the only one to blind the cystoscopist to instillation of the photosensitizer and found no effect.[25] Like our report, prior reviews found no effect of fluorescent cystoscopy on risk of progression or mortality. Although prior reviews also found that fluorescent cystoscopy detected more bladder cancers on initial cystoscopy, this was not an assessed outcome for our review.

Our findings regarding the comparative effectiveness and harms of intravesical therapies are generally consistent with prior reviews that found intravesical therapy to be associated with decreased risk of bladder cancer recurrence versus no intravesical therapy[35,36] and found BCG to be associated with decreased risk of bladder cancer progression. Prior systematic reviews that focused on immediate single-instillation therapy also found intravesical therapy to be more effective than no intravesical therapy in reducing risk of bladder cancer recurrence, a conclusion consistent with our finding of no clear difference in risk estimates based on the type of instillation regimen.[37-39] Like our review, a prior systematic review found that maintenance therapy with BCG was associated with decreased risk of bladder cancer versus MMC, despite some differences in the trials that were included, definitions of maintenance therapy, and use of

individual patient data in the prior review.[40] Our findings are also consistent with prior systematic reviews that found BCG to be associated with decreased risk of bladder cancer versus epirubicin,[41] that the evidence on intravesical gemcitabine is limited,[42] and that the optimal dose and duration of intravesical therapy cannot be determined based on the available evidence.[43]

Applicability

Some issues could impact the applicability of our findings. Some studies of diagnostic accuracy did not report results separately for patients undergoing evaluation of signs and symptoms of bladder cancer and those undergoing surveillance, although there is some evidence that diagnostic accuracy may vary based on the indication for testing. Studies of intravesical therapy varied in the doses used; the timing, number, frequency, and duration of instillations; and other factors (e.g., the BCG strain), making it difficult to reach conclusions that are widely generalizable. In addition, trials varied with regard to tumor characteristics in the patient populations evaluated. Another factor that potentially impacts applicability is that most studies focused on effects of intravesical therapy on recurrence of bladder cancer. Fewer trials evaluated more potentially serious distal outcomes, such as progression or mortality. A number of studies were conducted in Japan, where management of bladder cancer may differ from that in the United States. Treatment studies tended to exclude patients with significant comorbidities or poor general performance status, which could limit applicability to these populations. Very little information was available to determine whether diagnostic accuracy or treatment effects vary according to patient factors, such as age, sex, race/ethnicity, performance status, or comorbidities.

Implications for Clinical and Policy Decisionmaking

Our review has implications for clinical and policy decisionmaking. As there are no studies evaluating effects of using urinary biomarkers for diagnosis or surveillance of bladder cancer on clinical outcomes, decisions regarding their use must necessarily be made on the basis of diagnostic test performance. Table B shows estimated probabilities for bladder cancer following use of urinary biomarkers, based on likelihood ratios calculated from pooled sensitivities and specificities. In populations with a pretest probability of 5 percent, the post-test probability increased to 16 to 24 percent following a positive result and decreased to 1.8 to 2.5 percent following a negative result. In settings with a pretest probability of 20 percent, the post-test probability increased to 37 to 60 percent following positive results and decreased to 8.0 to 11 percent following a negative result. Whether urinary biomarkers are sufficiently accurate to rule out bladder cancer and thereby reduce the need for cystoscopy depends on the ability of clinicians to estimate the pretest probability of disease and the acceptable threshold for a missed or delayed diagnosis. Use of urinary biomarkers in combination with urinary cytology increases the sensitivity for bladder cancer, but still misses about 10 percent of cases. Regarding fluorescent cystoscopy, studies have not shown an effect on progression or mortality, and trials that found reduced risk of recurrence may have been affected by performance bias. These findings might inform decisions regarding widespread adoption of fluorescent cystoscopy.

Our findings also have implications for use of intravesical therapy. Although intravesical therapy was associated with decreased risk of bladder cancer recurrence, there were no clear effects on bladder cancer–specific or all-cause mortality, and intravesical therapies were associated with local and systemic adverse events. Our findings are consistent with guidelines that recommend BCG as first-line therapy.[10,44] As no intravesical agent was more effective than

BCG at reducing risk of bladder cancer recurrence, BCG is the only intravesical agent associated with decreased risk of bladder cancer progression versus no intravesical therapy, and some evidence indicates that BCG is associated with decreased risk of bladder cancer recurrence versus other intravesical agents. However, BCG is also associated with a high risk of adverse events. Some evidence indicates that using lower than standard doses of BCG maintains effectiveness while reducing harms. Other evidence suggests that longer courses of therapy may be necessary for optimal effects, particularly in higher risk patients. Therefore, decisions to use intravesical therapy and regarding the intravesical agent, doses, and regimen selected should take into account the tradeoffs between potential benefits and harms. Benefits are likely to be higher in patients at higher risk for disease progression and harms.

Table B. Post-test probability of bladder cancer using different biomarkers

Urinary Biomarker	Pretest Probability of Bladder Cancer	Positive Likelihood Ratio (95% CI)	Post-Test Probability of HCC Following a Positive Test	Negative Likelihood Ratio (95% CI)	Post-Test Probability of HCC Following a Negative Test
Quantitative NMP22	5%	3.05 (2.28 to 4.10)	14%	0.40 (0.32 to 0.50)	2.1%
	20%	3.05 (2.28 to 4.10)	43%	0.40 (0.32 to 0.50)	9.1%
Qualitative NMP22	5%	4.89 (3.23 to 7.40)	20%	0.48 (0.33 to 0.71)	2.5%
	20%	4.89 (3.23 to 7.40)	55%	0.48 (0.33 to 0.71)	11%
Qualitative BTA	5%	2.80 (2.31 to 3.39)	13%	0.47 (0.30 to 0.55)	2.4%
	20%	2.80 (2.31 to 3.39)	41%	0.47 (0.30 to 0.55)	11%
Quantitative BTA	5%	2.52 (1.86 to 3.41)	12%	0.47 (0.37 to 0.61)	2.4%
	20%	2.52 (1.86 to 3.41)	39%	0.47 (0.37 to 0.61)	11%
FISH	5%	5.02 (2.93 to 8.60)	21%	0.42 (0.30 to 0.59)	2.2%
	20%	5.02 (2.93 to 8.60)	56%	0.42 (0.30 to 0.59)	9.5%
ImmunoCyt™	5%	3.49 (2.82 to 4.32)	16%	0.29 (0.20 to 0.41)	1.5%
	20%	3.49 (2.82 to 4.32)	47%	0.29 (0.20 to 0.41)	6.8%

BTA = bladder tumor antigen; CI = confidence interval; FISH = fluorescence in situ hybridization; HCC = hepatocellular carcinoma; NMP22 = nuclear matrix protein 22

Limitations of the Review Process

Substantial statistical heterogeneity was present in most pooled analyses of diagnostic accuracy; this situation is common in meta-analyses of diagnostic accuracy.[45-47] As noted in the "Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy," "heterogeneity is to be expected in meta-analyses of diagnostic test accuracy."[47] To address the anticipated heterogeneity, we used random-effects models to pool studies and stratified studies according to the reason that imaging was performed and the unit of analysis used. We also performed additional stratified and sensitivity analyses based on the reference standard used, study characteristics (such as country in which the study was conducted, factors related to risk of bias), patient characteristics, and technical factors related to the imaging tests under investigation.

Results were generally robust in sensitivity analyses, despite the heterogeneity. We also focused on evaluations of comparative test performance based on within-study comparisons of imaging modalities, which tended to be associated with less heterogeneity than pooled across-study estimates. A limitation of our analysis of within-group comparisons is that we had to treat the two compared groups as independent because we had aggregated data only. Individual patient-level data would be required to take into account the paired nature of the comparisons. Such correlations are generally positive and would be expected to result in more narrow CIs. Although it is possible that this could have caused us not to detect statistically significant differences, the point estimates indicated very little difference between tests.

We did not construct summary receiver operating characteristic curves. Almost all studies of a specific urinary biomarker used the same definition for a positive test, including tests based on a quantitative threshold. Estimates of sensitivity and specificity at different thresholds are needed to construct informative receiver operating characteristic curves.[48]

Statistical heterogeneity was also present in some analyses of intravesical therapies and fluorescent cystoscopy. To address this, we used the Dersimonian-Laird random-effects model to pool studies. The Dersimonian-Laird random-effects model may result in CIs that are too narrow when heterogeneity is present, particularly when the number of studies is small.[24] Therefore, we repeated analyses using the profile likelihood method, which resulted in similar findings. Regardless of the method used, meta-analyses based on small numbers of trials can underestimate statistical heterogeneity and must be interpreted with caution.[24] We also stratified trials according to factors such as risk-of-bias rating, dose, number of instillations, duration of followup, enrollment of patients with high-risk NMIBC, and other factors. Although statistical heterogeneity remained present in some analyses, with some unexplained outlier trials, results were generally robust.

We excluded non–English-language articles and did not search for studies published only as abstracts. Because of small numbers of trials for meta-analyses involving intravesical therapies, we did not formally assess for publication bias using statistical or graphical methods for assessing sample size effects, as research indicates that such methods can be seriously misleading in such situations.[49,50] For fluorescent cystoscopy, we found one relatively large trial that showed no effect on risk of recurrence versus white light cystoscopy, suggesting that publication bias could have impacted results.[51]

Limitations of the Evidence Base

Several limitations of the evidence base limited our ability to reach strong conclusions with regard to several aspects of diagnosis and treatment of NMIBC. Other than quantitative NMP22 and qualitative BTA, urinary biomarkers were assessed in small numbers of studies (6 or fewer), resulting in less precise estimates. In addition, most of the evidence on comparative accuracy was indirect, as few studies directly compared the accuracy of two or more biomarkers against cystoscopy and histopathology.

For fluorescent cystoscopy, a limitation of the evidence base is that few trials reported effects on progression or mortality, and instead mostly focused on evaluating effects on recurrence. In addition, only one trial of fluorescent cystoscopy blinded the cystoscopist to whether the photosensitizer had been instilled, which may have an impact on assessments of recurrence because of performance bias related to knowledge of the type of initial cystoscopy performed.

A limitation of the evidence for all Key Questions addressed in our review is that very few trials were assessed as low risk of bias. Methodological shortcomings included failure to

adequately describe randomization and allocation concealment methods, and unblended design. Findings would be stronger if more high-quality trials were available.

Other limitations include the lack of evidence on how use of urinary biomarkers impacts clinical outcomes (including harms), the evidence from only a single randomized trial on effects of radiation therapy for NMIBC, no trials on effects of using a risk-adapted approach, and no studies on how using different surveillance intervals impacts outcomes. Few studies evaluated effects of patient characteristics, such as age, sex, race/ethnicity, performance status, or comorbidities, on diagnostic test performance or effectiveness of intravesical therapy.

Research Gaps

We identified a number of important research gaps. Given the increased sensitivity of urinary biomarkers with cytology, studies on how this combination impacts use of cystoscopy and subsequent clinical outcomes might be helpful for determining its role in diagnosis or surveillance. Randomized trials that adequately safeguard against performance bias associated with use of photosensitizers for fluorescent cystoscopy are needed to determine effects on recurrence, progression, and mortality. Additional head-to-head trials of intravesical therapies that use more standardized instillation regimens and doses, report outcomes in subgroups stratified by patient and tumor characteristics, and include long-term outcomes related to progression and mortality would help clarify optimal treatment strategies. Research is also needed to determine the effectiveness of risk-adapted approaches to guide selection of therapy, including use of nontraditional prognostic markers, effects of different surveillance intervals and protocols, and newer techniques such as electromotive administration of intravesical therapy.

Conclusions

Urinary biomarkers are falsely negative in a substantial proportion of patients with bladder cancer, and additional research is needed to clarify advantages of fluorescent cystoscopy over white light cystoscopy. Intravesical therapy reduces risk of bladder cancer recurrence versus no intravesical therapy. BCG is the only intravesical therapy shown to be associated with decreased risk of bladder cancer progression, but it is associated with a high rate of adverse events.

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Introduction

Background

Nature and Burden of Non–Muscle-Invasive Bladder Cancer

Bladder cancer is the fourth most commonly diagnosed cancer in men and tenth most commonly diagnosed cancer in women in the United States.[1] The American Cancer Society estimates there will be 74,690 new cases of bladder cancer in the United States in 2014 (about 56,390 men and 18,300 women), and about 15,580 deaths due to bladder cancer (about 11,170 men and 4,410 women).[1] The lifetime probability of developing bladder cancer in the United States is approximately 3.8 percent in men and 1.2 percent in women; the incidence of bladder cancer is increasing in women. Bladder cancer occurs primarily in men older than 60 and roughly twice as frequently in white compared to black men,[2] though the number of deaths due to bladder cancer is similar, presumably due to delayed diagnosis in black men.

Bladder cancer is an important health problem, with no improvement in associated mortality since 1975.[3] Economic analyses have shown bladder cancer to be the costliest cancer to treat in the United States on a per capita basis, taking into account diagnostic testing, management, and long-term followup.[4] The most common risk factor for bladder cancer is cigarette smoking, though other risk factors include occupational exposures and family history. The most common symptom of bladder cancer is painless hematuria (blood in the urine).

Bladder cancer is staged based on the extent of penetration or invasion into the bladder wall and adjacent structures (Table 1).[5] Bladder cancers that have not invaded the bladder smooth muscle layer (stage classifications Tis [carcinoma in situ], Ta [noninvasive papillary carcinoma], and T1 [cancer that invades the subepithelial connective tissue]) are broadly grouped as non–muscle-invasive bladder cancers (NMIBC). Stage T2 cancers are muscle-invasive, and higher stage cancers invade beyond the muscle layer into surrounding fat (stage classification T3 bladder cancer) or beyond the fat into nearby organs or structures (stage classification T4 bladder cancer). Approximately 75 percent of newly diagnosed bladder cancers are NMIBC.[6] Individuals with NMIBC generally have a good prognosis, with 5-year survival rates higher than 88 percent.[7] However, as many as 70 percent of NMIBC tumors will recur after initial treatment, with a 10-20 percent risk of progression to invasive bladder cancer.[6] The likelihood of progression from NMIBC to muscle invasive cancer depends on the tumor grade (based on the degree of cell differentiation), the tumor stage, the size of the cancer, and whether the cancer is recurrent or multifocal.[8] Prognosis is poorer for patients with muscle-invasive bladder cancers (5-year survival rates from 63% to 15%).[7]

Table 1. Bladder cancer tumor staging

	Cancer Stage	Description
T stages (tumor)	CIS (also called Tis)	Flat, high grade, cancer cells are only present in the innermost layer of the bladder lining.
	Ta	The cancer is just in the innermost layer of the bladder lining
	T1	The cancer has started to grow into the connective tissue beneath the bladder lining
	T2	The cancer has grown through the connective tissue into the muscle
	T2a	The cancer has grown into the superficial muscle
	T2b	The cancer has grown into the deeper muscle
	T3	The cancer has grown through the muscle into the fat layer
	T3a	The cancer in the fat layer can only be seen under a microscope
	T3b	The cancer in the fat layer can be seen on tests, or felt by a doctor during an examination under anesthetic
	T4	The cancer has spread outside the bladder
	T4a	The cancer has spread to the prostate, womb (uterus), or vagina
	T4b	The cancer has spread to the wall of the pelvis or abdomen
N stages (lymph nodes)	N0	No cancer in any lymph nodes
	N1	There is cancer in one lymph node in the pelvis
	N2	There is cancer in more than one lymph node in the pelvis
	N3	There is cancer in one or more lymph nodes in the groin
M stages (metastasized)	M0	There are no signs of distant spread
	M1	The cancer has spread to distant parts of the body
1973 WHO grading urothelial papilloma	Grade 1 (G1)	Well differentiated
	Grade 2 (G2)	Moderately differentiated
	Grade 3 (G3)	Poorly differentiated
2004 WHO grading		Flat lesions
		Hyperplasia (flat lesion without atypia or papillary)
		Reactive atypia (flat lesion with atypia)
		Atypia of unknown significance
		Urothelial dysplasia
		Urothelial carcinoma *in situ*
		Papillary lesions
		Urothelial papilloma (which is a completely benign lesion)
		Papillary urothelial neoplasm of low malignant potential
		Low-grade papillary urothelial carcinoma
		High-grade papillary urothelial carcinoma

CIS = carcinoma in situ; WHO = World Health Organization
Sources: Cancer Research UK, 2013.[9] American Cancer Society, 2014.[10] EUA Guidelines (Babjuk 2013)[8]

Diagnosis and Surveillance of Bladder Cancer

A number of tests are available for screening, diagnosis, and staging of bladder cancer. Standard methods for identification of bladder cancer include urine dipstick and microscopic urinalysis (to detect hematuria) and urine cytology (to detect abnormal or cancerous cells in the urine), followed by imaging tests and cystoscopy.[11] Urine-based biomarkers have been developed as potential diagnostic alternatives or supplements to cytology, imaging, and cystoscopy.[12] A number of biomarkers have been evaluated in conjunction with cytology for diagnosis of bladder cancer, potentially reducing the need for cystoscopy. In addition to initial diagnosis and staging, diagnostic surveillance with cystoscopy and cytology is also performed following treatment, to identify patients with recurrence or progression of cancer. Urine-based

biomarker tests may also be used to help identify recurrence and need for cystoscopy during surveillance.

There are five diagnostic biomarker tests approved by the US Food and Drug Administration (FDA) for diagnosis or surveillance of bladder cancer: quantitative NMP22 (Alere NMP22®), qualitative NMP22 (BladderChek®), qualitative BTA (BTAstat®), quantitative BTA (BTA TRAK®), fluorescence in situ hybridization (FISH, UroVysion®), and fluorescence immunohistochemistry (ImmunoCyt™, which uses monoclonal antibodies to test for carcinoembryonic antigens and mucin glycoproteins). The qualitative NMP22 and BTA tests can be used as point-of-care tests and the others are performed in a laboratory. The CxBladder™ test, which tests for five specific mRNA biomarkers, is a "Laboratory Developed Test" that does not require FDA approval. A number of other biomarkers, including those based on detection of fibroblast growth factor receptor 3 (FGFR3); cytokeratin fragments (e.g., CYFRA 21-1, TPA, TPS); survivin; telomerase; vascular endothelial growth factor (VEGF); aurora kinase, or metalloproteinases (MMP-2 and MMP-9) have also been developed, but are not FDA-approved. The large number of available tests and testing strategies and potential trade-offs in diagnostic accuracy, risks, and patient preferences pose significant challenges in determining optimal testing and monitoring strategies. Tests with high false positive rates could lead to unnecessary invasive procedures for further evaluation and tests with high false negative rates could lead to missed diagnoses.

Interventions and Outcomes For Non–Muscle-Invasive Bladder Cancer

Once bladder cancer has been diagnosed, a number of factors affect prognosis and treatment options. These include the stage of the cancer, tumor grade, whether the tumor is an initial tumor or a recurrence, the number and size of tumors, the patient's age and general health, and other factors. The main treatment for NMIBC is local resection with transurethral resection of the bladder tumor (TURBT), often with adjuvant intravesical therapy to destroy residual tumor cells using chemotherapeutic agents (e.g., mitomycin C [MMC], apaziquone, paclitaxel, gemcitabine, thiotepa, valrubicin, doxorubicin, epirubicin), bacillus Calmette-Guérin (BCG), or interferon immunotherapy.[13] All of these treatments are FDA-approved and available in the United States. Electromotive drug administration is a method for enhancing the effectiveness of intravesical chemotherapy that is increasingly used, especially in Europe. Clinical trials of electromotive drug administration of intravesical therapy are ongoing in the United States, but the method is not widely available or used in the United States, and is not FDA-approved for this purpose.

Post-TURBT adjuvant intravesical therapy is associated with potential local (e.g., dysuria frequency, and hematuria) and systemic side effects. However, not using adjuvant intravesical therapy may increase the risk of bladder cancer recurrence or progression, particularly in patients with higher risk lesions. The European Association of Urology advocates an assessed risk-adapted approach to treatment decisionmaking, based on prognostic factors such as tumor grade, tumor stage, and the number and size of tumors.[14] This approach, which stratifies patients into three risk groups based on the presence of risk factors, helps identify patients in the intermediate and high risk groups who are more likely to benefit from intravesical therapy.

Rationale for Evidence Review

The purpose of this report is to review the currently available evidence on the comparative effectiveness of diagnostic tests and treatments for NMIBC. Although updated guidelines for the treatment and followup of NMIBC from the European Association of Urology were published in 2013,[8] the literature continues to evolve, with much of the new evidence focusing on diagnostic techniques such as fluorescence cystoscopy or urine-based biomarkers, and treatments with intravesical therapy alternatives to MMC and BCG. A systematic evidence review that includes recently published research may provide a better understanding of the comparative effectiveness of currently available approaches to diagnosis, treatment, and post-treatment surveillance for NMIBC. The systematic review may be used to update existing clinical recommendations that are several years old or may be out-of-date due to the development of new technologies and therapies.

Scope of Review and Key Questions

This topic was nominated for review by the American Urological Association and focuses on diagnosis of bladder cancer and treatment of NMIBC. The Key Questions and analytic framework used to guide this report are shown below. The analytic framework (Figure 1) shows the scope of this review, including the target population, interventions, comparisons, and health outcomes we examined.

The list of Key Questions follows.

Key Question 1. What is the diagnostic accuracy of various urinary biomarkers compared with other urinary biomarkers or standard diagnostic methods (cystoscopy, cytology, and imaging) in (1) people with signs or symptoms warranting evaluation for possible bladder cancer or (2) people undergoing surveillance for previously treated bladder cancer?

a. Does the diagnostic accuracy differ according to patient characteristics (e.g., age, sex, race/ethnicity) or according to the nature of the presenting signs or symptoms?

Key Question 2. For patients with non–muscle-invasive bladder cancer, does the use of a formal risk-adapted assessment approach to treatment decisions (e.g., based on Guidelines of the European Association of Urology or on urinary biomarker tests) decrease mortality or improve other outcomes (e.g., recurrence, progression, need for cystectomy, quality of life) compared with treatment not guided by a formal assessed risk-adapted approach?

Key Question 3. For patients with non–muscle-invasive bladder cancer treated with transurethral resection of bladder tumor, what is the effectiveness of various intravesical chemotherapeutic or immunotherapeutic agents for decreasing mortality or improving other outcomes (e.g., recurrence, progression, need for cystectomy, quality of life) compared with TURBT alone?

a. What is the comparative effectiveness of various chemotherapeutic or immunotherapeutic agents, as monotherapy or in combination?
b. Does the comparative effectiveness differ according to tumor characteristics, such as stage, grade, size, multiplicity, whether the tumor is primary or recurrent, or molecular/genetic markers?
c. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, race/ethnicity, performance status, or medical comorbidities?
d. Does the comparative effectiveness of various chemotherapeutic or immunotherapeutic agents differ according to dosing frequency, duration of treatment, and/or the timing of administration relative to TURBT?

Key Question 4. For patients with high-risk non–muscle-invasive bladder cancer treated with TURBT, what is the effectiveness of external beam radiation therapy (either alone or with systemic chemotherapy/immunotherapy) for decreasing mortality or improving other outcomes compared with intravesical chemotherapy/immunotherapy alone or cystectomy?

Key Question 5. In surveillance of patients treated for non–muscle-invasive bladder cancer, what is the effectiveness of various urinary biomarkers to decrease mortality or improve other outcomes compared with other urinary biomarkers or standard diagnostic methods (cystoscopy, cytology, and imaging)?

a. Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?
b. Does the comparative effectiveness differ according to the treatment used (i.e., specific chemotherapeutic or immunotherapeutic agents and/or TURBT)?
c. Does the comparative effectiveness differ according to the length of surveillance intervals?

d. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, or race/ethnicity?

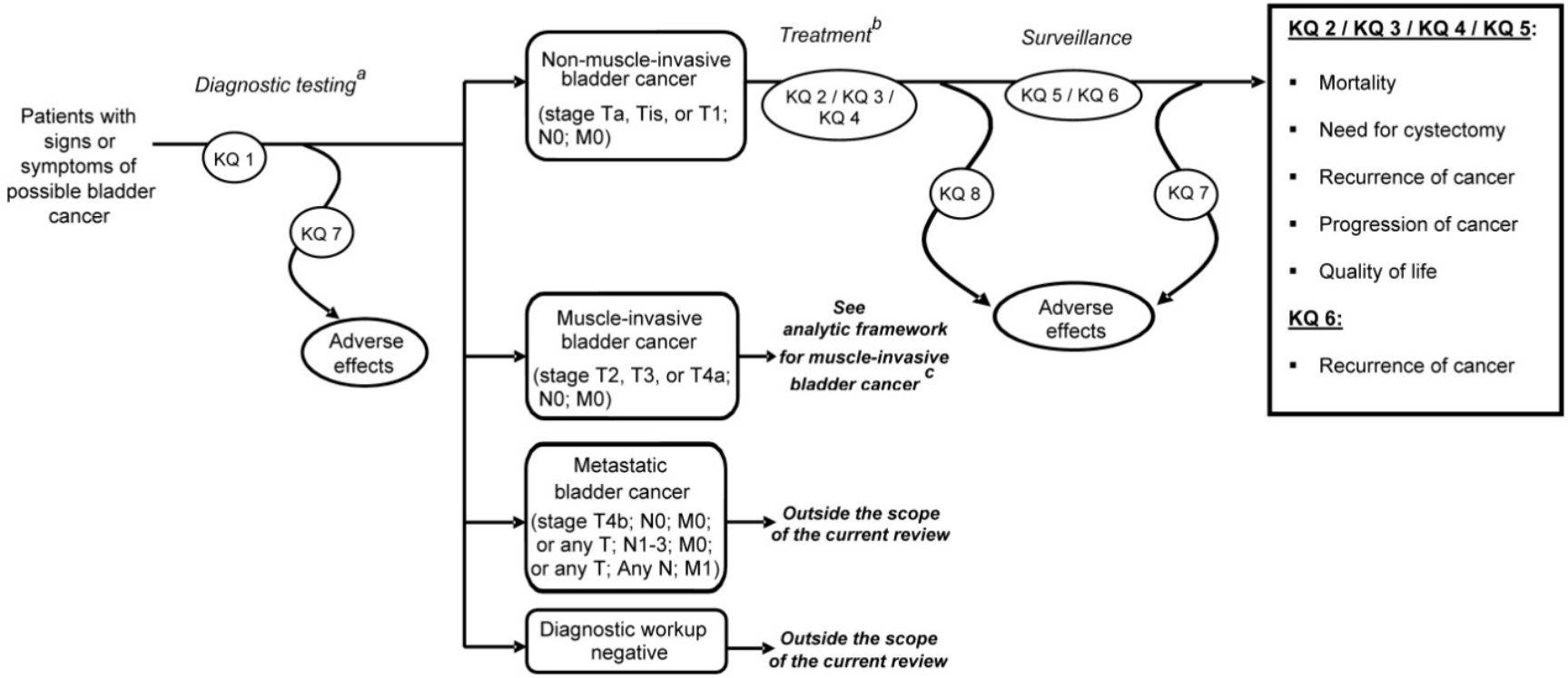
Key Question 6. For initial diagnosis or surveillance of patients treated for non–muscle-invasive bladder cancer, what is the effectiveness of blue light or other methods of augmented cystoscopy compared with standard cystoscopy for recurrence rates, progression of bladder cancer, mortality, or other clinical outcomes?

Key Question 7. What are the comparative adverse effects of various tests for diagnosis and post-treatment surveillance of bladder cancer, including urinary biomarkers, cytology, and cystoscopy?

Key Question 8. What are the comparative adverse effects of various treatments for non–muscle-invasive bladder cancer, including intravesical chemotherapeutic or immunotherapeutic agents and TURBT?

a. How do adverse effects of treatment vary by patient characteristics, such as age, sex, race/ethnicity, performance status, or medical comorbidities such as chronic kidney disease?

Figure 1. Analytic framework



KQ = Key Question. Cancer stages shown are the TNM (tumor, node, metastasis) classification.

[a]Urinary biomarkers of interest are restricted to tests that are approved for diagnosis of bladder cancer by the U.S. Food and Drug Administration (BTAstat® [bladder tumor antigen], Alere NMP22®, BladderChek® [nuclear matrix protein 22], UroVysion® [fluorescence in situ hybridization], and ImmunoCyt™ [immunocytology]) or available in the United States and classified as a Laboratory Developed Test by the Food and Drug Administration (CxBladder™).

[b]Chemotherapeutic and immunotherapeutic agents of interest include mitomycin C, apaziquone, paclitaxel, gemcitabine, thiotepa, epirubicin, valrubicin, doxorubicin, bacillus Calmette-Guérin, and interferon.

[c] Muscle-Invasive Bladder Cancer Comparative Effectiveness Review: Chou R, Selph S, Buckley D, et al. Treatment of Nonmetastatic Muscle-Invasive Bladder Cancer. Comparative Effectiveness Review No. 152. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2012-00014-1.) AHRQ Publication No. 15-EHC015-EF. Rockville, MD: Agency for Healthcare Research and Quality; June 2015. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Methods

This comparative effectiveness review (CER) follows the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (hereafter AHRQ Methods Guide).[15] All methods were determined a priori.

Topic Development and Refinement

AHRQ initially received this topic as a nomination via the Effective Healthcare Web site (http://www.effectivehealthcare.ahrq.gov/index.cfm/submit-a-suggestion-for-research/). The Scientific Resource Center developed preliminary Key Questions based on input from the topic nominator. The Evidence-based Practice Center revised the Key Questions and developed eligibility criteria to identify the populations, interventions, comparators, outcomes, timing, and study designs (PICOTS) of interest. The Evidence-based Practice Center further refined the Key Questions and PICOTS based on input from interviews with eight Key Informants. Key Informants included experts in urology (including experts in urinary biomarkers and urologic oncology), medical oncology, and radiation oncology, as well as patient representatives and payers. Key Informants disclosed financial and other conflicts of interest prior to participation. The AHRQ Task Order Officer and the investigators reviewed the disclosures and determined that the Key Informants had no conflicts of interest that precluded participation. The Key Questions were posted for public comment from February 6, 2014 through February 26, 2014, and comments were received from four individuals.

After reviewing the public comments and obtaining additional input from a Technical Expert Panel (TEP) convened for this report, the research team revised the Key Questions. The TEP consisted of eight experts, specializing in urology (including urinary biomarkers and urologic oncology), radiation oncology, and medical oncology. The procedure for reviewing potential conflicts of interests of TEP members was similar to the procedure used for the Key Informants. The research team developed the final protocol with input from the TEP and AHRQ and was posted on the AHRQ Web site on July 21, 2014 (www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1940). The protocol was also registered in the PROSPERO international database of prospectively registered systematic reviews.

Searching for the Evidence

A research librarian experienced in conducting literature searches for CERs searched in Ovid MEDLINE (January 1990–October 2014), Cochrane Central Register of Controlled Trials (through September 2014), Cochrane Database of Systematic Reviews (through September 2014), Health Technology Assessment (through 3rd Quarter, 2014), National Health Sciences Economic Evaluation Database (through 3rd Quarter, 2014), and Database of Abstracts of Reviews of Effects (through 3rd Quarter, 2014) to capture both published and grey literature. See Appendix A for the full search strategies. We searched for unpublished studies in clinical trial registries (ClinicalTrials.gov, Current Controlled Trials, ClinicalStudyResults.org and the WHO International Clinical Trials Registry Platform) and regulatory documents (Drugs@FDA.gov and FDA Medical Devices Registration and Listing). Reference lists of relevant studies and previous systematic reviews were hand-searched for additional studies, including studies published prior to 1990. Scientific information packets were solicited from drug and device manufacturers and

via a notice published in the Federal Register that invited interested parties to submit relevant published and unpublished studies using the publicly accessibly AHRQ Effective Health Care online scientific information packet portal.

Library searches were updated while the draft report was posted for public comment. Literature identified during the update search was assessed following the same process of dual review as for studies identified during the initial searches. New literature identified for inclusion was incorporated before the final submission of the report.

Study Selection

We developed criteria for inclusion and exclusion of studies based on the Key Questions and PICOTS approach, in accordance with the AHRQ Methods Guide.[15] Inclusion and exclusion criteria are summarized below and available in more detail in Appendix B. Abstracts were reviewed by two investigators, and all citations deemed appropriate for inclusion by at least one of the reviewers was retrieved. Two investigators independently reviewed all full-text articles for inclusion. Discrepancies were resolved by discussion and consensus. A list of the included studies can be found in Appendix C; excluded studies and primary reason for exclusion can be found in Appendix D.

Population and Condition of Interest

For Key Questions related to diagnosis, we included studies of adults with signs or symptoms of possible bladder cancer (e.g., macroscopic or microscopic hematuria, irritative voiding symptoms) or undergoing surveillance following treatment for bladder cancer. For Key Questions related to treatment of non–muscle-invasive bladder cancer (NMIBC), we included studies of adults with NMIBC (defined as TNM stages Ta, Tis, or T1; N0; M0) undergoing treatment. Key Question 4 focused on adults with high-risk NMIBC.

Interventions, Comparisons, and Study Designs of Interest

We included studies of US Food and Drug Administration (FDA)-approved urinary biomarkers for the diagnosis of bladder cancer (quantitative or qualitative NMP22, qualitative or quantitative BTA, FISH, and ImmunoCyt™) or available in the United States and classified as a Laboratory Developed Test by the FDA (CxBladder™). We excluded studies of diagnostic accuracy of other biomarkers or studies of included biomarkers that did not evaluate diagnostic accuracy of biomarkers against standard diagnostic methods (cystoscopy and histopathology). For cystoscopic methods, we included studies of fluorescent cystoscopy following intravesical instillation of a photosensitizing agent or other methods of augmented cystoscopy (e.g., narrow band imaging) for the initial diagnosis or surveillance of bladder cancer compared with standard (white light) cystoscopy.

For treatments, we include studies of intravesical therapies (mitomycin C [MMC], apaziquone, paclitaxel, gemcitabine, thiotepa, valrubicin, doxorubicin, epirubicin, bacillus Calmette-Guérin [BCG] and interferon) and external beam radiation therapy with or without systemic chemotherapy or immunotherapy versus transurethral resection of the bladder tumor (TURBT), other intravesical therapies, or cystectomy. We also included studies that compared different dosing regimens, different surveillance intervals, and risk adapted versus other approaches. We also included studies on the effects of patient and tumor characteristics on estimates of effectiveness.

For all Key Questions, we included randomized trials and cohort studies with concurrent controls, when randomized trials were not available. For diagnostic accuracy, we also included cross-sectional studies. We excluded uncontrolled observational studies, case-control studies, case series, and case reports, as these studies are less informative than studies with a control group. For studies on diagnostic accuracy of urinary biomarkers, case-control studies were defined as studies that selected patients known to have bladder cancer [cases] and patients known to not have bladder cancer [controls]).[16] We did not include systematic reviews, though we reviewed reference lists for relevant studies.

Outcomes of Interest

For diagnostic accuracy of urinary biomarkers, we evaluated sensitivity, specificity, predictive values, and likelihood ratios, using cystoscopy with biopsy as the reference standard. Clinical outcomes for trials of diagnostic methods and treatments were mortality, need for cystectomy, progression to muscle invasive bladder cancer, bladder cancer recurrence, and quality of life. We also evaluated adverse effects of diagnostic testing (e.g., false-positives, labeling, anxiety, and complications of cystoscopy) and adverse effects of treatment (e.g., cystitis, urinary urgency, urinary frequency, incontinence, hematuria, pain, and urosepsis, myelosuppression).

Timing and Setting of Interest

For all Key Questions, we included studies conducted in inpatient or outpatient settings, with any duration of followup.

Data Extraction and Data Management

For treatment studies, we extracted the following information into evidence tables: study design, setting, inclusion and exclusion criteria, dose and duration of treatment for experimental and control groups, duration of followup, number of subjects screened, eligible and enrolled, population characteristics (including age, race/ethnicity, sex, tumor stage and grade, and functional status), results, adverse events, withdrawals due to adverse events, and sources of funding. We calculated relative risks and associated 95% confidence intervals (CI) based on the information provided (sample sizes and incidence of outcomes in each intervention group). We noted discrepancies between calculated and reported results when present.

For diagnostic accuracy studies, we abstracted the following information: setting, screening test or tests, method of data collection, reference standard, inclusion criteria, population characteristics (including age, sex, race/ethnicity, smoking status, signs or symptoms, and prior bladder cancer stage or grade), proportion of individuals with bladder cancer, bladder cancer stage and grade, definition of a positive screening exam, proportion of individuals unexaminable by the screening test, proportion who did not undergo reference standard test, results, and sources of funding. We attempted to create two-by-two tables from information provided (sample size, prevalence, sensitivity, and specificity) and compared calculated measures of diagnostic accuracy based on the two-by-two tables with reported results. We noted discrepancies between calculated and reported results when present. When reported, we also recorded the area under the receiver operating characteristic curve.[17,18]

Data extraction for each study was completed by one investigator and independently reviewed for accuracy and completeness by a second investigator. See Appendix E for evidence tables with extracted data.

Assessment of the Risk of Bias of Individual Studies

We assessed the risk of bias for randomized trials and observational studies using criteria adapted from those developed by the U.S. Preventive Services Task Force.[19] Studies of diagnostic accuracy were rated using criteria adapted from QUADAS-2.[16] These criteria were applied in conjunction with the approaches recommended in the AHRQ Methods Guide for medical interventions and the AHRQ Methods Guide for Medical Test Reviews.[15,20]

Two investigators independently assessed the risk of bias of each study. Discrepancies were resolved through discussion and consensus.

Each study was rated as "low," "medium," or "high" risk of bias.[15] We rated the quality of each randomized trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; whether attrition was adequately reported and acceptable; similarity in use of cointerventions; compliance to allocated treatments; the use of intent-to-treat analysis; and avoidance of selective outcomes reporting.[19]

We rated the quality of each cohort study based on whether it enrolled a consecutive or random sample of patients meeting inclusion criteria; whether it evaluated comparable groups; whether rates of loss to followup were reported and acceptable; whether it used accurate methods for ascertaining exposures, potential confounders, and outcomes; and whether it performed adjustment for important potential confounders.[19]

We rated the quality of each study on diagnostic accuracy based on whether it evaluated a consecutive or random sample of patients meeting predefined criteria, whether the index test was performed in all patients, whether the index test results were interpreted without knowledge of the reference standard, whether a prespecified threshold was used to define a positive index test, whether the reference standard was interpreted without knowledge of the reference standard, whether there was an appropriate interval between the index test and the reference standard, whether the same reference standard was applied in all patients, and whether all patients were included in the analysis.[16,20]

Studies rated "low risk of bias" were considered to have no more than very minor methodological shortcomings and their results are likely to be valid. Studies rated "medium risk of bias" have some methodological shortcomings, but no flaw or combination of flaws judged likely to cause major bias. In some cases, the article did not report important information, making it difficult to assess its methods or potential limitations. The "medium risk of bias" category is broad and studies with this rating vary in their strengths and weaknesses; the results of some studies assessed to have medium risk of bias are likely to be valid, while others may be only possibly valid. Studies rated "high risk of bias" have significant flaws that may invalidate the results. They have a serious or "fatal" flaw or combination of flaws in design, analysis, or reporting; large amounts of missing information (including publication of only preliminary results in a subgroup of patients randomized); or serious discrepancies in reporting. An example of a fatally flawed study would be one with very high loss to followup (e.g., >50%), failure to perform intention-to-treat analysis, lack of blinding and failure to adequately describe randomization procedures. The results of these studies are at least as likely to reflect flaws in the study design as the differences between the compared interventions. We did not exclude studies

rated as having high risk of bias *a priori*, but they were considered the least reliable when synthesizing the evidence, particularly when discrepancies between studies were present.

For further details about the assessment of the risk of bias see Appendix F.

Assessing Applicability

We recorded factors important for understanding the applicability of studies, such as whether the publication adequately described the study sample, the country in which the study was conducted, the characteristics of the patient sample (e.g., age, sex, race/ethnicity, risk factors for bladder cancer, presenting symptoms, and medical comorbidities), tumor characteristics (e.g., stage and grade, primary or recurrent, unifocal or multifocal lesions), the characteristics of the diagnostic tests (e.g., specific test evaluated and cutoffs used) and interventions (e.g., treatment dose, duration and interval) used, and the magnitude of effects on clinical outcomes.[15] We also recorded the funding source and role of the sponsor.

Applicability depends on the particular question and the needs of the user of the review. There is no generally accepted universal rating system for applicability. In addition, applicability depends in part on context. Therefore, a rating of applicability (such as "high" or "low") was not assigned because applicability may differ based on the user of this report.

Data Synthesis

For studies on diagnostic accuracy of urinary biomarkers, we performed meta-analyses to help summarize data and obtain more precise estimates.[21] All quantitative analyses were conducted using SAS® 10.0 (SAS Institute Inc., Cary, NC). We used a bivariate logistic mixed effects model[22] to analyze sensitivity and specificity, incorporating the correlation between sensitivity and specificity. We assumed random effects across studies with a bivariate normal distribution for sensitivity and specificity, and heterogeneity among the studies was measured based on the random effect variance (τ^2). The advantage of using a logistic mixed effects model is that it handles sparse data better and does not need to assume an ad hoc continuity correction when a study has zero events.[22] When few studies were available for an analysis, we used the moment estimates of correlation between sensitivity and specificity in the bivariate model. We calculated positive likelihood ratio (LR+) and negative likelihood ratio (LR-) using the summarized sensitivity and specificity.[23,24] Because studies of a particular biomarker generally used the same definition for a positive test, we did not attempt to plot summary receiver operating characteristic (ROC), which are based on estimates of sensitivity and specificity at different thresholds.[25] For head-to-head comparisons, we used the same bivariate logistic mixed effects model as described above, but added an indicator variable for imaging modalities (equivalent to a meta-regression approach).

We conducted analyses for each biomarker based on data from all patients who underwent testing, as well as stratified according to whether testing was performed for evaluation of signs or symptoms of bladder cancer or for surveillance for previously treated bladder cancer. We also performed analyses stratified according to aspects of study design (retrospective or prospective design, use of prespecified threshold to define a positive test), risk of bias (overall risk of bias rating and whether the study performed blinded to the results of the index test), and setting (based on the country in which the study was performed), and in subgroups defined by tumor grade and stage. We performed separate analyses on the subset of studies that directly compared two or more imaging modalities or techniques in the same population against a common reference standard. Research indicates that results based on such direct comparisons differ from

results based on noncomparative studies, and may be better suited for evaluating comparative diagnostic test performance.[26]

We also conducted meta-analyses on trials of intravesical therapy that reported effects on clinical outcomes and were homogeneous enough to provide a meaningful combined estimate. We used the Dersimonian-Laird random effects method using SAS software, Version 10.0 (SAS Institute Inc., Cary, NC).[27] We assessed the presence of statistical heterogeneity among the studies using the standard Cochran's chi-square test, and the magnitude of heterogeneity by using the I^2 statistic.[28] When statistical heterogeneity was present, we performed sensitivity analyses by conducting meta-analysis using the profile likelihood method.[29] We also performed sensitivity and subgroup analyses based on ratings for risk of bias, dose of intravesical therapy, inclusion of high-risk patients, and duration of followup. We also stratified trials according to the type of instillation regimen, classified as single instillation, induction therapy (treatment for 4 to 8 weeks), maintenance therapy (treatment for longer than 8 weeks), or other. We calculated pooled relative risks for the dichotomous outcomes bladder cancer recurrence, bladder cancer progression, all-cause mortality, bladder cancer mortality, and local and systemic adverse events. Similar analyses were performed for trials of augmented cystoscopy (fluorescent light or narrow band imaging) versus white light cystoscopy.

Grading the Strength of Evidence for Each Key Question

We assessed the strength of evidence for each Key Question and outcome using the approach described in the AHRQ Methods Guide,[15] based on the overall quality of each body of evidence, the risk of bias (graded low, medium, or high); the consistency of results across studies (graded consistent, inconsistent, or unable to determine when only one study was available); the directness of the evidence linking the intervention and health outcomes (graded direct or indirect); the precision of the estimate of effect, based on the number and size of studies and confidence intervals for the estimates (graded precise or imprecise); and reporting bias (suspected of undetected)

Assessments of reporting bias were based on whether studies defined and reported primary outcomes, identification of relevant unpublished studies, and when available, by comparing published results to results reported in trial registries.

We graded the strength of evidence for each Key Question using the four key categories recommended in the AHRQ Methods Guide.[15] A "high" grade indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect. A "moderate" grade indicates moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate. A "low" grade indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. An "insufficient" grade indicates evidence either is unavailable or is too limited to permit any conclusion, due to the availability of only poor-quality studies, extreme inconsistency, or extreme imprecision.

See Appendix G for the strength of evidence tables.

Peer Review and Public Commentary

Experts in urology (including experts in urologic oncology and urinary biomarkers), medical oncology, and radiation oncology, were invited to provide peer review of the draft report. The AHRQ Task Order Officer and an Evidence-based Practice Center Associate Editor also

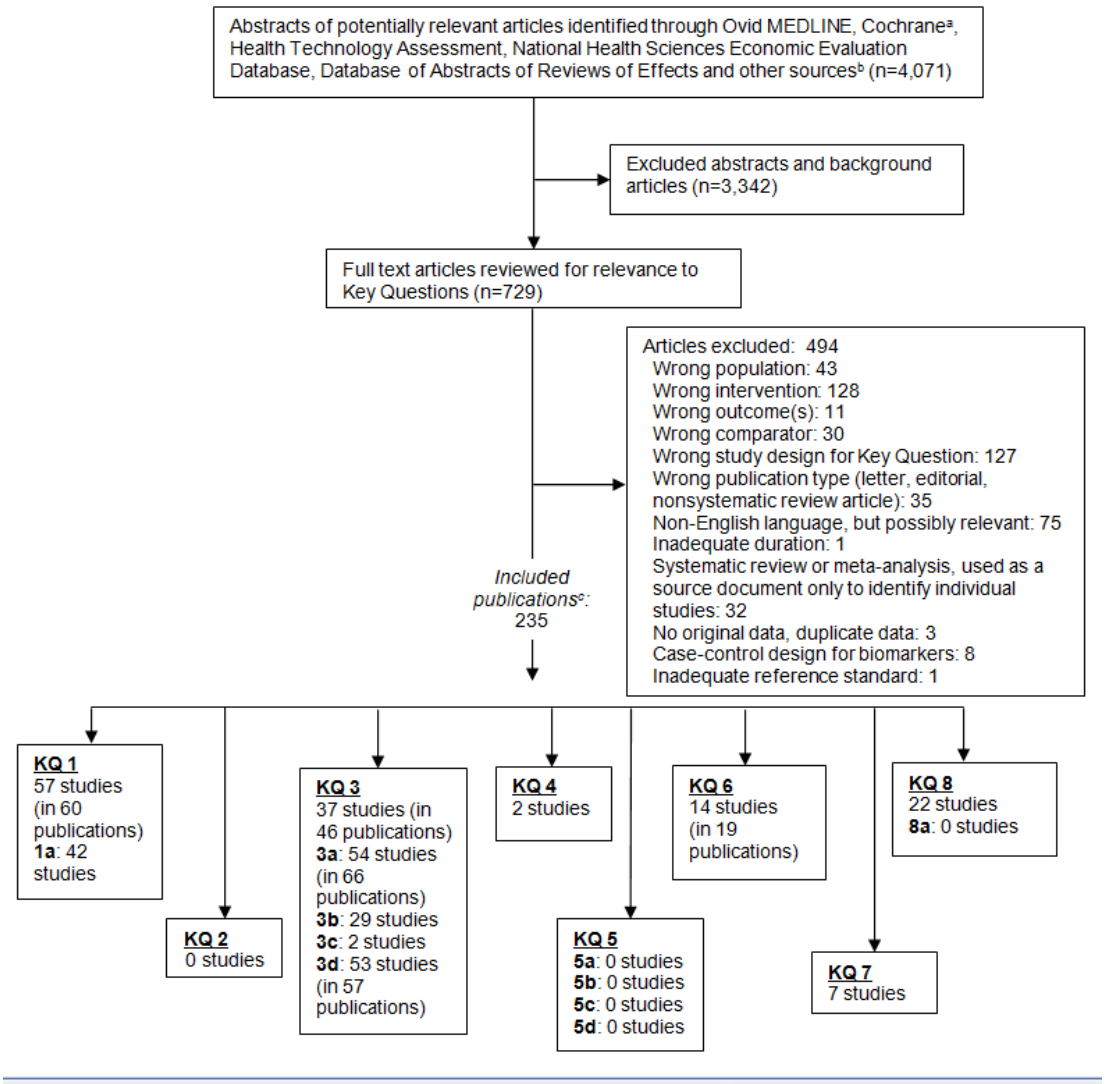
provided comments and editorial review. The draft report was posted on the AHRQ Web site for 4 weeks for public comment. A disposition of comments report with authors' responses to the peer and public review comments will be posted after publication of the final CER on the public Web site.

Results

Results of Literature Searches

The search and selection of articles are summarized in the literature flow diagram (Figure 2). Database searches resulted in 4,071 potentially relevant articles. After dual review of abstracts and titles, 729 articles were selected for full-text dual review and 201 studies (in 235 publications) were determined to meet inclusion criteria and were included in this review. Data extraction and risk of bias assessment tables for all included studies are available in Appendixes E and F.

Figure 2. Literature flow diagram



KQ = Key Question

[a] Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.

[b] Other sources include prior reports, reference lists of relevant articles, systematic reviews, etc.

[c] Some studies have multiple publications and some are included for more than one Key Question.

Key Question 1. What is the diagnostic accuracy of various urinary biomarkers compared with other urinary biomarkers or standard diagnostic methods (cystoscopy, cytology, and imaging) in (1) people with signs or symptoms warranting evaluation for possible bladder cancer or (2) people undergoing surveillance for previously treated bladder cancer?

Key Points

- Quantitative NMP22: Sensitivity was 0.69 (95% CI 0.62 to 0.75) and specificity 0.77 (95% CI 0.70 to 0.83), based on 19 studies, for a positive likelihood ratio of 3.05 (95% CI 2.28 to 4.10) and negative likelihood ratio of 0.40 (95% CI 0.32 to 0.50) (SOE: moderate)
  - For evaluation of symptoms: Sensitivity was 0.67 (95% CI 0.55 to 0.77; 9 studies) and specificity 0.84 (95% CI 0.75 to 0.90; 7 studies).
  - For surveillance: Sensitivity was 0.61 (95% CI 0.49 to 0.71; 10 studies) and specificity 0.71 (95% CI 0.60 to 0.81; 8 studies).
- Qualitative NMP22: Sensitivity of qualitative NMP22 was 0.58 (95% CI 0.39 to 0.75) and specificity 0.88 (95% CI 0.78 to 0.94), based on four studies, for a positive likelihood ratio of 4.89 (95% CI 3.23 to 7.40) and negative likelihood ratio of 0.48 (95% CI 0.33 to 0.71) (SOE: low).
  - For evaluation of symptoms: Sensitivity was 0.47 (95% CI 0.33 to 0.61) and specificity 0.93 (95% CI 0.81 to 0.97), based on two studies.
  - For surveillance: Sensitivity was 0.70 (95% CI 0.40 to 0.89) and specificity 0.83 (95% 0.75 to 0.89), based on two studies.
- Qualitative BTA: Sensitivity was 0.64 (95% CI 0.58 to 0.69, 22 studies) and specificity 0.77 (95% CI 0.73 to 0.81, 21 studies), for a positive likelihood ratio of 2.80 (95% CI 2.31 to 3.39) and negative likelihood ratio of 0.47 (95% CI 0.30 to 0.55 (SOE: moderate).
  - For evaluation of symptoms: Sensitivity was 0.76 (95% CI 0.67 to 0.83; 8 studies), and specificity 0.78 (95% CI 0.66 to 0.87; 6 studies).
  - For surveillance: Sensitivity was 0.60 (95% CI 0.55 to 0.65; 11 studies) and specificity 0.76 (95% CI 0.69 to 0.83; 8 studies).
- Quantitative BTA: Sensitivity was 0.65 (95% CI 0.54 to 0.75) and specificity 0.74 (95% CI 0.64 to 0.82), based on four studies, for a positive likelihood ratio of 2.52 (95% CI 1.86 to 3.41) and negative likelihood ratio of 0.47 (95% CI 0.37 to 0.61) (SOE: low).
  - For evaluation of symptoms: Sensitivity was 0.76 (95% CI 0.61 to 0.87) and specificity 0.53 (95% CI 0.38 to 0.68), based on one study.
  - For surveillance: Sensitivity was 0.58 (95% CI 0.46 to 0.69) and specificity 0.79 (95% CI 0.72 to 0.85), based on two studies.
- FISH: Sensitivity was 0.63 (95% CI 0.50 to 0.75) and specificity 0.87 (95% CI 0.79 to 0.93), based on 11 studies, for a positive likelihood ratio of 5.02 (95% CI 2.93 to 8.60) and negative likelihood ratio of 0.42 (95% CI 0.30 to 0.59) (SOE: moderate).
  - For evaluation of symptoms: Sensitivity was 0.73 (95% CI 0.50 to 0.88) and specificity was 0.95 (0.87 to 0.98), based on two studies, for a positive likelihood ratio of 14.2 (95% CI 5.2 to 39) and negative likelihood ratio of 0.29 (95% CI 0.14 to 0.60).
  - For surveillance: Sensitivity was 0.55 (95% CI 0.36 to 0.72; 7 studies) and specificity was 0.80 (95% CI 0.66 to 0.89; 6 studies).

- ImmunoCyt: Sensitivity was 0.78 (95% CI 0.68 to 0.85) and specificity 0.78 (95% CI 0.72 to 0.82), based on 14 studies, for a positive likelihood ratio of 3.49 (95% 2.82 to 4.32) and negative likelihood ratio of 0.29 (95% CI 0.20 to 0.41) (SOE: moderate).
  - For evaluation of symptoms: Sensitivity was 0.85 (95% CI 0.78 to 0.90; 6 studies) and specificity was 0.83 (95% CI 0.77 to 0.87; 7 studies).
  - For surveillance: Sensitivity was 0.75 (95% CI 0.64 to 0.83; 7 studies) and specificity was 0.76 (95% CI 0.70 to 0.81; 8 studies).
- CxBladder: Sensitivity was 0.82 (95% CI 0.70 to 0.90) and specificity of 0.85 (95% CI 0.81 to 0.88) for evaluation of symptoms, based on one study, for a positive likelihood ratio of 5.53 (95% CI 4.28 to 7.15) and negative likelihood ratio of 0.21 (95% CI 0.13 to 0.36) (SOE: low).
- Direct (within-study) comparisons
  - There was no difference between quantitative NMP22 (cutoff >10 U/mL)versus qualitative BTA in sensitivity (0.69, 95% CI 0.62 to 0.76 vs. 0.66, 95% CIO 0.59 to 0.73, for a difference of 0.03, 95% CI -0.04 to 0.10) or specificity (0.73, 95% CI 0.62 to 0.82 vs. 0.76, 95% CI 0.66 to 0.84, for a difference of 0.03, 95% CI -0.08 to 0.01), based on seven studies (SOE: moderate).
  - ImmunoCyt was associated with higher sensitivity than FISH (0.71, 95% CI 0.54 to 0.84 vs. 0.61, 95% CI 0.43 to 0.76, for a difference of 0.11, 95% CI 0.001 to 0.21) but lower specificity (0.71, 95% CI 0.62 to 0.79 vs. 0.79, 95% CI 0.71 to 0.85, for a difference of -0.08, 95% CI -0.15 to -0.001), based on three studies (SOE: low).
  - Evidence for other head-to-head comparisons of urinary biomarkers was based on small numbers of studies with imprecise estimates and methodological shortcomings, precluding reliable conclusions regarding comparative test performance (SOE: insufficient).
  - Sixteen studies found sensitivity of various urinary biomarkers plus cytology associated with higher sensitivity than the urinary biomarker alone (0.81, 95% CI 0.75 to 0.86 vs. 0.69, 95% CI 0.61 to 0.76, for a difference of 0.13, 95% CI 0.08 to 0.17), with no difference in specificity (SOE: moderate).

Detailed Synthesis

Fifty-seven studies in 60 publications evaluated the diagnostic accuracy of urinary biomarkers for diagnosis of bladder cancer (Table 2, Appendix E1, F1).[30-89] Quantitative NMP22 was evaluated in 19 studies,[30,32,33,39,52,53,57,60,61,63,65-67,72,73,75,83,87,89] 4 studies in 5 publications evaluated qualitative NMP 22,[35,36,38,47,52] 23 studies in 24 publications evaluated qualitative BTA,[32,33,39-42,44,45,49,51,56,58-60,62,64,67-70,77,80,83,87,89] 4 studies evaluated quantitative BTA,[34,42,69,83] 10 studies evaluated FISH,[37,43,55,62,71,75,76,84,85,87] 13 studies in 14 publications evaluated ImmunoCyt,[31,46,48,50,54,74,78,79,81,82,85-88] and 1 study evaluated CxBladder.[52] Sample sizes ranged from 26 to 3,916 and the proportion of patients with bladder cancer ranged from 3 to 81 percent. The focus of 8 studies in 9 publications was diagnostic testing for patients with signs or symptoms suggestive of bladder cancer for initial diagnosis, 16 studies focused on diagnostic testing for surveillance in patients previously treated for non–muscle-invasive bladder cancer (NMIBC), and 19 studies evaluated mixed populations. Forty-three studies in 44 publications were conducted in the United States or Europe[30-37,39-51,53-55,57,59-68,70-73,75,83,87,89] and 26 studies in 27 publications used a prospective design.[30,35-38,41,42,44-47,50,52,54,56-62,64,66,68,69,71,89] Two studies were rated low risk of bias,[35,36] 52 studies medium risk of bias,[30-34,37-39,41-46,48-76,78-82,84-89] and

three studies high risk of bias[40,77,83] (See Appendix F). Eleven studies reported blinded interpretation of the reference standard,[30,35,36,38,44,45,54,57,62,71,73] 12 studies reported enrollment of a random or consecutive sample of patients,[30,31,35,36,38,43,46,50,52,54,55,59] and 38 studies reported predefined criteria for a positive test.[30-42,44-51,53-73,75,83,87,89]

Quantitative NMP22

Sensitivity of quantitative NMP22 was 0.69 (95% CI 0.62 to 0.75) and specificity was 0.77 (95% CI 0.70 to 0.83), based on 19 studies, for a positive likelihood ratio of 3.05 (95% CI 2.28 to 4.10) and negative likelihood ratio of 0.40 (95% CI 0.32 to 0.50) (Table 3; Figure 3).[30,32,33,39,52,53,57,60,61,63,65-67,72,73,75,83,87,89] All studies except for two[33,52] used a cutoff of >10 for a positive test. Excluding these two studies resulted in similar sensitivity (0.70, 95% CI 0.63 to 0.77) and specificity (0.77, 95% CI 0.69 to 0.83). Diagnostic accuracy was similar for evaluation of symptoms (sensitivity 0.67 [95% CI 0.55 to 0.77]; 9 studies and specificity 0.84 [95% CI 0.75 to 0.90]; 7 studies)[30,33,52,53,60,61,67,73,89] and for surveillance (sensitivity 0.61 [95% CI 0.49 to 0.71]; 10 studies and specificity 0.71 [95% CI 0.60 to 0.81]; 8 studies).[30,33,63,65-67,72,75,83,89] Excluding one study rated high risk of bias[83] and restricting the analysis to studies that used a prospective design, were conducted in the United States or Europe, or used a prespecified threshold to define a positive test, had little effect on pooled estimates and did not reduce statistical heterogeneity. Restricting the analysis to studies t hat reported blinded interpretation of the reference standard resulted in higher specificity, but the pooled estimate was only based on three studies (0.89, 95% CI 0.78 to 0.95).[30,57,73]

Qualitative NMP22

Sensitivity of qualitative NMP22 was 0.58 (95% CI 0.39 to 0.75) and specificity was 0.88 (95% CI 0.78 to 0.94), based on four studies, for a positive likelihood ratio of 4.89 (95% CI 3.23 to 7.40) and negative likelihood ratio of 0.48 (95% CI 0.33 to 0.71) (Table 3; Figure 4).[35,36,38,52] Restricting the analysis to two studies that were rated low risk of bias resulted in similar estimates (sensitivity 0.53 [95% CI 0.29 to 0.75] and specificity 0.87 [95% CI 0.74 to 0.94]).[35,36] Two studies each reported diagnostic accuracy for evaluation of symptoms (sensitivity 0.47 [95% CI 0.33 to 0.61] and specificity 0.93 [95% CI 0.81 to 0.97])[35,52] and for surveillance (sensitivity 0.70 [95% CI 0.40 to 0.89] and specificity 0.83 [95% 0.75 to 0.89]),[36,38] resulting in imprecise estimates. Other subgroup and sensitivity analysis were also limited by the small numbers of studies.

Qualitative BTA

Sensitivity of qualitative BTA was 0.64 (95% CI 0.58 to 0.69, 22 studies)[32,33,39-42,44,45,49,51,56,58,60,64,67,68,70,77,80,83,87,89] and specificity was 0.77 (95% CI 0.73 to 0.81, 21 studies),[32,33,39,40,42,44,45,49,51,56,58,60,64,67,68,70,77,80,83,87,89] for a positive likelihood ratio of 2.80 (95% CI 2.31 to 3.39) and negative likelihood ratio of 0.47 (95% CI 0.30 to 0.55) (Table 3; Figure 5). Excluding three studies rated high risk of bias[40,77,83] resulted in similar pooled estimates and did not reduce statistical heterogeneity. Sensitivity was higher for evaluation of symptoms (0.76, 95% CI 0.67 to 0.83; 8 studies)[33,45,51,56,60,67,77,89] than for surveillance (0.60, 95% CI 0.55 to 0.65; 11 studies),[33,41,44,45,56,59,67,68,77,80,83,89] but specificity was similar (0.78 [95% CI 0.66 to 0.87]; 6 studies and 0.76 [95% CI 0.69 to 0.83]; 8 studies, respectively. Restricting analyses to studies that used a prospective design, were conducted in the United States or Europe, or reported

interpretation of the reference standard blinded to BTA test results, had little effect on pooled estimates and did not reduce statistical heterogeneity.

Quantitative BTA

Sensitivity of quantitative BTA was 0.65 (95% CI 0.54 to 0.75) and specificity was 0.74 (95% CI 0.64 to 0.82), based on four studies, for a positive likelihood ratio of 2.52 (95% CI 1.86 to 3.41) and negative likelihood ratio of 0.47 (95% CI 0.37 to 0.61) (Table 3; Figure 6).[34,42,69,83] Estimates were similar in three studies that used a threshold of >14 to define a positive test[42,69,83] and when one high risk of bias study[83] was excluded from the analysis. Only one study[69] reported diagnostic accuracy for evaluation of symptoms (sensitivity 0.76 [95% CI 0.61 to 0.87]; specificity 0.53 [95% CI 0.38 to 0.68]) and two studies[69,83] for surveillance (sensitivity 0.58 [95% CI 0.46 to 0.69]; specificity 0.79 [95% CI 0.72 to 0.85]).

FISH

Sensitivity of FISH was 0.63 (95% CI 0.50 to 0.75) and specificity was 0.87 (95% CI 0.79 to 0.93), based on 11 studies, for a positive likelihood ratio of 5.02 (95% CI 2.93 to 8.60) and negative likelihood ratio of 0.42 (95% CI 0.30 to 0.59) (Table 3; Figure 7).[37,40,43,55,62,71,75,76,84,85,87] Estimates were similar when one high risk of bias study[40] was excluded, prostatitis or when the analysis was restricted to studies that used a prospective design or reported interpretation of the reference standard blinded to FISH results. For surveillance, sensitivity was 0.55 (95% CI 0.36 to 0.72; 7 studies) and specificity was 0.80- (95% CI 0.66 to 0.89; 6 studies).[37,43,55,62,71,75,85] For evaluation of symptoms, sensitivity of FISH was 0.73 (95% CI 0.50 to 0.88), based on two studies.[55,84] Only one study reported specificity of FISH for evaluation of symptoms (0.95, 95% CI 0.87 to 0.98)).[84]

ImmunoCyt

Sensitivity of ImmunoCyt was 0.78 (95% CI 0.68 to 0.85) and specificity was 0.78 (95% CI 0.72 to 0.82), based on 14 studies, for a positive likelihood ratio of 3.49 (95% CI 2.82 to 4.32) and negative likelihood ratio of 0.29 (95% CI 0.20 to 0.41) (Table 3; Figure 8).[31,46,48,50,74,75,78,79,81,82,85-88] Excluding one high risk of bias study[86] or restricting the analysis to studies that used a prospective design had little effect on estimates. For evaluation of symptoms, sensitivity was 0.85 (95% CI 0.78 to 0.90; 6 studies) and specificity was 0.83 (95% CI 0.77 to 0.87; 7 studies), [46,50,74,78,79,81,82] and for surveillance, sensitivity was 0.75 (95% CI 0.64 to 0.83; 7 studies) and specificity was 0.76 (95% CI 0.70 to 0.81; 8 studies).[46,48,50,75,78,79,85,88]

CxBladder

One study (rated medium risk of bias) of CxBladder reported a sensitivity of 0.82 (95% CI 0.70 to 0.90) and specificity of 0.85 (95% CI 0.81 to 0.88) for evaluation of symptoms, for a positive likelihood ratio of 5.53 (95% CI 4.28 to 7.15) and negative likelihood ratio of 0.21 (95% CI 0.13 to 0.36) (Table 3).[52]

Head-to-Head Comparisons

Relatively few studies directly compared the diagnostic accuracy of different urinary biomarkers in the same population against cystoscopy and biopsy (Table 4). In seven studies, there were no differences between quantitative NMP22 (based on a cutoff of >10 U/mL) versus qualitative BTA in sensitivity (0.69, 95% CI 0.62 to 0.76 vs. 0.66, 95% CI 0.59 to 0.73, for a

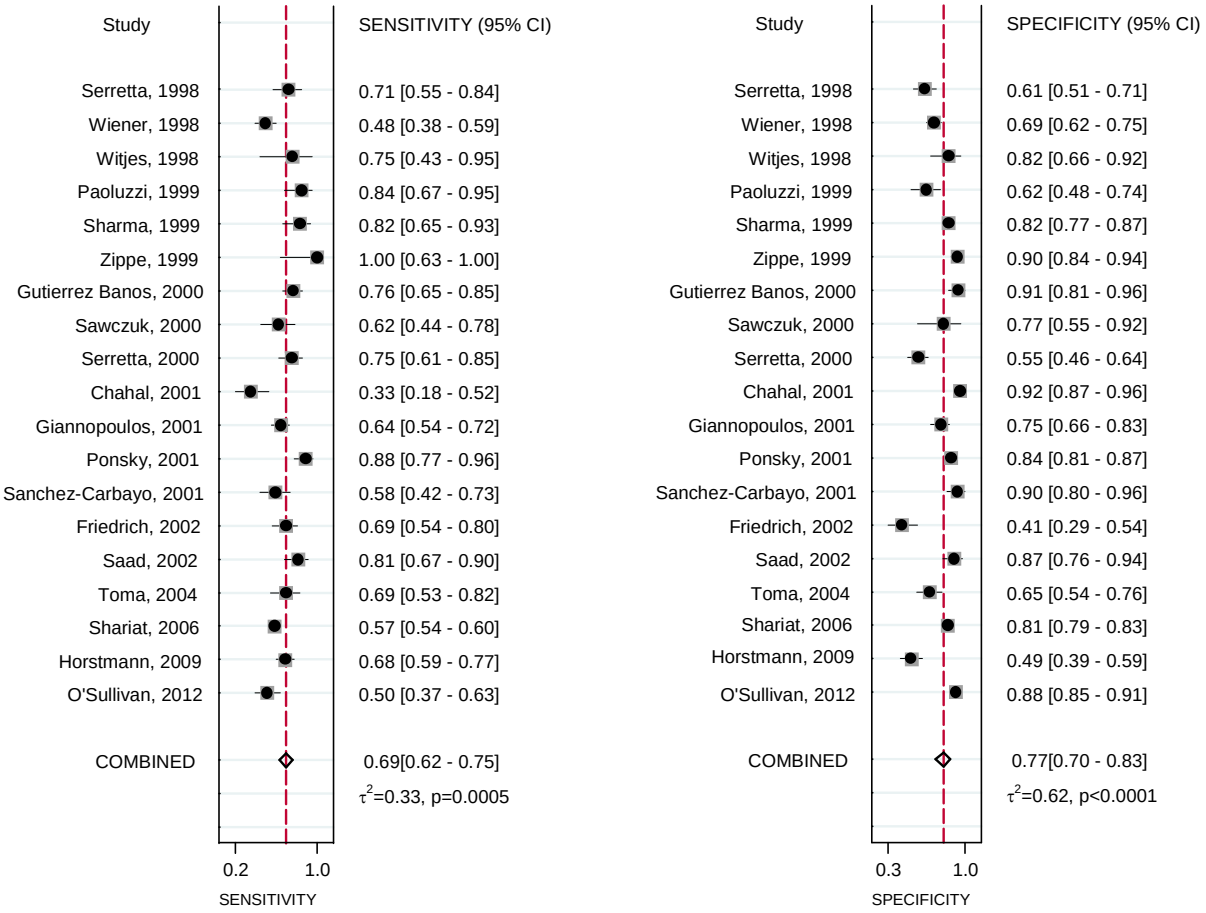
difference of 0.03, 95% CI -0.04 to 0.10) or specificity (0.73, 95% CI 0.62 to 0.82 vs. 0.76, 95% CI 0.66 to 0.84, for a difference of 0.03, 95% CI -0.08 to 0.01).[32,39,60,67,83,87,89] Findings were similar when one high risk of bias study was excluded,[83] when the analysis was restricted to studies that used a prospective design,[60,67,89] or when analyses were stratified according to different tumor stages or grades.

Three studies found ImmunoCyt associated with higher sensitivity than FISH (0.71 [95% CI 0.54 to 0.84] vs. 0.61 [95% CI 0.43 to 0.76], for a difference of 0.11 [95% CI 0.001 to 0.21]) but lower specificity (0.71 [95% CI 0.62 to 0.79] vs. 0.79 [95% CI 0.71 to 0.85], for a difference of -0.08 [95% CI -0.15 to -0.001]).[75,85,87] ImmunoCyt was also associated with higher sensitivity than FISH for Ta, T1, and low grade numbers (differences in sensitivity ranged from 0.24 to 0.35).

Two studies found qualitative BTA associated with lower specificity than FISH (difference -0.16, 95% CI -0.24 to -0.08),[40,87] two studies found quantitative NMP22 associated with lower specificity than ImmunoCyt (difference -0.16, 95% CI -0.28 to -0.04),[75,87] and two studies found quantitative NMP22 associated with lower specificity than FISH (difference -0.18, 95% CI -0.28 to -0.08),[75,87] with no clear differences in sensitivity. Evidence for other head-to-head comparisons of urinary biomarkers was based on one or two studies with imprecise estimates and methodological shortcomings, precluding reliable conclusions regarding comparative test performance (Table 4).

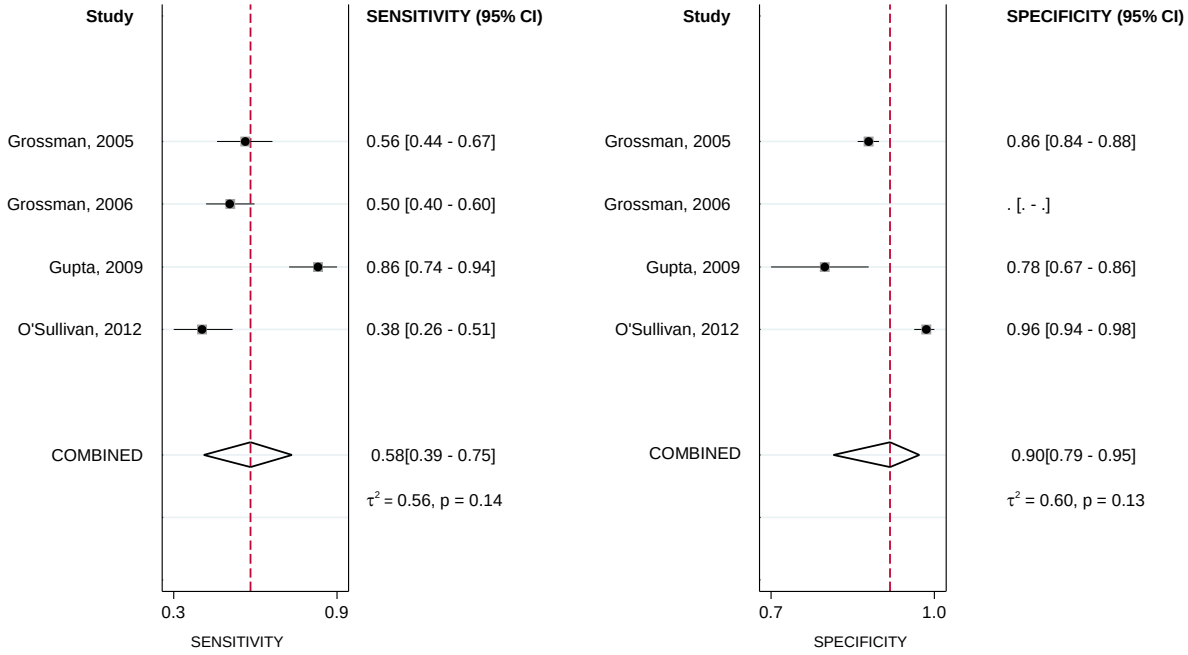
Sixteen studies found sensitivity of various urinary biomarkers plus cytology associated with higher sensitivity than the urinary biomarker alone (0.81, 95% CI 0.75 to 0.86 vs. 0.69, 95% CI 0.61 to 0.76, for a difference of 0.13, 95% CI 0.08 to 0.17), with no difference in specificity (Table 4);[31,34,36,38,45,48,50,53,55,69,77,79,85-88] results were similar in a subgroup of eight studies of ImmunoCyt plus Cytology versus ImmunoCyt alone.[31,48,50,79,85-88] In studies that stratified analyses according to tumor stage and grade, there were no clear differences in sensitivity for Ta, T1, or low grade (G1, low grade, or low malignant potential).[31,48,50,79,85-88]

Figure 3. Sensitivity and specificity of quantitative NMP22



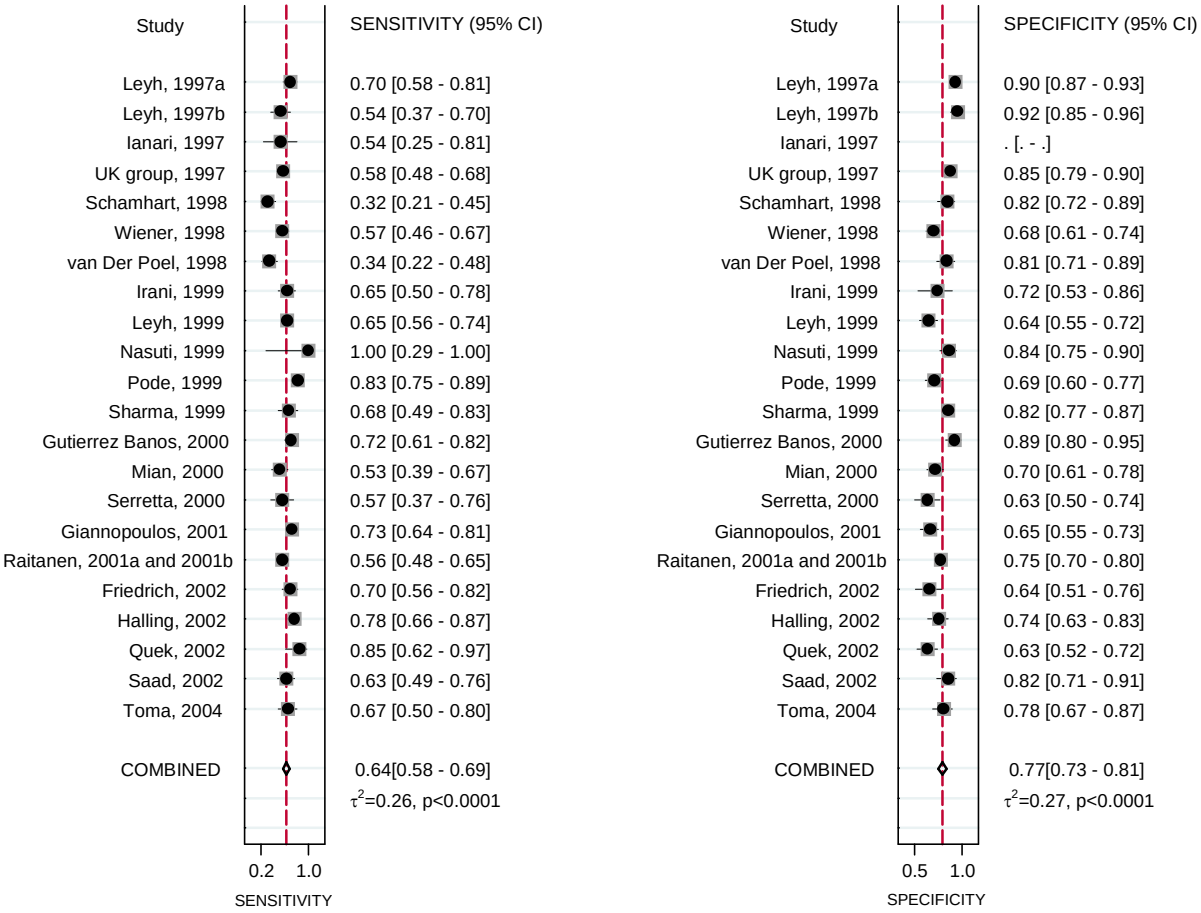
CI = confidence interval; NMP22 = nuclear matrix protein-22

Figure 4. Sensitivity and specificity of qualitative NMP22



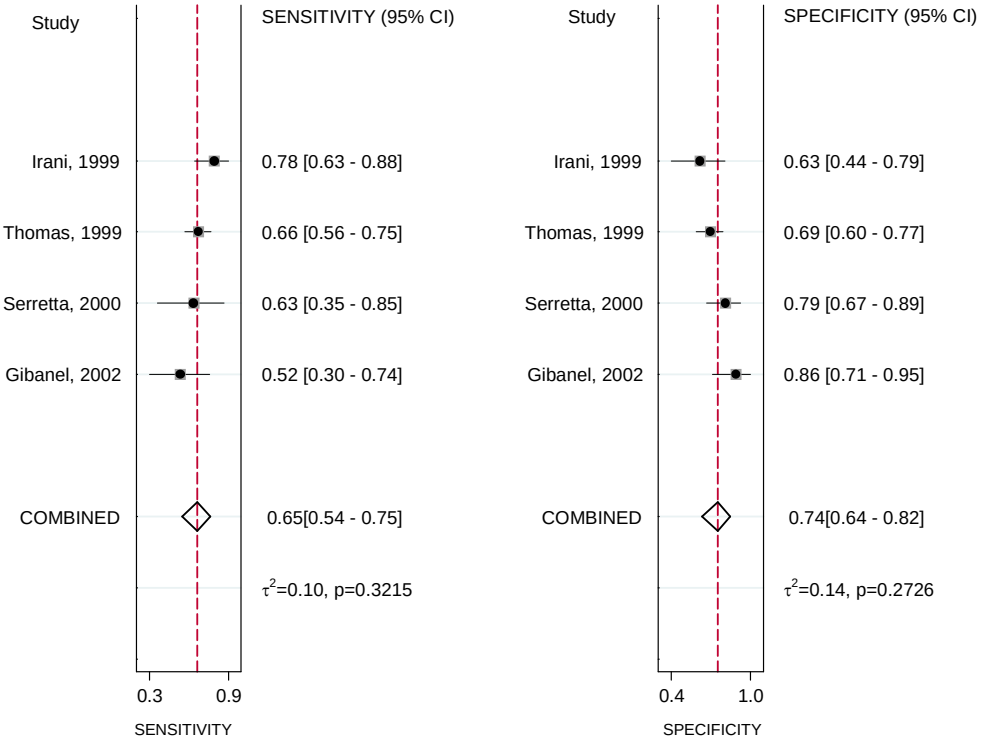
CI = confidence interval; NMP22 = nuclear matrix protein-22

Figure 5. Sensitivity and specificity of qualitative BTA



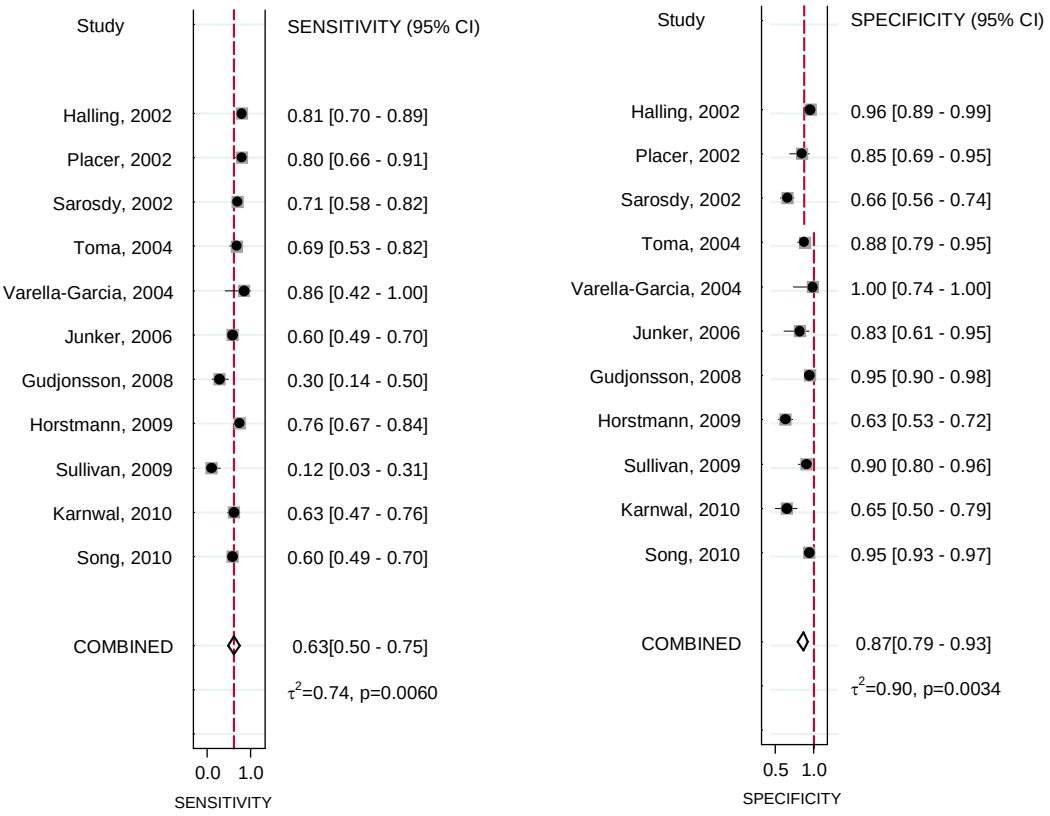
BTA = bladder tumor antigen; CI = confidence interval

Figure 6. Sensitivity and specificity of quantitative BTA



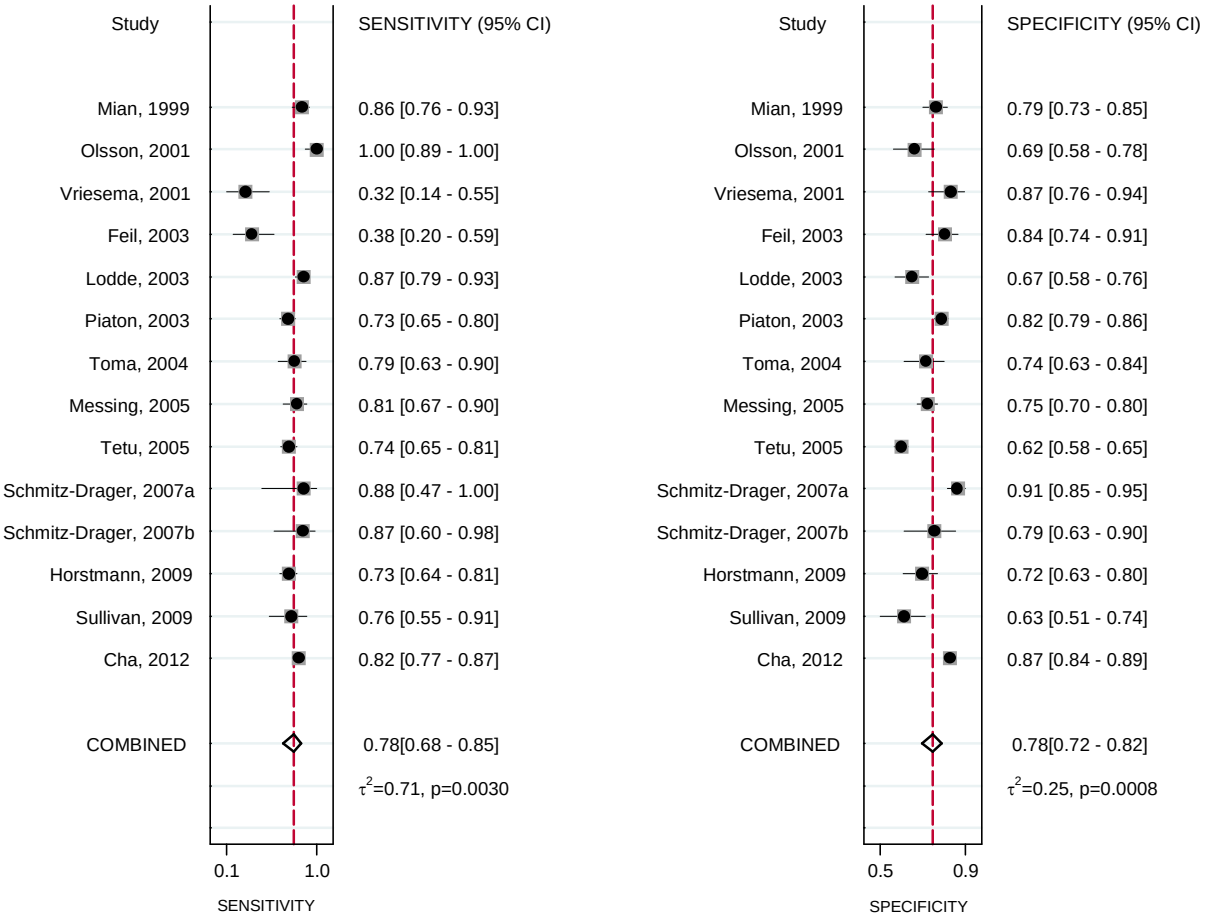
BTA = bladder tumor antigen; CI = confidence interval

Figure 7. Sensitivity and specificity of FISH



CI = confidence interval; FISH = fluorescence in situ hybridization

Figure 8. Sensitivity and specificity of ImmunoCyt



CI = confidence interval

Key Question 1a. Does the diagnostic accuracy differ according to patient characteristics (e.g., age, sex, race/ethnicity) or according to the nature of the presenting signs or symptoms?

Key Points

- Effects of tumor stage: Across urinary biomarkers, sensitivity increased with higher tumor stage. Evidence was most robust for quantitative NMP22 (11 studies), qualitative BTA (18 studies), and FISH (8 studies); the association between higher tumor stage and increased sensitivity was least pronounced for ImmunoCyt (10 studies). Sensitivity for CIS tumors was generally similar to or slight lower than for T1 tumors (SOE: high).
- Effects of tumor grade: Across urinary biomarkers, sensitivity increased with higher tumor grade. Evidence was most robust for quantitative NMP22 (12 studies), ImmunoCyt (10 studies), qualitative BTA (18 studies), and FISH (9 studies) (SOE: high).
- Effects of tumor size: Two studies found sensitivity was higher for larger (>1 cm or >2 cm) smaller tumors (SOE: low).

- Evidence on the effects of patient characteristics such as age, sex, smoking status, and presence of other clinical conditions on diagnostic accuracy of urinary biomarkers was limited, but did not clearly or consistently indicate effects on sensitivity or specificity (SOE: low).

Detailed Synthesis

Across urinary biomarkers, sensitivity increased with higher tumor stage (Table 5). For quantitative NMP 22, sensitivity for Ta tumors was 0.48 (95% CI 0.36 to 0.60; 10 studies), for T1 tumors was 0.72 (95% CI 0.60 to 0.81; 11 studies), and for ≥T2 tumors was 0.82 (95% CI 0.70 to 0.89; 11 studies; p=0.002 for overall difference between categories).[30,32,33,39,52,60,61,83,87,89] The difference in sensitivity between T1 and Ta tumors was 0.23 (95% CI 0.14 to 0.32) and between ≥T2 and T1 tumors was 0.10 (95% CI 0.01 to 0.20). For qualitative BTA, sensitivity for Ta tumors was 0.49 (95% CI 0.41 to 0.56; 18 studies), for T1 tumors was 0.74 (95% CI 0.66 to 0.80; 17 studies), and for ≥T2 tumors was 0.89 (95% CI 0.83 to 0.93; 17 studies; p<0.0001 for overall difference between categories).[32,33,39,40,42,44,45,49,56,58,60,62,64,70,77,83,87,89] The difference in sensitivity between T1 and Ta tumors was 0.25 (95% CI 0.18 to 0.32) and between ≥T2 and T1 tumors was 0.15 (95% CI 0.08 to 0.22). A similar pattern was observed for FISH, based on eight studies (Table 4).[40,55,62,71,76,84,85,87] For quantitative NMP22, FISH, and qualitative BTA, sensitivity for CIS tumors was similar or slightly lower than for T1 tumors. For ImmunoCyt, the association between higher tumor stage and increased sensitivity was less clear. Sensitivity for Ta tumors was 0.74 (0.63 to 0.83) and for T1 and ≥T2 tumors was 0.81, based on 10 studies.[31,46,48,50,81,82,85-87]

Sensitivity also increased across urinary biomarkers with higher tumor grade (Table 5). For quantitative NMP22, sensitivity for G1 tumors was 0.44 (95% CI 0.32 to 0.57), for G2 tumors was 0.58 (95% CI 0.47 to 0.69), and for G3 tumors was 0.75 (95% CI 0.65 to 0.83), based on 12 studies (p<0.0001 for difference between categories).[30,32,33,39,52,60,61,63,75,83,87,89] The difference in sensitivity between G2 and G1 tumors was 0.14 (95% CI 0.05 to 0.24) and between G3 and G2 tumors was 0.16 (95% CI 0.09 to 0.24). For qualitative BTA, sensitivity for G1 tumors was 0.39 (95% CI 0.30 to 0.48), for G2 tumors was 0.63 (95% CI 0.54 to 0.71), and for G3 tumors was 0.81 (95% CI 0.75 to 0.87), based on 19 studies (p<0.0001 for difference between categories).[32,33,39-42,44,45,49,56,58,60,62,64,70,77,83,87,89] The difference in sensitivity between G2 and G1 tumors was 0.24 (95% CI 0.17 to 0.32) and between G3 and G2 tumors was 0.18 (95% CI 0.12 to 0.25). A similar pattern was observed for FISH, based on seven studies (Table 5).[40,55,62,71,75,84,87] For ImmunoCyt, sensitivity for low-grade (G1, low grade, or low malignant potential) tumors was 0.74 (95% CI 0.66 to 0.80) and for high-grade tumors (G2, G3, or high grade) was 0.83 (95% CI 0.78 to 0.88), for a difference of 0.10 (95% CI 0.03 to 0.17), based on 10 studies.[46,48,50,75,79,81,82,85-87]

Similar patterns for effects of tumor stage and grade were observed for other urinary biomarkers (Table 5). However, estimates were based on smaller numbers of studies and were less precise, and differences were not always statistically significant.

One study found higher sensitivity of qualitative BTA for tumors 2 to 5 cm (0.96) and >5 cm (1.0) than for tumors <2 cm (0.60, Fisher's exact p<0.0005)[56] and one study found higher sensitivity of FISH for tumors 1-3 cm (0.93) or >3 cm (0.94) than for tumors <1 cm (0.46, Fisher's exact p=0.001).[55]

Few studies evaluated effects of patient characteristics on diagnostic accuracy of urinary biomarkers. One study found quantitative and qualitative NMP22 and CxBladder each associated

with higher sensitivity for multifocal versus unifocal tumors, though differences were not statistically significant.[52] There were no clear differences in diagnostic accuracy according to sex, age, or smoking status.[35,52,58] Three studies[74,81,82] of ImmunoCyt that specifically enrolled patients with microscopic or macroscopic hematuria reported sensitivity and specificity that was similar to the overall estimates from studies of patients with signs or symptoms of bladder cancer. One study of quantitative NMP22 did not find a difference in sensitivity between patients who had received prior intravesical therapy and those who had not.[65]

Eight studies of various urinary biomarkers did not find consistent differences in specificity according to factors such as presence of other urological cancers, renal calculi, prostatitis, benign prostatic hypertrophy, urinary tract infection, or hematuria, though specificity was higher when other urological conditions were not present in some studies.[50,52,67,69,77,81,82,89]

Key Question 2. For patients with non–muscle-invasive bladder cancer, does the use of a formal risk-adapted assessment approach to treatment decisions (e.g., based on Guidelines of the European Association of Urology or on urinary biomarker tests) decrease mortality or improve other outcomes (e.g., recurrence, progression, need for cystectomy, quality of life) compared with treatment not guided by a formal assessed risk-adapted approach?

Key Points

- No study compared clinical outcomes associated with use of a formal risk-adapted approach to guide treatment of NMIBC versus treatment not guided by a risk-adapted approach (SOE: insufficient).

Detailed Synthesis

Though scoring systems to predict the risk of bladder cancer recurrence and disease progression are available and have undergone some validation,[90-94] no study compared clinical outcomes associated with use of a formal risk-adapted approach to guide treatment of NMIBC versus treatment not guided by a risk-adapted approach.

Key Question 3. For patients with non–muscle-invasive bladder cancer treated with transurethral resection of bladder tumor, what is the effectiveness of various intravesical chemotherapeutic or immunotherapeutic agents for decreasing mortality or improving other outcomes (e.g., recurrence, progression, need for cystectomy, quality of life) compared with TURBT alone?

Key Points

BCG

- BCG was associated with decreased risk of bladder cancer recurrence (3 trials, RR 0.56, 95% CI 0.43 to 0.71, I^2=0%) and progression (4 trials, RR 0.39, 95% CI 0.24 to 0.64,

I^2=40%) versus no intravesical therapy. No trial evaluated effects of BCG versus no intravesical therapy on risk of all cause mortality. One trial found BCG associated with decreased risk of bladder cancer mortality, but the difference was not statistically significant (RR 0.62, 95% CI 0.32 to 1.19). (SOE: insufficient for all-cause and bladder cancer mortality; SOE: low for recurrence and progression).

MMC

- Mitomycin C (MMC) was associated with decreased risk of bladder cancer recurrence versus no intravesical therapy (8 trials, RR 0.71, 95% CI 0.57 to 0.89, I^2=72%), but there was no difference in risk of all cause-mortality (1 trial, HR 1.17, 95% CI 0.89 to 1.53) and effects on bladder cancer-specific mortality (1 trial, HR 0.71, 95% CI 0.34 to 1.46) and bladder cancer progression (5 trials, RR 0.68, 95% CI 0.39 to 1.20, I^2=0%) were not statistically significant (SOE: moderate for recurrence, low for progression, all-cause mortality, and bladder cancer-specific mortality).

Doxorubicin

- Doxorubicin was associated with decreased risk of bladder cancer recurrence versus no intravesical therapy (10 trials, RR 0.80, 95% CI 0.72 to 0.88, I^2=46%), no difference in risk of bladder cancer progression (5 trials, RR 1.03, 95% CI 0.72 to 1.46, I^2=0%), and no clear effects on all-cause mortality (2 trials) or bladder cancer specific mortality (1 trial) (SOE: moderate for recurrence, low for progression, all-cause mortality, and bladder-cancer specific mortality).

Epirubicin

- Epirubicin was associated with decreased risk of bladder cancer recurrence (9 trials, RR 0.63, 95% CI 0.53 to 0.75, I^2=64%) (SOE: moderate) but the effect on bladder cancer progression was not statistically significant (8 trials, RR 0.79, 95% CI 0.84 to 1.30, I^2=27%) (SOE: low).

Gemcitabine

- One trial found no difference between single instillation gemcitabine versus no intravesical therapy in risk of bladder cancer recurrence (RR 0.98, 95% CI 0.70 to 1.36); estimates for progression (RR 3.00, 95% CI 0.32 to 28.4), all-cause mortality (RR 0.50, 95% CI 0.13 to 2.00), and bladder cancer-specific mortality were very imprecise (RR 1.00, 95% CI 0.06 to 15.81) (SOE: low for bladder cancer recurrence; SOE: insufficient for all-cause and bladder cancer mortality and progression).

Interferon Alpha

- Interferon alpha was associated with decreased risk of bladder cancer recurrence versus no intravesical therapy that was not statistically significant (3 trials, RR 0.75, 95% CI 0.53 to 1.06, I^2=50%), decreased risk of bladder cancer progression (2 trials, RR 0.33, 95% CI 0.14 to 0.76, I^2=0%), and no difference in risk of bladder cancer specific mortality (1 trial, RR 1.00, 95% CI 0.15 to 6.75) (SOE: low).

Interferon Gamma

- Interferon-gamma was associated with decreased risk of bladder cancer recurrence versus no intravesical therapy (1 trial, RR 0.72, 95% CI 0.51 to 1.01), with no difference in risk of bladder cancer progression (1 trial, RR 1.08, 95% CI 0.07 to 16.4) (SOE: low).

Thiotepa

- Thiotepa was associated with decreased risk of bladder cancer recurrence versus no intravesical therapy that was not statistically significant (5 trials, RR 0.78, 95% CI 0.58 to 1.06, I^2=69%), with insufficient evidence to determine effects on progression or mortality (SOE: low for recurrence, insufficient for all-cause and bladder cancer mortality and progression).

Detailed Synthesis

Thirty-seven trials (reported in 46 publications) evaluated intravesical therapy plus TURBT versus TURBT without intravesical therapy (Tables 6, 7, 8, 9, 10, 11, 12; Appendixes E2, F2).[95-140] Five trials evaluated BCG,[102-111] seven trials MMC,[111-118] nine trials doxorubicin,[112,113,115,116,119-125] 10 trials epirubicin,[103,119,126-134] 3 trials interferon alpha,[132,133,137,141] one trial interferon-gamma,[138] two trials thiotepa,[139,140] and one trial gemcitabine.[135] Samples sizes ranged from 24 to 553 and duration of followup from a median of 9 months to 10.7 years. Mean age ranged from 52.1 to 71 years and the proportion of patients who were male ranged from 62.9 to 98 percent. Eight trials excluded patients with G3 tumors and 15 trials excluded patients with CIS lesions. In the other trials, the proportion with G3 tumors ranged from 0 to 43 percent and the proportion with CIS lesions ranged from 0 to 88 percent. Seven trials focused on patients with primary tumors and 11 trials focused on patients with recurrent tumors. One trial was rated high risk of bias,[105,110] and 35 trials medium risk of bias (Appendix F2)[102-104,106-109,111-140] Two trials reported blinding of outcomes assessors;[127,132,133] no trial blinded care provider or patients. Other methodological limitations included inadequate description of randomization and allocation concealment, and high attrition or failure to report attrition. Results are summarized in Table 15.

BCG

Five trials (reported in 10 publications) randomized patients to BCG versus no intravesical therapy following TURBT (Table 6; Appendixes E2, F2).[102-111] The dose of BCG ranged from 75 mg to 150 mg. All trials evaluated maintenance therapy with BCG, except for one trial that was limited to 6-week induction therapy.[106]

No trial evaluated effects of BCG versus no intravesical therapy on risk of all cause mortality. One trial found BCG associated with decreased risk of bladder cancer mortality, but the difference was not statistically significant (RR 0.62, 95% CI 0.32 to 1.19).[102] BCG was associated with reduced risk of bladder cancer recurrence (3 trials, 29% vs. 50%, RR 0.56, 95% CI 0.43 to 0.71, I^2=0%) (Figure 9)[103,104,111] and progression (4 trials, 15% vs. 42%, RR 0.39, 95% CI 0.24 to 0.64, I^2=40%) (Figure 10).[103-106] One trial found BCG associated with a trend towards decreased risk of cystectomy versus no intravesical therapy, but the difference was not statistically significant (RR 0.61, 95% CI 0.33 to 1.14).[106]

All BCG trials that reported recurrence evaluated maintenance regimens. Statistical heterogeneity was present in the analysis of progression. Excluding one trial[106] that evaluated an induction regimen (also the only trial to focus on treatment of recurrent cancer, RR 0.56, 95% CI

0.42 to 0.75) eliminated statistical heterogeneity, but resulted in a similar estimate (RR 0.27, 95% CI 0.15 to 0.48, I^2=0%).

MMC

Nine trials (reported in 10 publications) evaluated MMC versus no intravesical therapy[97,101,111-118] (Tables 7, 8; Appendixes E2, F2). The doses of MMC ranged from 5 mg to 40 mg. The number of instillations varied from one to 58: three trials evaluated a single instillation,[114,117,118] two trials evaluated an induction regimen (8 instillations over 4 or 8 weeks),[97,112,116] and 4 trials evaluated maintenance regimens (ranging from 5 instillations over 1 year to 38 instillations over 2 years).[101,111-113,115,118] Duration of followup ranged from a mean of 35 months to a median of 94 months.

One trial found no difference between MMC administered as a single dose or as a maintenance regimen (5 instillations every 1 year) versus no intravesical therapy in risk of all cause-mortality (HR 1.17, 95% CI 0.89 to 1.53) or bladder cancer-specific mortality (HR 0.71, 95% CI 0.34 to 1.46).[118]

MMC was associated with decreased risk of bladder cancer recurrence versus no intravesical therapy (8 trials, RR 0.71, 95% CI 0.57 to 0.89, I^2=72%) (Figure 11).[97,101,111,112,114-117] Results were very similar using the profile likelihood method (RR 0.71, 95% CI 0.52 to 0.91). Results favored MMC in all trials, including two trials of single dose therapy (RR 0.43, 95% CI 0.14 to 1.31),[114,117] as well as in other stratified and sensitivity analyses. Restricting the analysis to trials of multiple MMC instillations gave results similar to the overall pooled estimate (6 trials, RR 0.80 95% CI 0.67 to 0.95, I^2=50%).[97,101,111,112,115,116] Findings were also consistent in a ninth trial that could not be pooled, which found MMC associated with greater recurrence-free survival over two years (log-rank test, p=0.01) and lower annual recurrence rate over two years (42% vs. 82%, p=0.001).[118]

MMC was associated with lower risk than no intravesical therapy of bladder cancer progression, but the difference was not statistically significant (5 trials, RR 0.68, 95% CI 0.39 to 1.20, I^2=0%) (Figure 12).[97,113-115,117] Excluding two trials of single dose therapy resulted in a similar estimate (3 trials, RR 0.67, 95% CI 0.38 5to 1.20, I^2=0%).[114,117] One trial that did not provide poolable data also reported no statistically significant difference in risk of progression with either single dose or maintenance MMC.[118]

Doxorubicin

Eleven trials (reported in 13 publications) evaluated doxorubicin versus no intravesical therapy[95,101,112,113,115,116,119-125] (Tables 9, 10; Appendixes E2, F2). The doses of doxorubicin ranged from 10 mg to 80 mg; the most commonly studied doses were 20 mg, 30 mg, and 50 mg. The number of instillations varied from 1 to 58: 2 trials used a single instillation,[95,125] 1 trial used an induction regimen (8 instillations over 4 weeks),[112,116] and 1 trial used a regimen of 6 instillations in the 2 weeks prior to TURBT.[123] The remaining trials used maintenance regimens (ranging from 15 instillations over 1 year to 58 instillations over 2 years). Duration of followup for recurrence ranged from 6 months to a median of 5 years, with followup as long as 10.9 years for mortality.

Two trials found no clear differences between maintenance regimens of doxorubicin versus no intravesical therapy in risk of all-cause or bladder cancer-specific mortality after 10 years of followup. In one trial, doxorubicin was associated with increased risk of all-cause mortality (30% vs. 17%, RR 1.83, 95% CI 0.78 to 4.28) and disease-specific mortality (6.5% vs. 2.8%, RR

2.35, 95% CI 0.25 to 21.6), but estimates were imprecise and the differences were not statistically significant.[120] A second trial found no differences between doxorubicin versus no intravesical therapy in all-cause mortality (54% vs. 58%; RR 0.93, 95% CI 0.73 to 1.18) or deaths due to bladder or other primary cancers (18% vs. 18%; RR 0.97, 95% CI 0.54 to 1.76).[121]

Doxorubicin was associated with decreased risk of bladder cancer recurrence versus no intravesical therapy (10 trials, RR 0.80, 95% CI 0.72 to 0.88, I^2=46%%) (Figure 13).[95,101,112,115,116,119-121,123,124] Results were similar using the profile likelihood method. Findings were also similar in sensitivity and stratified analyses. The only trial that found no difference in risk of recurrence used doses of doxorubicin (10 to 80 mg) that varied depending on the patient's bladder capacity (RR 0.94, 95% CI 0.79 to 1.13).[115] Excluding one trial of single instillation therapy (RR 0.89, 95% CI 0.63 to 1.01)[95] had no effect on the pooled estimate and did not reduce heterogeneity (9 trials, RR 0.79, 95% CI 0.71 to 0.87, I^2=49%). One trial that did not provide poolable data also found a single instillation with doxorubicin associated with improved recurrence-free survival at a median followup of 41 months (log-rank test, p=0.0026).[125]

There was no difference between doxorubicin versus no intravesical therapy in risk of bladder cancer progression (5 trials, RR 1.03, 95% CI 0.72 to 1.46, I^2=0.0%).[113,115,119,120,122] Findings were similar in sensitivity and subgroup analyses.

Epirubicin

Ten trials (reported in 11 publications) evaluated epirubicin versus no intravesical therapy (Tables 11, 12; Appendixes E2, F2).[103,119,126-134] The doses of epirubicin ranged from 20 mg to 100 mg, with 50 mg and 80 mg the most commonly studied dosages. The number of instillations varied from 1 to 24: 5 trials used a single instillation,[126-128,131,132] 1 trial evaluated 2 instillations over 2 days,[134] 2 trials used an induction regimen (6 instillations over 6 weeks) followed by up to 7 additional maintenance doses over 2 years for recurrence-free patients,[103,130] and 3 trials used maintenance regimens (ranging from 18 instillations over 1 year to 24 instillations over 2 years).[119,126,129] Duration of followup ranged from a median of 20 months to 72 months.

Epirubicin was associated with reduced risk of bladder cancer recurrence versus no intravesical therapy (9 trials, RR 0.63, 95% CI 0.53 to 0.75, I^2=64%) (Figure 14).[103,119,126-132] Findings were similar in sensitivity and stratified analyses. One trial which didn't report poolable data for recurrence reported longer median recurrence-free survival for epirubicin, 50 mg (2 instillations) compared with no adjuvant therapy (38 months vs. 13 months, log-rank test, p=0.05).[134]

Epirubicin was also associated with reduced risk of bladder cancer progression versus no intravesical therapy, but the difference was not statistically significant (8 trials, RR 0.79, 95% CI 0.48 to 1.30, I^2=27%) (Figure 15).[103,119,126,127,129-131,134] In stratified analyses, there was no clear pattern to suggest that longer duration of therapy was associated with decreased risk of progression. An outlier trial found a maintenance regimen of epirubicin 20 mg (24 instillations over 2 years) associated with an increased risk in progression (21% [9/43] vs. 3% [1/32]; RR 6.70, 95% CI 0.89 to 50.22), though the difference was not statistically significant and the estimate was very imprecise.[129]

No trial evaluated effects of intravesical epirubicin on overall or bladder cancer-specific mortality.

Gemcitabine

One trial (n=248) evaluated a single instillation of gemcitabine versus placebo (Tables 13, 14; Appendixes E2, F2).[135] It found no difference between gemcitabine and placebo in risk of bladder cancer recurrence after 24 months (RR 0.98, 95% CI 0.70 to 1.36). Estimates for progression (RR 3.00, 95% CI 0.32 to 28.4), all-cause mortality (2.4% vs. 4.8%, RR 0.50, 95% CI 0.13 to 2.00), and bladder cancer-mortality (0.8% vs. 0.8%, RR 1.00, 95% CI 0.06 to 15.81) were very imprecise.

Interferon Alpha

Three trials (reported in 4 publications) evaluated interferon alpha versus no intravesical therapy (Tables 13, 14; Appendixes E2, F2).[132,133,136,137] The doses of interferon alpha ranged from 40 million units (MU) to 80 MU. One trial evaluated a single instillation[132,133] and two trials evaluated maintenance regimens (21 or 22 instillations over 1 year).[136,137] Duration of followup ranged from 2 years to a median of 72 months.

One trial found no difference between interferon alpha and placebo in risk of overall and bladder cancer-specific mortality (5% [2/39] vs. 5% [2/39], RR 1.00, 95% CI 0.15 to 6.75).[137]

Interferon alpha was associated with decreased risk of bladder cancer recurrence versus no intravesical therapy, but the difference was not statistically significant (3 trials, RR 0.75, 95% CI 0.53 to 1.06, I^2=50%) (Figure 16).[132,136,137] Results were similar using the profile likelihood method. One trial found interferon alpha associated with decreased risk[136] and two trials no effect.[132,137] The trial that found interferon alpha associated with decreased risk of bladder cancer evaluated interferon alpha using doses of 40, 60, and 80 MU; only the 80 MU dose was associated with decreased risk of recurrence (RR 0.35, 95% CI 0.14 to 0.89).[136] The other two trials evaluated doses of 60 MU or less and one[132,133] evaluated single instillation therapy.

Interferon alpha was associated with lower risk of bladder cancer progression versus no intravesical therapy (2 trials, RR 0.33, 95% CI 0.14 to 0.76, I^2=0.0%) (Figure 17).[136,137]

Interferon Gamma

One trial (n=54) found induction therapy (8 instillations over 8 weeks) with interferon-gamma 21 MU (8 instillations over 8 weeks) patients with recurrent and/or multiple TaG2, TaG3, or T1/G2-G3 tumors associated with decreased risk of bladder cancer recurrence versus no intravesical therapy (62% vs. 86%, RR 0.72, 95% CI 0.51 to 1.01) (Tables 13, 14; Appendixes E2, F2).[138] There was no difference in risk of bladder cancer progression (3.8% vs. 3.6%, RR 1.08, 95% CI 0.07 to 16.4) after a median followup of 9 months, but the estimate was imprecise. The trial did not report mortality.

Thiotepa

Five trials (reported in 6 publications) evaluated thiotepa versus no intravesical therapy (Tables 13, 14; Appendixes E2, F2).[96,98-100,139,140] The doses of thiotepa ranged from 30 mg to 90 mg, with the most commonly studied dose 30 mg. The number of instillations varied from 1 to 32: 2 trials used a single instillation[96,98,99] and 4 trials used maintenance regimens (ranging from 5 instillations over 1 year to 32 instillations over 2 years).[98-100,139,140] Duration of followup ranged from a mean of 14.9 months to a median of 8.75 years.

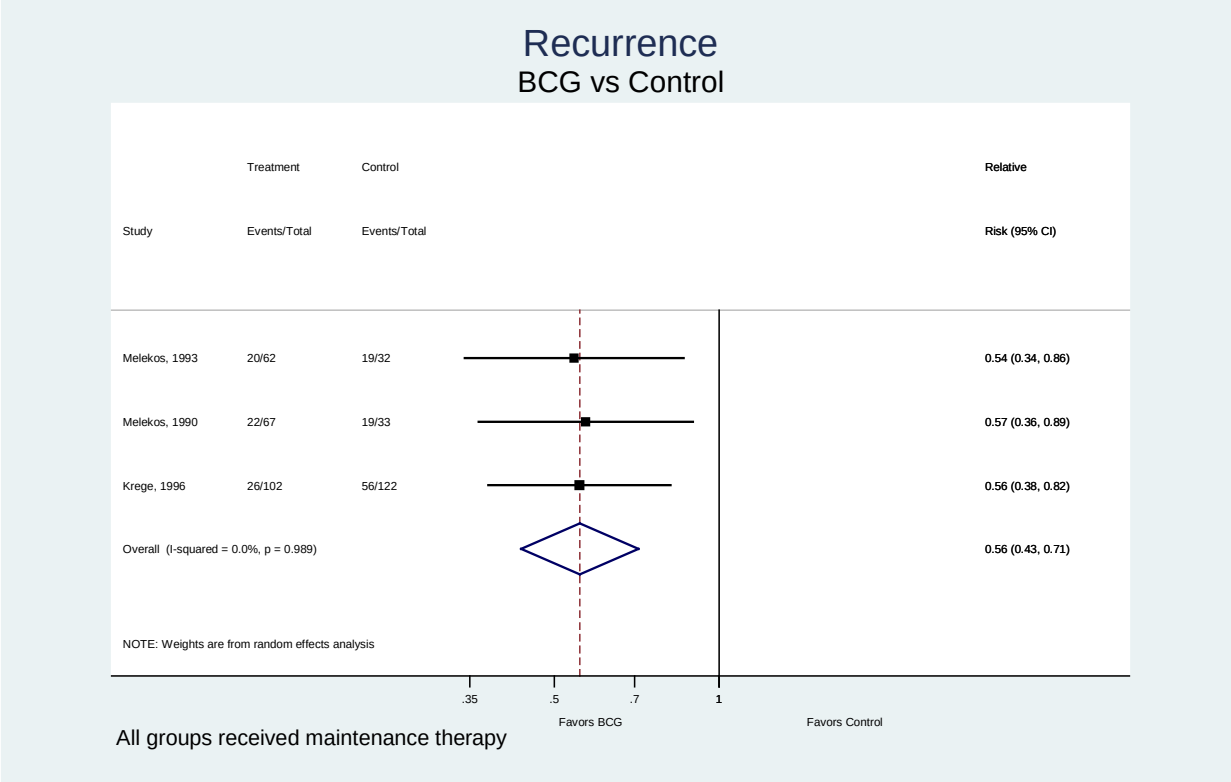
One trial found no difference between thiotepa 30 mg five instillations or single dose versus no intravescial therapy in risk of all-cause mortality (HR 0.99, 95% CI 0.56 to 1.82); estimates for bladder cancer-specific mortality favored no intravesical therapy, but were imprecise (HR

1.61 [95% CI 0.59 to 4.39] and HR 1.73 [95% CI 0.65 to 4.63] for multi-instillation and single dose regimens, respectively).[98,99] Estimates for the combined outcome of bladder cancer progression or bladder cancer mortality were similar, but results were not reported separately for bladder cancer progression alone.

Thiotepa was associated with decreased risk of bladder cancer recurrence versus no intravesical therapy, but the difference was not statistically significant (5 trials, RR 0.78, 95% CI 0.58 to 1.06, I^2=69%) (Figure 18).[96,98,100,139,140] Results were similar using the profile likelihood method. Estimates from trials that evaluated a single instillation (2 trials, RR 0.83, 95% CI 0.44 to 1.56, I^2=83%)[96,98] and multiple instillations (4 trials, RR 0.74, 95% CI 0.49 to 1.12, I^2=70%)[99,100,139,140] were similar. Stratification according to duration of followup eliminated statistical heterogeneity. Trials with followup greater than 1 year found thiotepa associated with decreased risk of recurrence (3 trials that evaluated 4 regimens, RR 0.55, 95% CI 0.42 to 0.73, I^2=0%),[96,139,140] but there was no difference in trials that evaluated regimens at 1 year or less (2 trials that evaluated 3 regimens, RR 1.10, 95% CI 0.90 to 1.34, I^2=0%).[98,100] Other sensitivity and stratified analyses had no effect on pooled estimates.

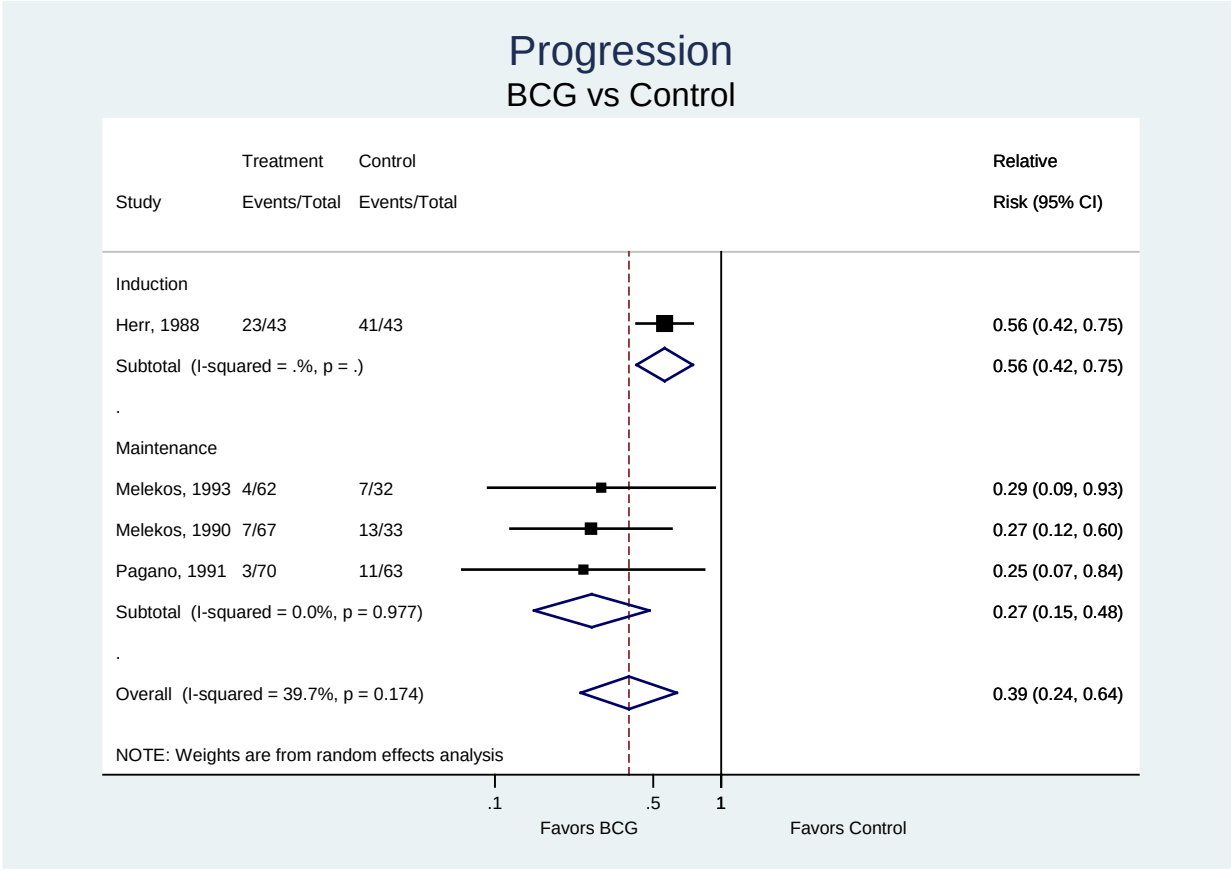
There was no difference in risk of bladder cancer progression of stage (4.0% vs. 5.8%, RR 0.69, 95% CI 0.16 to 2.97), grade (6.7% vs. 7.2%, RR 0.92, 95% CI 0.28 to 3.04), or both stage and grade (2.7% vs. 2.9%, RR 0.92, 95% CI 0.13 to 6.36) in one study.[100]

Figure 9. Meta-analysis of bacillus Calmette-Guérin versus no intravesical therapy: Risk of recurrence



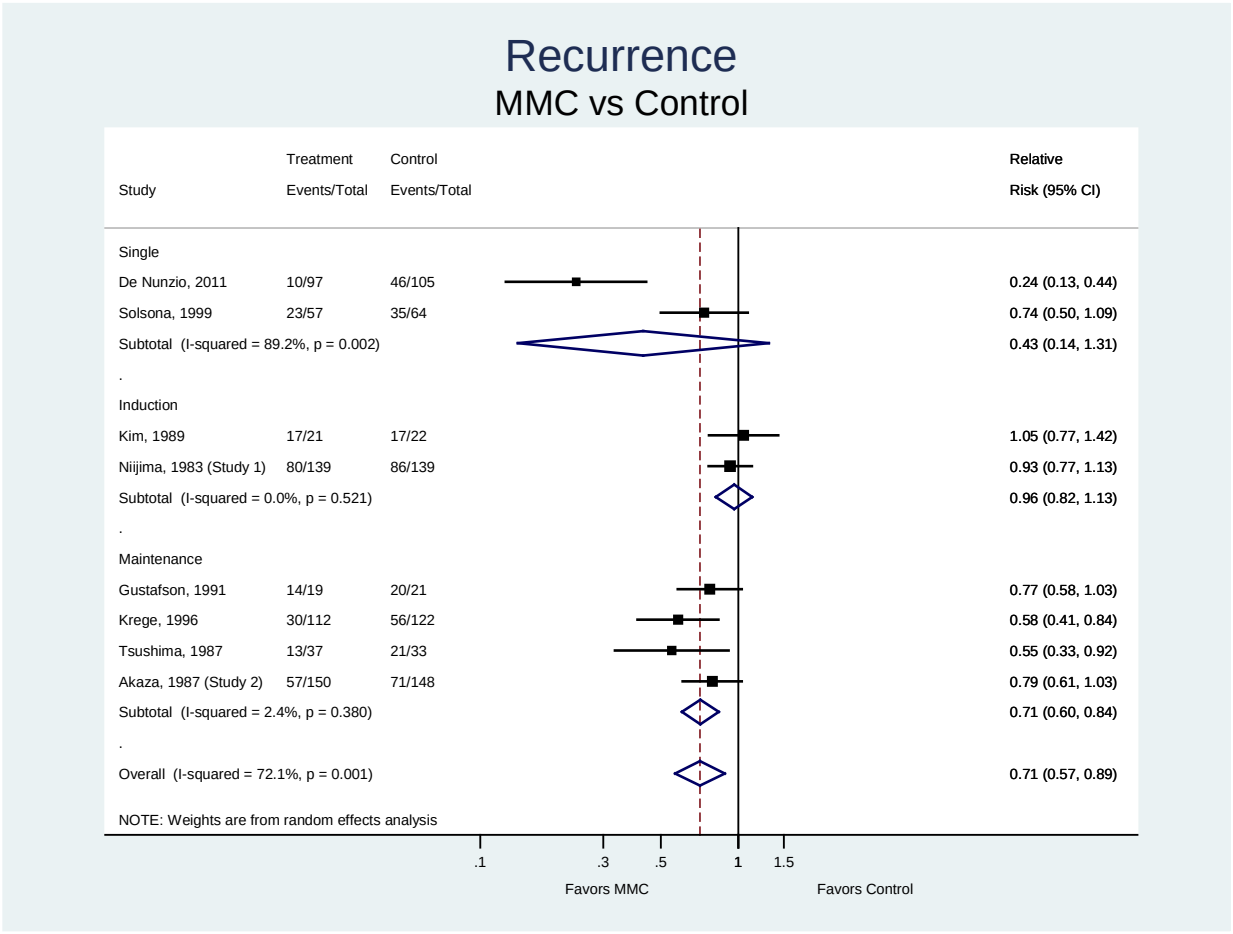
BCG = bacillus Calmette-Guérin; CI = confidence interval

Figure 10. Meta-analysis of bacillus Calmette-Guérin versus no intravesical therapy: Risk of progression



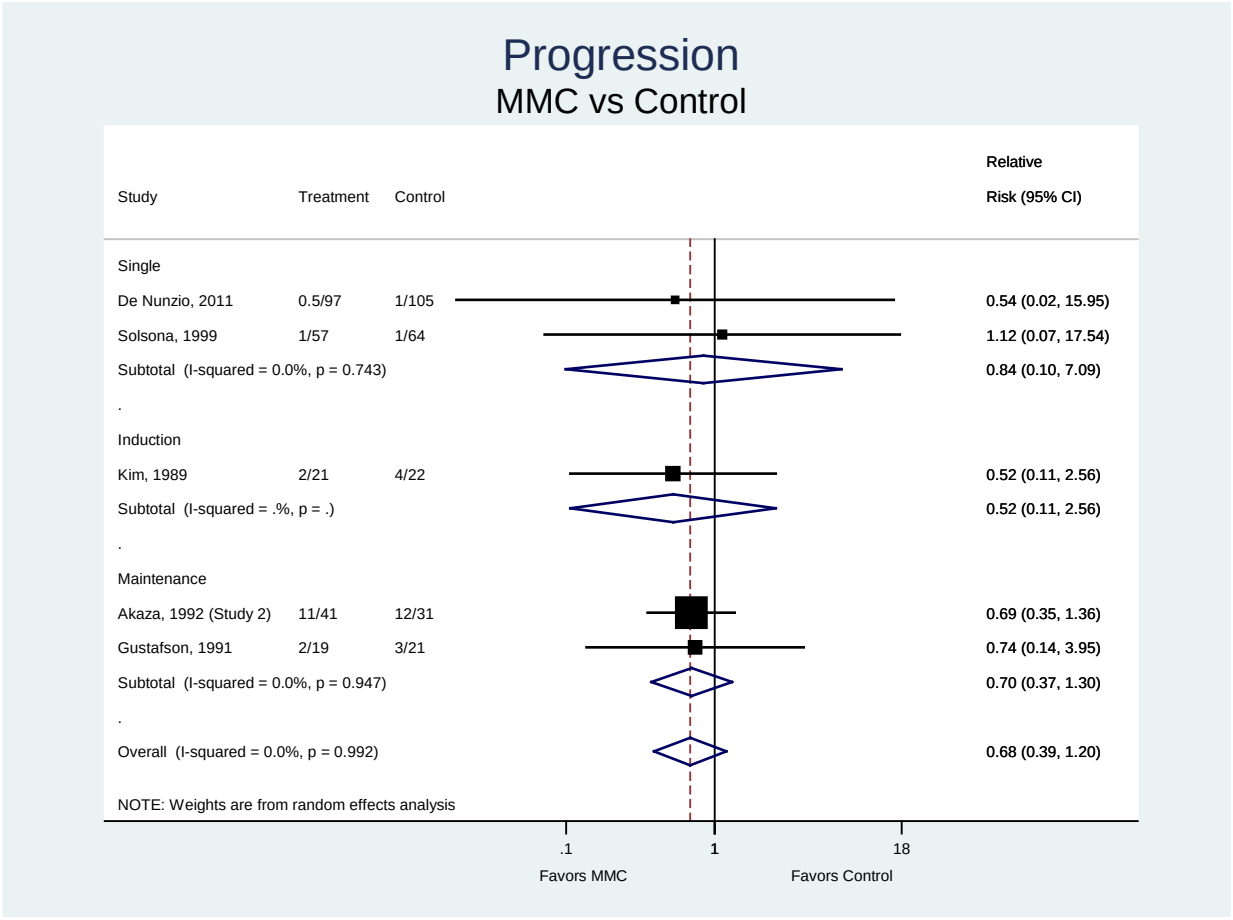
BCG = bacillus Calmette-Guérin; CI = confidence interval

Figure 11. Meta-analysis of MMC versus no intravesical therapy: Risk of recurrence



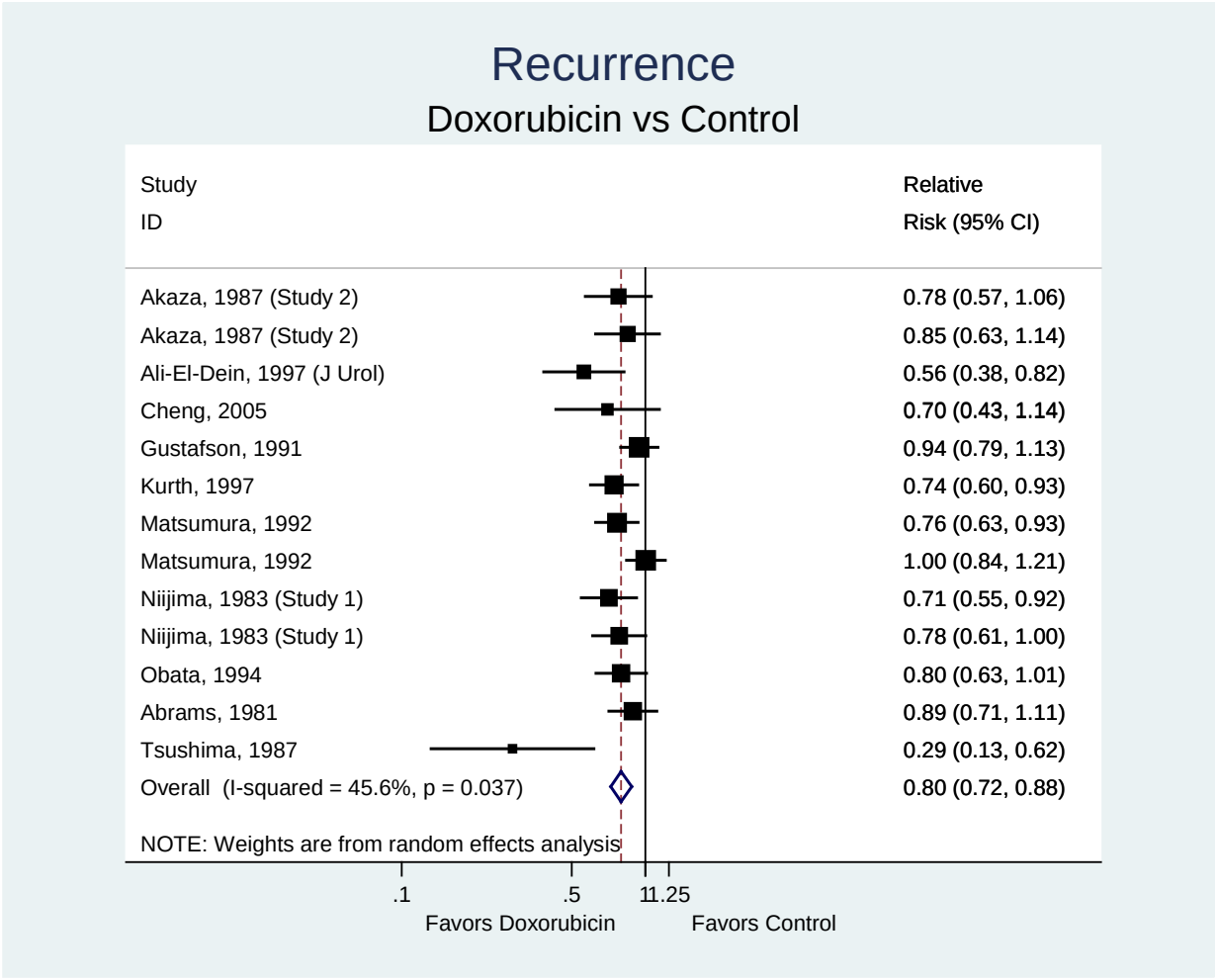
CI = confidence interval; MMC = Mitomycin C

Figure 12. Meta-analysis of MMC versus no intravesical therapy: Risk of progression



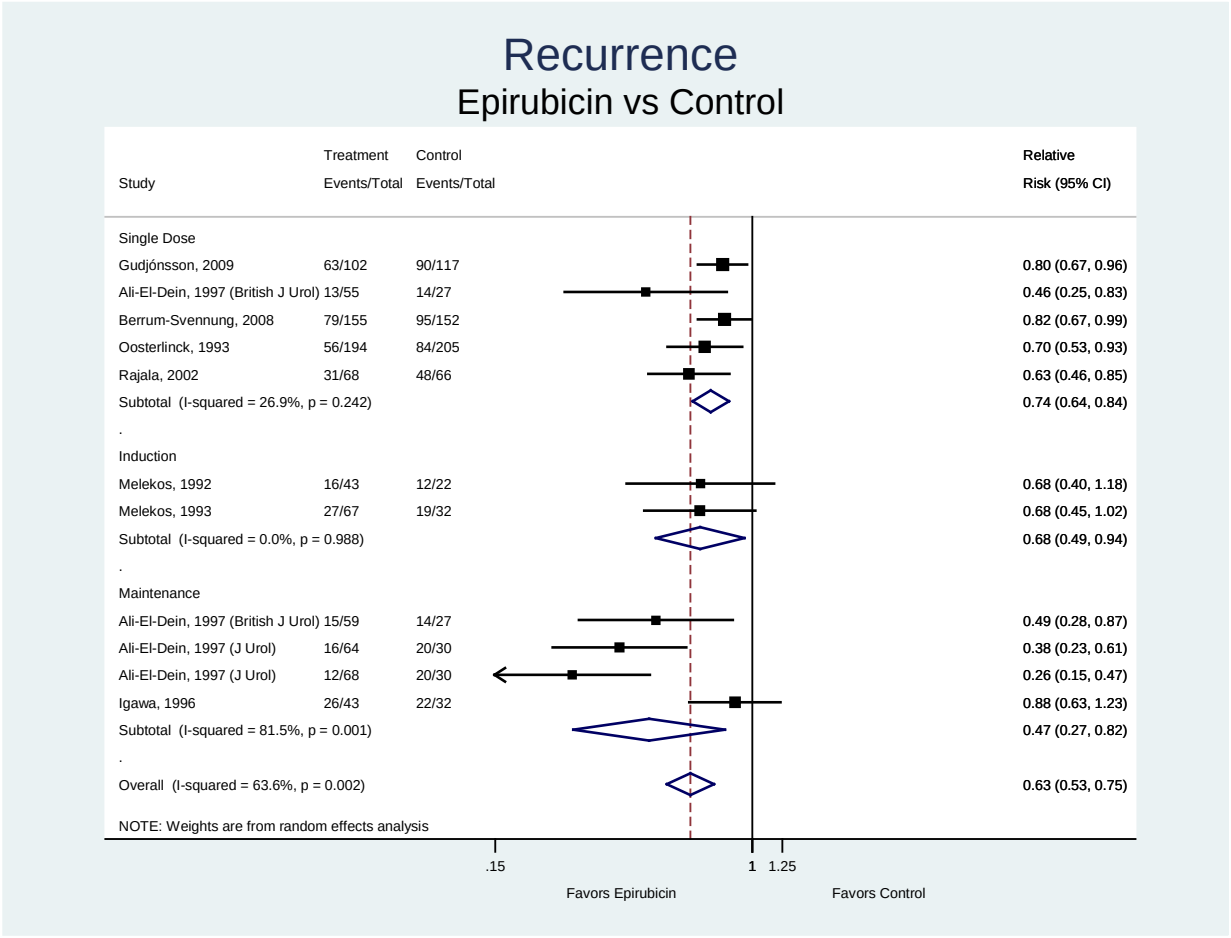
CI = confidence interval; MMC = Mitomycin C

Figure 13. Meta-analysis of doxorubicin versus no intravesical therapy: Risk of recurrence



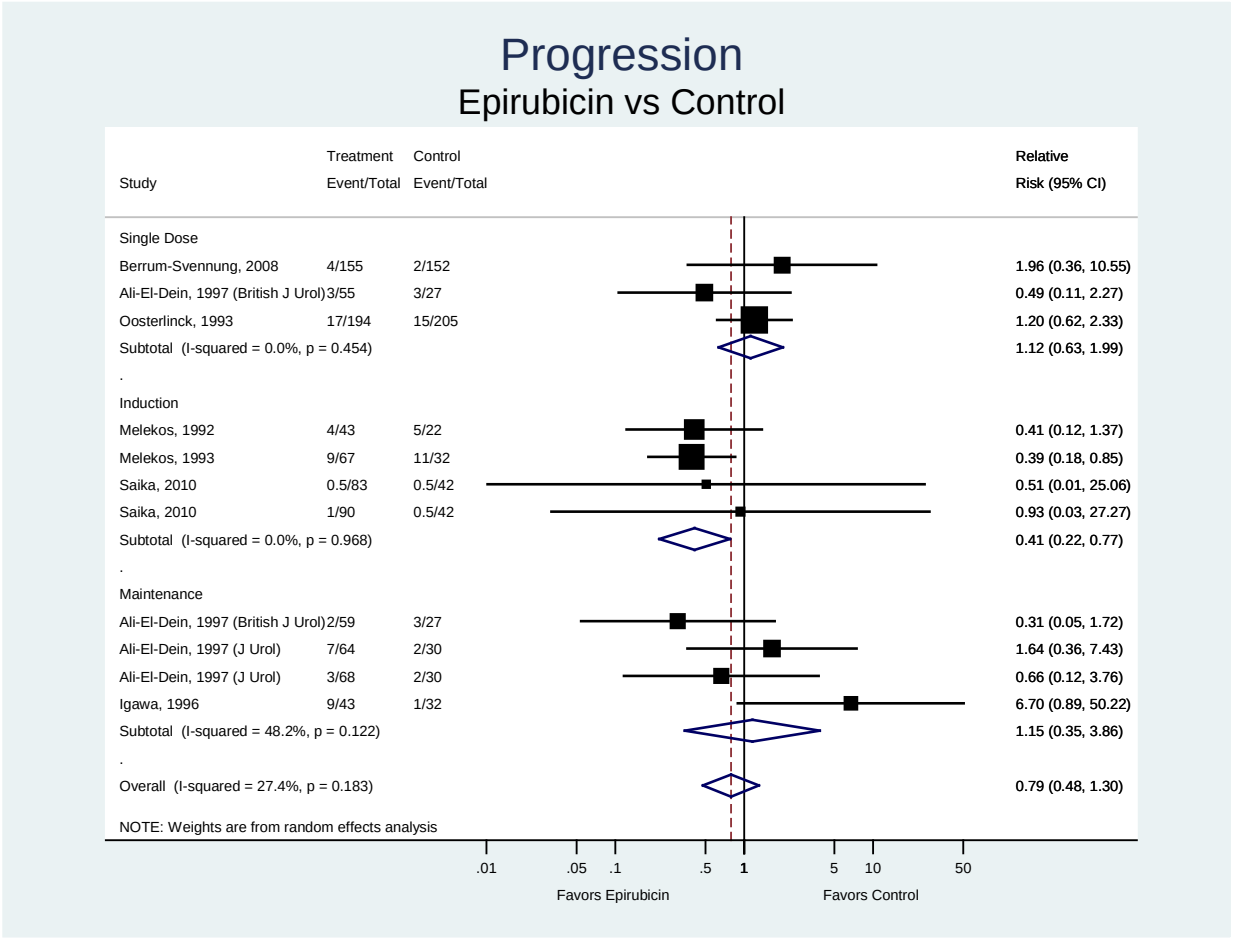
CI = confidence interval
Note: Akaza, 1987 (Study 2), Matsumura, 1992, Niijima, 1983 (Study 1) reported effects for two different regimens.

Figure 14. Meta-analysis of epirubicin versus no intravesical therapy: Risk of recurrence



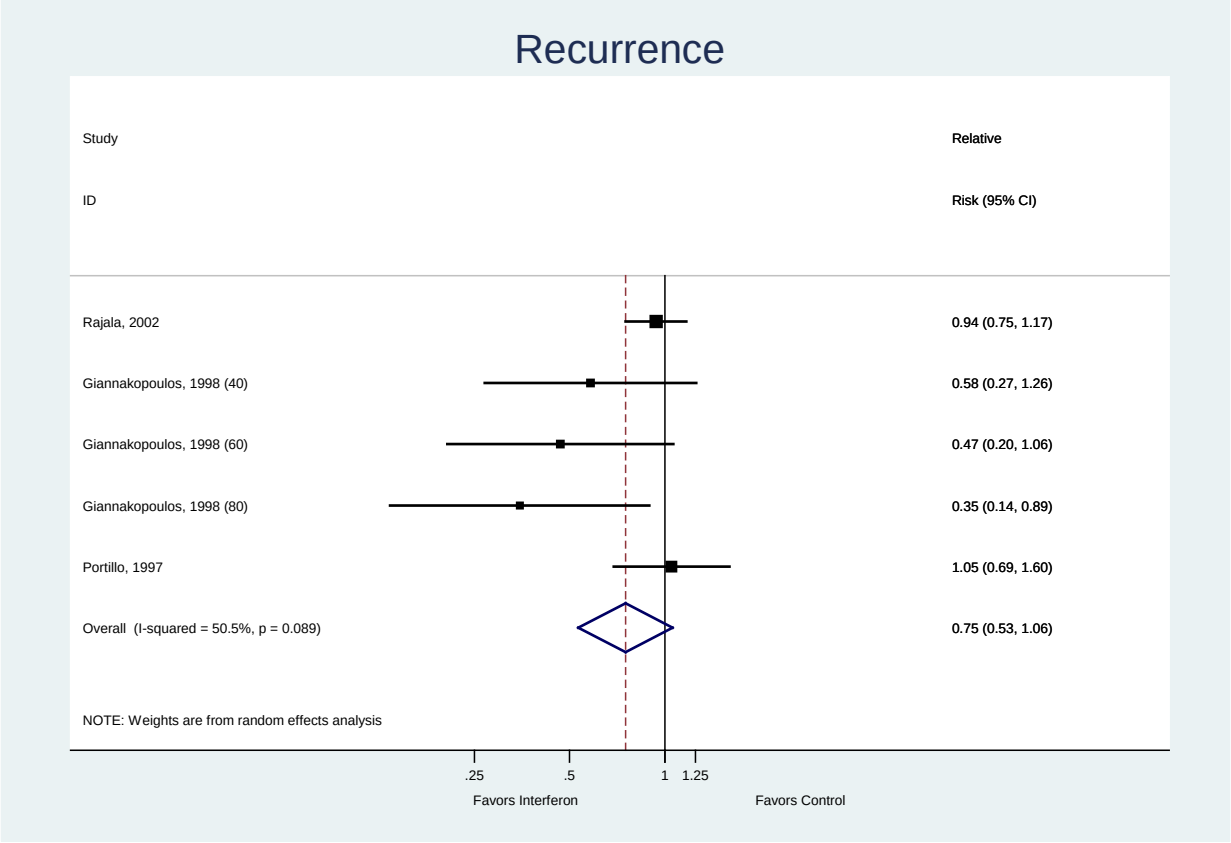
CI = confidence interval
Note: Ali-El-Dein, 1997 (Brittish J Urol), Ali-El-Dein, 1997 (J Urol) each reported effects for two different regimens.

Figure 15. Meta-analysis of epirubicin versus no intravesical therapy: Risk of progression



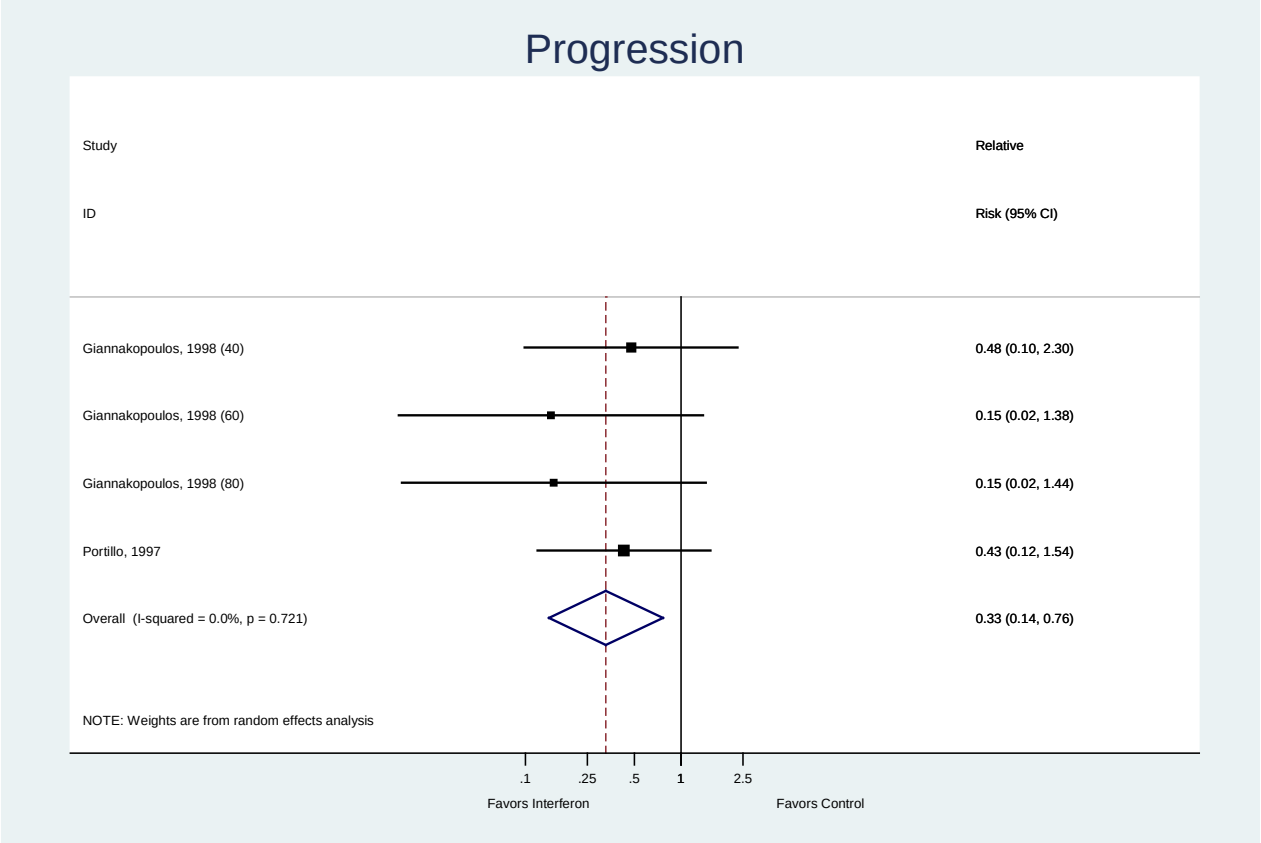
CI = confidence interval
Note: Ali-El-Dein, 1997 (Brittish J Urol), Ali-El-Dein, 1997 (J Urol), Saika, 2010 each reported effects for two different regimens.

Figure 16. Meta-analysis of interferon alpha-2b versus no intravesical therapy: Risk of recurrence



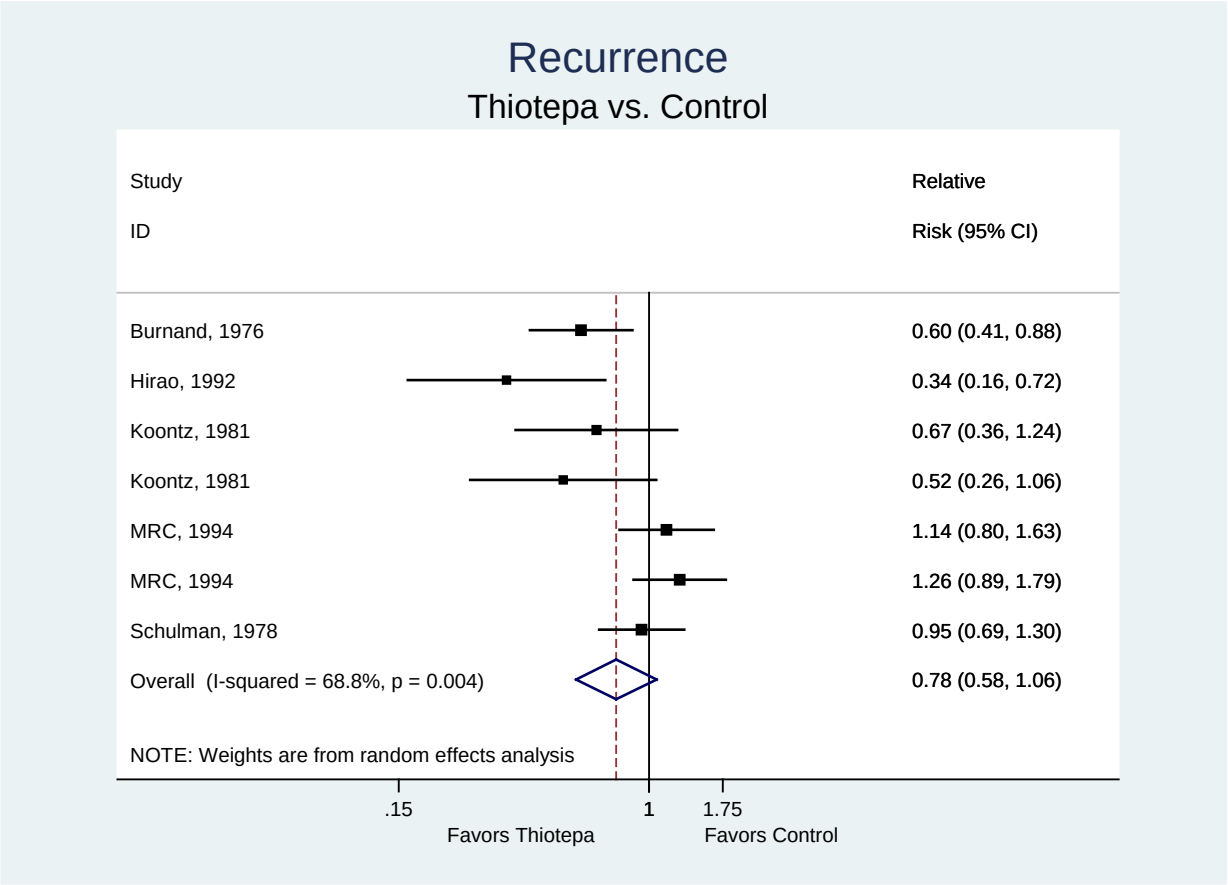
CI = confidence interval

Figure 17. Meta-analysis of interferon alpha-2b versus no intravesical therapy: Risk of progression



CI = confidence interval

Figure 18. Meta-analysis of thiotepa versus no intravesical therapy: Risk of recurrence



CI = confidence interval
Note: Koontz, 1981 and MRC, 1994 each reported effects for two different regimens.

Key Question 3a. What is the comparative effectiveness of various chemotherapeutic or immunotherapeutic agents, as monotherapy or in combination?

Key Points

BCG Versus MMC

- There were no differences between BCG versus MMC in risk of bladder cancer recurrence overall (10 trials, RR 0.95, 95% CI 0.81 to 1.11, I^2=67%), but BCG was associated with decreased risk in the subgroup of trials that evaluated maintenance regimens (5 trials, RR 0.79, 95% CI 0.71 to 0.87, I^2=0%). There was no difference in risk of all-cause (7 trials, RR 0.94, 95% CI 0.83 to 1.06, I^2=0%) or bladder cancer-specific mortality (5 trials, RR 0.77, 95% CI 0.54 to 1.10, I^2=0%), or progression (7 trials, RR 0.88, 95% CI 0.66 to 1.17, I^2=18%) (SOE: moderate for all-cause mortality, bladder cancer-specific mortality, and progression; low for recurrence).
- There were no differences between BCG versus BCG plus MMC given sequentially in risk of all-cause (1 trial, RR 1.57, 95% CI 0.67 to 3.71) or bladder cancer-specific

mortality (2 trials, RR 1.10, 95% CI 0.50 to 2.38, I^2=17%), bladder cancer recurrence (4 trials, RR 1.03, 95% CI 0.70 to 1.52, I^2=75%), progression (3 trials, RR 0.87, 95% CI 0.40 to 1.91, I^2=22%), or cystectomy (4 trials, RR 0.87, 95% CI 0.41 to 1.84, I^2=0%) (SOE: low for mortality, recurrence, progression, and cystectomy).

- There were no differences between BCG plus MMC administered sequentially versus MMC in risk of all-cause (2 trials, RR 1.53, 95% CI 0.72 to 1.74 and RR 0.95, 95% CI 0.71 to 1.30) or bladder cancer mortality (2 trials, RR 0.64, 95% CI 0.22 to 1.88 and RR 0.95, 95% CI 0.45 to 1.56), bladder cancer recurrence (2 trials, RR 0.88, 95% CI 0.75 to 1.03, I^2=0%), or progression (2 trials, RR 0.82 [95% CI 0.40 to 1.68] and RR 1.28 [95% CI 0.35 to 4.61]) (SOE: low).

BCG Versus Doxorubicin

- BCG was associated with decreased risk of bladder cancer recurrence versus doxorubicin (2 trials [RR 0.31, 95% CI 0.16 to 0.61] and RR 0.75 [95% CI 0.64 to 0.88]), but there were no differences in risk of all-cause mortality (2 trials, RR 0.40 [95% CI 0.01 to 12] and RR 1.00 [95% CI 0.71 to 1.37]), bladder cancer progression (1 trial, RR 0.20, 95% CI 0.02 to 1.72) (SOE: low for mortality, recurrence progression, and cystectomy).

BCG Versus Epirubicin

- BCG was associated with reduced risk of bladder cancer recurrence versus epirubicin, but statistical heterogeneity was high (5 trials, RR 0.54, 95% CI 0.40 to 0.74, I^2=76%). Estimates favored BCG for all-cause (3 trials, RR 0.72, 95% CI 0.44 to 1.19, I^2=87%) and bladder cancer-specific mortality (3 trials, RR 0.72, 95% CI 0.25 to 2.08, I^2=80%), and bladder cancer progression (5 trials, RR 0.60, 95% CI 0.36 to 1.01, I^2=47%), but differences were not statistically significant (SOE: moderate for recurrence, low for all-cause mortality, bladder cancer-specific mortality, and progression).
- There was no difference between BCG versus BCG plus epirubicin administered sequentially in risk of bladder cancer recurrence (3 trials, RR 1.25, 95% CI 0.92 to 1.69, I^2=0%). BCG was associated with increased risk of bladder cancer progression (3 trials, RR 1.92, 95% CI 0.73 to 5.07, I^2=0%), but the difference was not statistically significant (SOE: low).
- One trial found no differences between BCG versus epirubicin plus interferon alpha-2b in risk of bladder cancer mortality (RR 0.79, 95% CI 0.32 to 1.63) or progression-free survival, though BCG was associated with decreased risk of bladder cancer recurrence (RR 0.66, 95% CI 0.51 to 0.85) (SOE: low).

BCG Versus Gemcitabine

- There were no differences between BCG versus gemcitabine in risk of all-cause mortality (1 trial, RR 1.20, 95% CI 0.04 to 34), progression (2 trials, RR 1.11 [95% CI 0.53 to 2.34] and RR 0.52 [95% CI 0.13 to 2.06]) or quality of life (1 trial) (SOE: low for mortality, quality of life, and progression).
- Evidence from three trials was insufficient to determine effects of BCG versus gemcitabine on risk of bladder recurrence, due to clinical heterogeneity and inconsistent findings (RR 1.67 [95% CI 1.21 to 2.29], RR 0.53 [95% CI 0.28 to 1.01], and RR 0.76 [95% CI 0.44 to 1.90]) (SOE: insufficient).

- There were no differences between BCG versus BCG plus gemcitabine administered sequentially in risk of bladder cancer recurrence (1 trial, RR 0.86, 95% CI 0.49 to 1.51) or progression (1 trial, RR 1.18, 95% CI 0.30 to 4.61) (SOE: low for progression and recurrence).

BCG Versus Interferon

- BCG was associated with reduced risk of bladder cancer recurrence versus interferon alpha-2a (1 trial, RR 0.57, 95% CI 0.39 to 0.82) but the difference in risk of bladder cancer progression was not statistically significant (1 trial, RR 0.69, 95% CI 0.25 to 1.92) (SOE: low for recurrence, and progression).
- In patients pretreated with MMC, BCG was associated with reduced risk of bladder cancer recurrence versus alternating BCG plus interferon alpha-2b (1 trial, RR 0.42, 95% CI 0.30 to 0.59) (SOE: low).
- Differences between BCG versus coadministration of BCG and interferon alpha-2b in risk of bladder cancer recurrence (1 trial, RR 0.88, 95% CI .71 to 1.08) or progression (1 trial, RR 0.76, 95% CI 0.17 to 3.30) did not reach statistical significance (SOE: low for recurrence and progression).

BCG Versus Thiotepa

- Two trials found maintenance therapy with BCG associated with decreased risk of recurrence versus thiotepa (RR 0.38 [95% CI 0.19 to 0.76] and RR 0.04 [95% CI 0.00 to 0.63]), but estimates for other outcomes were too imprecise to evaluate effects (SOE: low for recurrence, insufficient for progression, death, and cystectomy).

MMC Versus Doxorubicin

- There was no difference between MMC versus doxorubicin in risk of bladder cancer recurrence (6 trials, RR 1.00, 95% CI 0.82 to 1.22, I^2=44%), but MMC was associated with a nonstatistically significant trends towards decreased risk of bladder cancer progression (4 trials, RR 0.63, 95% CI 0.37 to 1.08, I^2=21%) (SOE: low).

MMC Versus Epirubicin

- There was no difference between MMC versus epirubicin in risk of bladder cancer recurrence in one trial (RR 1.16, 95% CI 0.52 to 2.58) (SOE: low).

MMC Versus Gemcitabine

- In one trial, MMC was associated with no difference in risk of bladder cancer progression (p=0.29). MMC was associated with increased risk of recurrence but the difference was not statistically significant (RR 1.64, 95% CI 0.64 to 4.19) (SOE: low).

MMC Versus Interferon Alpha

- One trial found no difference between MMC versus interferon alpha in risk of bladder cancer recurrence (RR 0.77, 95% CI 0.58 to 1.01) or bladder cancer progression (RR 1.38, 95% CI 0.49 to 3.88) (SOE: low).

MMC Versus Interferon Gamma

- MMC was associated with increased risk of bladder cancer recurrence versus interferon-gamma in one trial (RR 1.61, 95% CI 0.97 to 2.67) (SOE: low).

MMC Versus Thiotepa

- Two trials found no difference between MMC versus thiotepa in risk of recurrence (RR 1.76 [95% CI 0.36 to 8.70] and RR 1.14 [95% CI 0.60 to 2.16]) (SOE: low).

Doxorubicin Versus Epirubicin

- Doxorubicin was associated with increased risk of bladder cancer recurrence versus epirubicin (3 trials, RR 1.56, 95% CI 1.08 to 2.22, I^2=0%); the difference in risk of progression was not statistically significant (1 trial, RR 1.32, 95% CI 0.50 to 3.47) (SOE: low for recurrence and progression).

Doxorubicin Versus Thiotepa

- There was no statistically significant difference between doxorubicin versus thiotepa in risk of bladder cancer recurrence (RR 1.22, 95% CI 0.76 to 1.94). Estimates from one trial for progression (RR 2.11, 95% CI 0.40 to 11.06), noncancer mortality (RR 0.35, 95% CI 0.01 to 8.45), and cancer-specific mortality (RR 3.17, 95% CI 0.13 to 76.1) were very imprecise (SOE: low for recurrence; SOE: insufficient for progression, noncancer mortality, and cancer-specific mortality).

Epirubicin Versus Interferon Alpha

- Epirubicin was associated with decreased risk of bladder cancer recurrence versus interferon alpha in one trial (RR 0.67, 95% CI 0.49 to 0.91) (SOE: low).

Detailed Synthesis

Fifty-four trials (reported in 66 publications) compared effects of intravesical therapy using one drug versus another (Tables 6, 7, 8, 9, 10, 11, 12; Appendixes E3, F2).[101,103,111-113,115,116,119,132,133,141-196] Fourteen trials evaluated BCG versus MMC,[111,147-165] two trials BCG and MMC versus MMC,[166-169] four trials BCG versus doxorubicin,[170-172] nine trials BCG versus epirubicin,[103,173-181] one trial BCG versus epirubicin plus interferon,[182,183] four trials BCG versus gemcitabine,[184-187] three trials BCG versus interferon alpha,[188-190] and one trial BCG versus thiotepa.[172] The comparison drugs were administered alone or as part of sequential therapy with BCG. Thirteen trials (reported in 15 publications) evaluated comparisons of intravesical therapies that did not involve BCG.[112,113,115,116,119,132,133,141,191-196] Four trials evaluated MMC versus doxorubicin,[112,113,115,116,191] one trial MMC versus epirubicin,[192] one trial MMC versus interferon alpha,[193] one trial MMC versus interferon-gamma,[141] one trial MMC versus gemcitabine,[194] three trials doxorubicin versus epirubicin,[119,195,196] one trial doxorubicin versus thiotepa,[172] and one trial epirubicin versus interferon alpha.[132,133]

Samples sizes ranged from 41 to 957 and duration of followup from 15 months to 9 years. Mean age ranged from 52.1 to 74 years and the proportion of patients who were male ranged from 55 to 97 percent. Five trials excluded patients with G3 tumors and 7 trials excluded patients with CIS lesions. In the other trials, the proportion with G3 tumors ranged from 0 to 73 percent and the proportion with CIS lesions ranged from 0 to 100 percent. Thirty-four trials focused on

patients with primary tumors and 29 trials focused on patients with recurrent tumors. Two trials were rated high risk of bias,[186,196] 41 trials medium risk of bias,[103,111-113,115,116,119,132,133,141,147-154,156-169,171-181,183,185,187-195] and 4 trials low risk of bias (Appendix F2).[155,170,182,184] Two trials reported blinding of outcomes assessors;[133 ,158] no trial blinded care provider or patients. Other methodological limitations included inadequate description of randomization and allocation concealment and high attrition or failure to report attrition. Results are summarized in Table 16.

BCG Versus MMC

Ten trials (reported in 16 publications) randomized patients to BCG versus MMC[111,147-161] and four trials randomized patients to BCG versus BCG plus MMC given sequentially (Table 6; Appendixes E3, F2).[162-165] The dose of BCG ranged from 13.5 mg to 120 mg and the dose of MMC from 20 mg to 40 mg with the number of instillations ranging from 6 weekly instillations[148,154] to 42 weekly instillations administered over 3 years.[154] No trial compared single instillation therapy with BCG versus MMC and no trial of MMC utilized an "optimized" regimen.[197,198]

There was no difference between BCG versus MMC in risk of bladder cancer recurrence (10 trials, RR 0.95, 95% CI 0.81 to 1.11, I^2=677%) (Figure 19).[111,147,151,153-156,159,158,161] However, statistical heterogeneity was present. Stratification of trials according to whether they evaluated maintenance or induction regimens reduced statistical heterogeneity. BCG was associated with decreased risk of bladder cancer recurrence in trials that evaluated maintenance regimens (5 trials, RR 0.79, 95% CI 0.71 to 0.87, I^2=0%),[147,151,153,111,161] but not in trials that evaluated induction regimens (4 trials, RR 1.22, 95% CI 0.99 to 1.51, I^2=50%).[111,154,156,159]

There were no differences between BCG versus MMC in all-cause (7 trials, RR 0.94, 95% CI 0.83 to 1.06, I^2=0%) (Figure 20)[147,151,153,155,157,159,161] or disease-specific mortality (5 trials, RR 0.77, 95% CI 0.54 to 1.10, I^2=0%) (Figure 21).[147,151,157,159,161] There were also no differences in risk of bladder cancer progression (Figure 22) (7 trials, RR 0.88, 95% CI 0.66 to 1.17, I^2=18%).[147,151,155-157,159,161] One trial (n=337) found no difference between BCG versus MMC in risk of cystectomy, but the estimate was very imprecise (RR 2.20, 95% CI 0.07 to 65).[111]

There were no differences between BCG versus BCG plus MMC given sequentially in risk of all-cause (1 trial, RR 1.57, 95% CI 0.67 to 3.71)[164] or bladder cancer mortality (Figure 23) (2 trials, RR 1.10, 95% CI 0.50 to 2.38, I^2=17%),[163,164] bladder cancer recurrence (Figure 24) (4 trials, RR 1.03, 95% CI 0.70 to 1.52, I^2=75%),[162-165] progression (Figure 25) (3 trials, RR 0.87, 95% CI 0.40 to 1.91, I^2=22%),[162-164] or cystectomy (4 trials, RR 0.87, 95% CI 0.41 to 1.84, I^2=0%).[162-165]

Statistical heterogeneity was present in the analysis of bladder cancer recurrence. Excluding one trial that compared BCG induction therapy for 6 weeks versus BCG induction therapy plus a single dose of perioperative MMC (RR 0.53, 95% CI 0.21 to 1.37)[162] (rather than sequential regimens involving multiple doses of BCG and MMC) resulted in a similar estimate and did not reduce heterogeneity (RR 1.13, 95% CI 0.75 to 1.68, I^2=79%). Estimates were also similar using the profile likelihood method, and other subgroup and other sensitivity analyses also did not reduce heterogeneity and resulted in similar findings.

BCG Plus MMC Versus MMC

Two trials (reported in four publications) compared MMC versus MMC and BCG given sequentially (Table 6; Appendixes E3, F2).[166-169] The Finnbladder study enrolled 256 patients and reported results for patients with (27%) and without CIS separately.[167-169] All patients

received 5 instillations of MMC and were then randomized to 15 additional instillations of MMC versus alternating MMC and BCG instillations over 2 years. The second trial analyzed 182 patients, of whom 36 percent had CIS.[166] Doses of BCG ranged from 50 mg to 75 mg and MMC dose from 20 mg to 40 mg. Patients received four instillations of MMC and were then randomized to 6 weekly instillations of BCG or MMC. Both trials were rated medium risk of bias.

One trial found no difference between BCG plus MMC given sequentially versus MMC alone in risk of all-cause (RR 1.53, 95% CI 0.72 to 1.74) or bladder cancer mortality (RR 0.64, 95% CI 0.22 to 1.88).[166] The other trial, which only reported mortality in patients with CIS, also found no difference in risk of all-cause (RR 0.95, 95% CI 0.71 to 1.30) or bladder cancer mortality (RR 0.95, 95% CI 0.45 to 1.56).[167]

There was no difference between BCG plus MMC given sequentially versus MMC alone in risk of bladder cancer recurrence (Figure 26) (2 trials, RR 0.88, 95% CI 0.75 to 1.03, I^2=0%).[166-168] One trial found no difference between BCG plus MMC versus MMC alone in risk of bladder cancer progression (RR 0.82, 95% CI 0.40 to 1.68).[159] The other trial also found no difference, but only reported data from the subgroup of patients with CIS (RR 1.28, 95% CI 0.35 to 4.61).[167] This trial also found no difference between BCG plus MMC given sequentially versus MMC alone in risk of cystectomy (1 trial, RR 0.20, 95% CI 0.03 to 1.57).

BCG Versus MMC Plus Doxorubicin

One small trial (n=27) of patients with CIS found no differences between BCG versus sequential therapy with MMC and doxorubicin in likelihood of complete response (RR 1.06, 95% CI 0.81 to 1.39), progression (RR 1.50, 95% CI 0.28 to 8.08), or bladder cancer mortality (RR 2.21, 95% CI 0.22 to 22.5), though estimates were imprecise.[145] BCG was associated with decreased risk of recurrence after complete response (11% vs. 52%, RR 0.18, 95% CI 0.05 to 0.72)

BCG Versus Doxorubicin

Three trials randomized patients to BCG versus doxorubicin (Table 6; Appendixes E3, F2).[170-172] The dose of BCG ranged from 80 mg to 150 mg and the dose of doxorubicin ranged from 20 mg to 50 mg. All trials administered maintenance therapy for patients randomized to doxorubicin, though treatment was limited to induction therapy in the BCG arm of one trial.[170]

One trial found no difference between BCG 150 mg versus doxorubicin in risk of all-cause mortality (all deaths were due to bladder cancer) after 3 years (RR 0.40, 95% CI 0.01 to 12), though the estimate was imprecise.[172] A second trial, in which half of the patients had CIS, found no difference between BCG 120 mg versus doxorubicin in risk of all-cause mortality after 5 years (RR 1.00, 95% CI 0.71 to 1.37).[171] Both trials found BCG associated with decreased risk of bladder cancer recurrence (13% vs. 43%, RR 0.31 [95% CI 0.16 to 0.61][172] and 61% vs. 81%, RR 0.75 [95% CI 0.64 to 0.88]).[171] One trial found no difference between BCG versus doxorubicin in risk of bladder cancer progression (RR 0.20, 95% CI 0.02 to 1.72) or cystectomy (RR 0.26, 95% CI 0.03 to 2.46).[172]

BCG Versus Epirubicin

Six trials (reported in 7 publications) randomized patients to BCG versus epirubicin[103,173-178] and three trials randomized patients to BCG versus BCG plus epirubicin given sequentially (3 studies) (Table 6; Appendixes E3, F2).[179-181] The dose of BCG ranged from 50 mg to 150 mg and

the dose of epirubicin from 40 mg to 80 mg. The number of bladder instillations ranged from 6 weekly instillations[181] to 27 over 3 years.[173]

BCG was associated with decreased risk of all-cause (Figure 27) (3 trials, RR 0.72, 95% CI 0.44 to 1.19, I^2=87%)[173,174,177] and disease-specific mortality (Figure 28) (3 trials, RR 0.72, 95% CI 0.25 to 2.08,I^2=80%)[173,174,177] versus epirubicin, but the differences were not statistically significant. Estimates were similar using the profile likelihood method. Excluding the trial[173] that used the lowest dose of BCG (50 mg, versus 81 mg in the other trials) reduced statistical heterogeneity for all-cause mortality (RR 0.92, 95% CI 0.67 to 1.25, I^2=26%), but the difference remained nonstatistically significant. Other subgroup and sensitivity analyses did not reduce statistical heterogeneity or affect findings.

BCG was associated with reduced risk of bladder cancer recurrence versus epirubicin (5 trials, 34% vs. 66%, RR 0.54, 95% CI 0.40 to 0.74, I^2=76%) (Figure 29).[103,173-176] The estimate was similar using the profile likelihood method. In stratified analyses, BCG was associated with reduced risk of recurrence in trials that excluded patients with CIS (3 trials, 33% vs. 73%, RR 0.44, 95% CI 0.36 to 0.53, I^2=25%)[173,174,176] but not in trials that included patients with CIS (2 trials, RR 0.80, 95% CI 0.60 to 1.07, I^2=0%).[103,175] Other subgroup and sensitivity analyses did not reduce statistical heterogeneity or affect findings.

BCG was also associated with decreased risk of bladder cancer progression versus epirubicin, though the difference was not quite statistically significant (5 trials, RR 0.60, 95% CI 0.36 to 1.01, I^2=47%) (Figure 30).[103,173-176] Estimates and findings were similar using the profile likelihood method. Statistical heterogeneity was reduced when one trial[176] that used a lower dose of epirubicin (40 mg, versus 50 mg in the other trials) was excluded (4 trials, RR 0.70, 95% CI 0.48 to 1.02, I^2=3%). This same trial also used the fewest number of scheduled epirubicin instillations (9 versus 11-27 in the other trials). Other sensitivity and subgroup estimates had little effect on findings.

There was no difference between BCG versus BCG plus epirubicin administered sequentially in risk of bladder cancer recurrence (Figure 31) (3 trials, RR 1.25, 95% CI 0.92 to 1.69, I^2=0%). BCG was associated with increased risk of bladder cancer progression, but the difference was not statistically significant (3 trials, RR 1.92, 95% CI 0.73 to 5.07, I^2=0%) (Figure 32).[179-181] Excluding one trial[179] of maintenance therapy with BCG versus maintenance therapy with BCG plus a single dose of perioperative epirubicin resulted in similar estimates. Trials did not report mortality.

BCG Versus Epirubicin Plus Interferon

One trial (n=256) randomized patients with newly detected stage T1, G2-G3 bladder cancer to 2 mL of OncoTICE strain BCG versus epirubicin 50 mg plus 10 MU of interferon alpha-2b given together (Table 6; Appendixes E3, F2).[182,183] Six weekly induction treatments were followed by maintenance therapy to 2 years. The trial was rated low risk of bias.

BCG was associated with reduced risk of bladder cancer recurrence (RR 0.66, 95% CI 0.51 to 0.85), cancer mortality at 5 years (RR 0.79, 95% CI 0.32 to 1.63), progression-free survival at 2 or 5 years, and risk of cystectomy at 2 years (RR 0.68, 95% CI 0.30 to 1.54)[182,183] versus epirubicin plus interferon, but the only statistically significant difference was for bladder cancer recurrence.

BCG Versus Gemcitabine

Three trials randomized patients to BCG versus gemcitabine[184-186] and one trial to BCG versus BCG plus gemcitabine administered sequentially (Table 6; Appendixes E3, F2).[187] Two trials enrolled patients at high risk for bladder cancer recurrence (based on higher tumor grade, presence of CIS, recurrent tumors, and multiplicity of tumors),[184,185] one enrolled patients at intermediate risk[186] and one enrolled patients who were intermediate or high risk.[187] The dose of BCG ranged from 27 mg to 81 mg. The dose of gemcitabine was 2000 mg in all studies, although the dose immediately after TURBT was 1000 mg in one study.[187] The number of instillations ranged from 6 weekly instillations[187] to 13 instillations over 3 years.[185] The number of gemcitabine instillations ranged from 2[187] to 15 to 18.[184,186]

One trial found no difference between BCG versus gemcitabine in all-cause mortality, but the estimate was very imprecise (RR 1.20, 95% CI 0.04 to 34).[184] No trial reported bladder cancer specific mortality.

Three trials reported effects of BCG versus gemcitabine on risk of bladder cancer recurrence.[184-186] Due to differences between trials in the populations and BCG doses evaluated, results were not pooled. One trial of patients with high risk Ta or T1 tumors found BCG 81 mg associated with increased risk of bladder cancer recurrence versus gemcitabine (RR 1.67, 95% CI 1.21 to 2.29)[184] One trial of patients with high-risk T1 and/or G3 and/or CIS found no difference between BCG 50 mg and gemcitabine in risk of bladder cancer recurrence (RR 0.53, 95% CI 0.28 to 1.01)[185] and one trial of patients with Ta tumors without CIS or G3 disease found no difference between BCG 27 mg versus gemcitabine (RR 0.76, 95% CI 0.44 to 1.90).[186]

Two trials found no difference between BCG versus gemcitabine in risk of bladder cancer progression (RR 1.11 [95% CI 0.53 to 2.34][184] and RR 0.52 [95% CI 0.13 to 2.06]).[186] One trial found no difference between BCG versus gemcitabine on all quality of life dimensions as measured by the EORTC-QLQ-C30[199] or the EORTC QLQ-BLS24,[186] with the exception that emotional functioning decreased slightly in the BCG group but improved in the gemcitabine group (p=0.03 for difference in a multivariate analysis).[186]

No trial of BCG versus BCG plus gemcitabine administered sequentially evaluated effects on mortality. One trial (n=87) found no difference between BCG versus BCG plus gemcitabine given sequentially in risk of bladder cancer recurrence (RR 0.86, 95% CI 0.49 to 1.51) or progression (RR 1.18, 95% CI 0.30 to 4.61).[187]

BCG Versus Interferon

One trial randomized patients to BCG versus interferon alpha-2a,[188] one trial randomized patients to BCG versus alternating BCG plus interferon alpha-2b,[189] and one trial to BCG versus combination therapy with BCG plus interferon alpha-2b (Table 6; Appendixes E3, F2).[190] One trial administered five bladder instillations of 40 mg of MMC to all patients prior to randomization to continued BCG or BCG and interferon alpha-2b administered sequentially.[189] The dose of BCG ranged from 16.6 mg to 150 mg and the dose of interferon from 50 mg to 54 MU. Interferon instillations ranged from six over 1 year alternating with BCG[189] to 24 given in addition to BCG over 3 years.[190] Up to 17 interferon instillations were given over 9 months in the trial of BCG versus interferon given alone.[188]

One trial found BCG associated with reduced risk of recurrence versus interferon alpha-2a alone (39% vs. 69%, RR 0.57, 95% CI 0.39 to 0.82).[188] There were no statistically significant differences in risk of bladder cancer progression (RR 0.69, 95% I 0.25 to 1.92) or cystectomy (RR 4.82, 95% CI 0.25 to 94), but estimates were imprecise.

One trial found BCG associated with lower risk of bladder cancer recurrence versus alternating BCG plus interferon alfa-2b (28% vs. 68%, 1 trial, RR 0.42, 95% CI 0.30 to 0.59).[189] All patients received MMC prior to randomization to BCG or alternating BCG plus interferon alfa-2b.

A third trial found no difference in risk of bladder cancer recurrence between BCG versus the combination of BCG plus interferon alfa-2b in patients who did not receive pretreatment with MMC (RR 0.88, 95% CI .71 to 1.08).[190] Patients received up to 24 instillations. The dose of BCG was approximately 50 mg during induction and 16.6 mg in the maintenance phase.

No trial of BCG versus regimens involving interferon evaluated mortality.

BCG Versus Thiotepa

Two trials randomized patients to BCG versus thiotepa (Table 6; Appendixes E3, F2).[142,172] One trial initially enrolled patients (n=123) with Ta or T1 tumors but later restricted enrollment to T1 tumors due to the low probability of recurrence with Ta disease.[172] BCG-Pasteur 150 mg or thiotepa 50 mg was administered weekly for 4 weeks, then monthly for 11 months. The other trial (n=46) randomized patients with recent recurrence (up to stage T1) to 6 x 10^9 CFUs BCG-TICE versus thiotepa 60 mg weekly for 6 weeks, followed by maintenance therapy for a total of 2 years.[142] Both trials found BCG associated with reduced risk of bladder cancer recurrence versus thiotepa (13% vs. 36%, RR 0.38 [95% CI 0.19 to 0.76][172] and 0% vs. 47%, RR 0.04 [95% CI 0.00 to 0.63][142]). Estimates for other outcomes, including progression, death, and cystectomy, were too imprecise to evaluate effects.

MMC Versus Doxorubicin

Six trials (reported in seven publications) evaluated MMC versus doxorubicin (Tables 7, 8; Appendixes E3, F2).[101,112,113,115,116,144,191] Three trials evaluated an MMC dose of 20 mg,[112,113,116,191] one trial evaluated a dose of 30 mg,[101] and in two trials doses ranged from 5 mg to 40 mg depending on the patient's bladder capacity.[115,144] In one trial, the doxorubicin dose ranged from 50 to 100 mg depending on the patient's bladder capacitiy.[144] In the other trials, doxorubicin doses ranged from 10 to 80 mg. Five trials[101,112,113,115,144,191] evaluated maintenance regimens (range 15 to 42 instillations) and one trial evaluated an induction regimen (8 doses over 4 weeks).[112,116] Duration of followup ranged from a median of 15 months to a mean of 60 months.

There was no difference between MMC versus doxorubicin in risk of bladder cancer recurrence (6 trials, RR 1.00, 95% CI 0.82 to 1.22, I^2=44%) (Figure 33).[112,115,116,191] Findings were similar in a subgroup analysis restricted to five trials that evaluated maintenance therapy regimens (RR 0.88, 95% CI 0.69 to 1.11, I^2=27%).[101,112,115,144,191] MMC was also associated with a decreased risk of bladder cancer progression versus doxorubicin that did not reach statistical significance (4 trials, RR 0.63, 95% CI 0.37 to 1.08, I^2=20%).[113,115,144,191] No trial evaluated effects on overall or bladder cancer-specific mortality.

MMC Versus Epirubicin

One small (n=44) trial evaluated MMC versus epirubicin in patients with single G1 or G2 tumors without CIS (Tables 7, 8; Appendixes E3, F2).[192] It found no difference in risk of bladder cancer recurrence at 5 years between maintenance therapy with MMC 40 mg (16 to 18 instillations over 1 year) versus either a single 80 mg dose of epirubicin (40% [6/15] vs. 36% [5/14]; RR 1.12, 95% CI 0.44 to 2.86) or maintenance therapy with epirubicin 40 mg (40%

[6/15] vs. 33% [5/15]; RR 1.20, 95% CI 0.47 to 3.10). The trial did not evaluate bladder cancer progression or mortality.

MMC Versus Gemcitabine

One trial (n=109) evaluated induction therapy with MMC versus gemcitabine in patients with recurrent G1-G3 tumors (Tables 7, 8; Appendixes E3, F2).[194] At a median followup of 36 months, there was no difference between MMC versus gemcitabine in risk of bladder cancer recurrence (p=0.29), but MMC was associated with lower likelihood of recurrence-free survival (log-rank test, p=0.0021). MMC was also associated with increased risk of bladder cancer progression, but the difference was not statistically significant (18% [10/55] vs. 11% [6/54]; RR 1.64, 95% CI 0.64 to 4.19). The trial did not assess mortality.

MMC Versus Interferon Alpha

One trial (n=287) evaluated induction therapy with MMC versus interferon-alpha for primary G1 or G2 tumors without CIS (Tables 7, 8; Appendixes E3, F2).[193] It found MMC associated with lower risk of bladder cancer recurrence than interferon-alpha 50 MU after 42 months of followup (37% [52/141] vs. 48% [70/146]; RR 0.77, 95% CI 0.58 to 1.01). MMC was associated with increased risk of bladder cancer progression, but the difference was not statistically significant (6% [8/141] vs. 4% [6/146], RR 1.38, 95% CI 0.49 to 3.88).[193] The trial did not assess effects on mortality.

MMC Versus Interferon Gamma

One trial (n=123) evaluated maintenance therapy (20 instillations over 1 year) with MMC 40 mg versus interferon-gamma 15 MU for primary G2 tumors (CIS excluded) (Tables 7, 8; Appendixes E3, F2).[141] MMC was associated with higher risk of recurrence after a median of 2 years followup [43% (27/63) vs. 27% (16/60); RR 1.61, 95% CI 0.97 to 2.67]. The trial did not assess effects on bladder cancer progression or mortality.

MMC Versus Thiotepa

Two trials compared maintenance therapy with MMC 40 mg versus thiotepa 60 mg.[143,146] One trial (n=47) of patients with recurrent or multiple bladder cancers (excluding Tis) reported no clear differences in risk of recurrence (RR 1.76, 95% CI 0.36 to 8.70) or progression (RR 2.64, 95% CI 0.30 to 23.6), but estimates were very imprecise.[143] Another trial (n=83) of patients with Ta or Tis lesions (not necessarily recurrent or multiple) found no difference in risk of recurrence (33% vs. 29%, RR 1.14, 95% CI 0.60 to 2.16).[146]

Doxorubicin Versus Epirubicin

Three trials evaluated doxorubicin versus epirubicin (Tables 9, 10; Appendixes E3, F2).[119,195,196] Doses of doxorubicin were 30 to 50 mg and doses of epirubicin 30 to 80 mg. All trials evaluated maintenance regimens.

Doxorubicin was associated with higher risk of recurrence versus epirubicin (3 trials, RR 1.56, 95% CI 1.08 to 2.22, I^2=0.0).[119,195,196] One trial found no difference between maintenance therapy with doxorubicin 50 mg versus epirubicin 50 mg (RR 0.91, 95% CI 0.33 to 2.57) or epirubicin 80 mg (RR 2.08, 95% CI 1.13 to 3.83) in risk of bladder cancer progression[119] and another trial reported no instances of progression in either treatment group.[196] None of the trials evaluated effects on mortality.

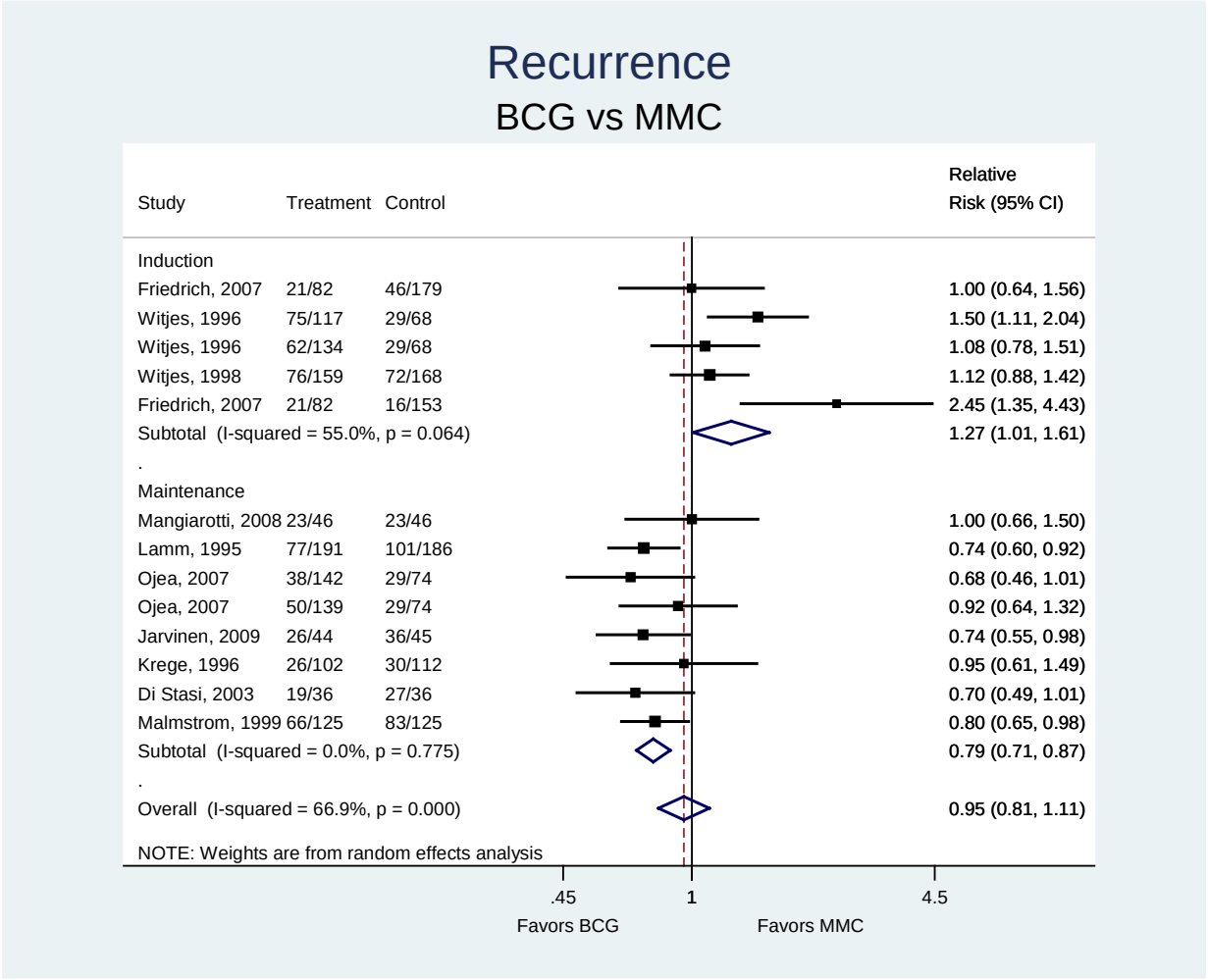
Doxorubicin Versus Thiotepa

One trial (n=109) evaluated maintenance therapy (15 instillations over 1 year) with doxorubicin 50 mg versus thiotepa 50 mg in patients with G1-G3 NMIBC (Tables 9, 10; Appendixes E3, F2).[172] There were no statistically significant differences in risk of bladder cancer recurrence (43% [23/53] vs. 36% [20/56]; RR 1.22, 95% CI 0.76 to 1.94) progression (8% [4/53] vs. 4% [2/56]; RR 2.11, 95% CI 0.40 to 11.06), noncancer mortality (0% [0/53] vs. 2% [1/56]; RR 0.35, 95% CI 0.01 to 8.45) or cancer-specific mortality (2% [1/53] vs. 0% [0/56]; RR 3.17, 95% CI 0.13 to 76.07) after a median followup of 36 months, though estimates were very imprecise.

Epirubicin Versus Interferon Alpha

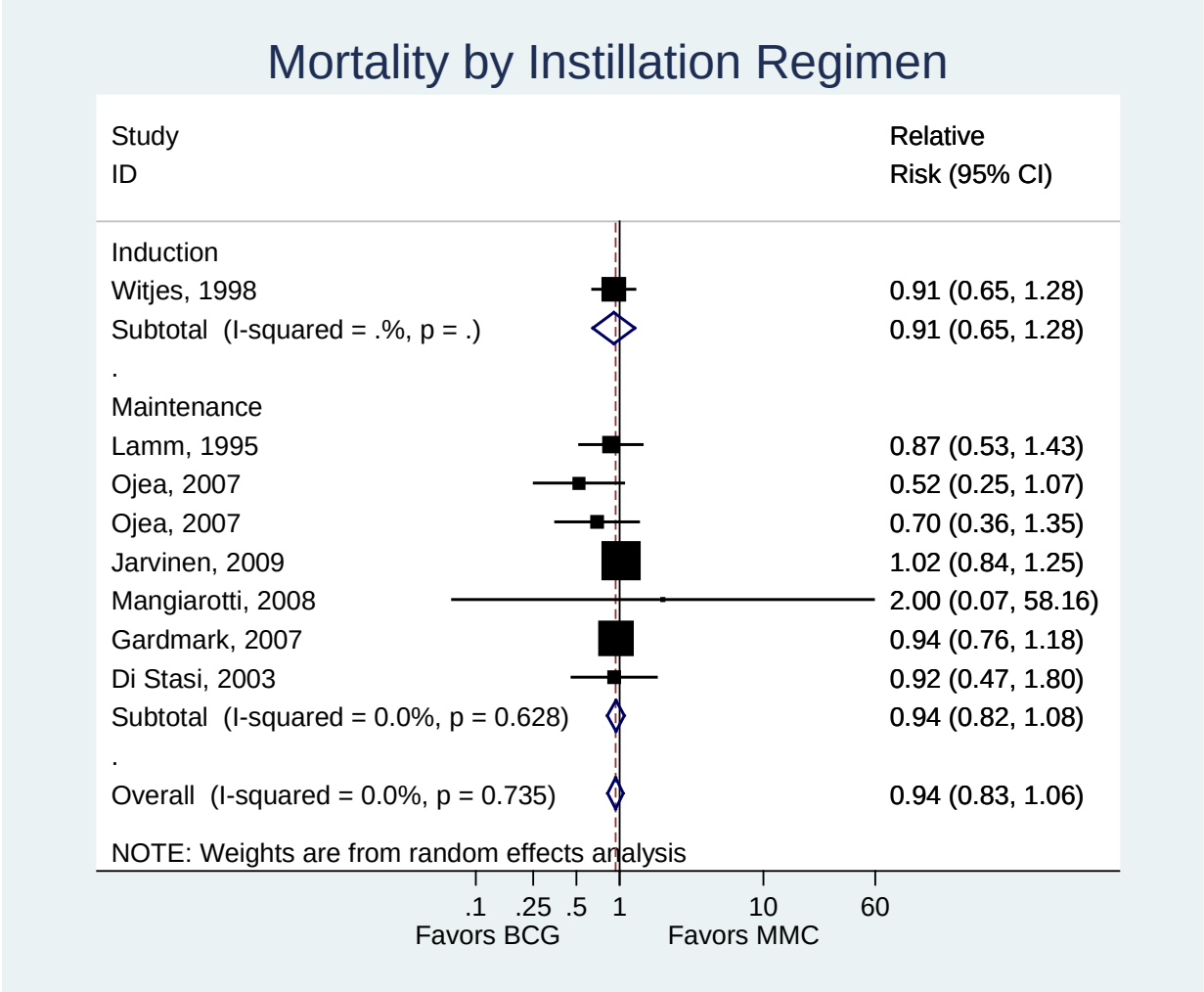
One trial (n=134) evaluated a single instillation of epirubicin 100 mg versus interferon-alpha 50 MU for primary G1-G3 tumors (Tables 11, 12; Appendixes E3, F2).[132,133] Epirubicin was associated with decreased risk of bladder cancer recurrence (46% [31/68] vs. 68% [45/66]; RR 0.67, 95% CI 0.49 to 0.91). Effects on bladder cancer progression or mortality were not reported.

Figure 19. Meta-analysis of bacillus Calmette-Guérin versus MMC: Risk of recurrence



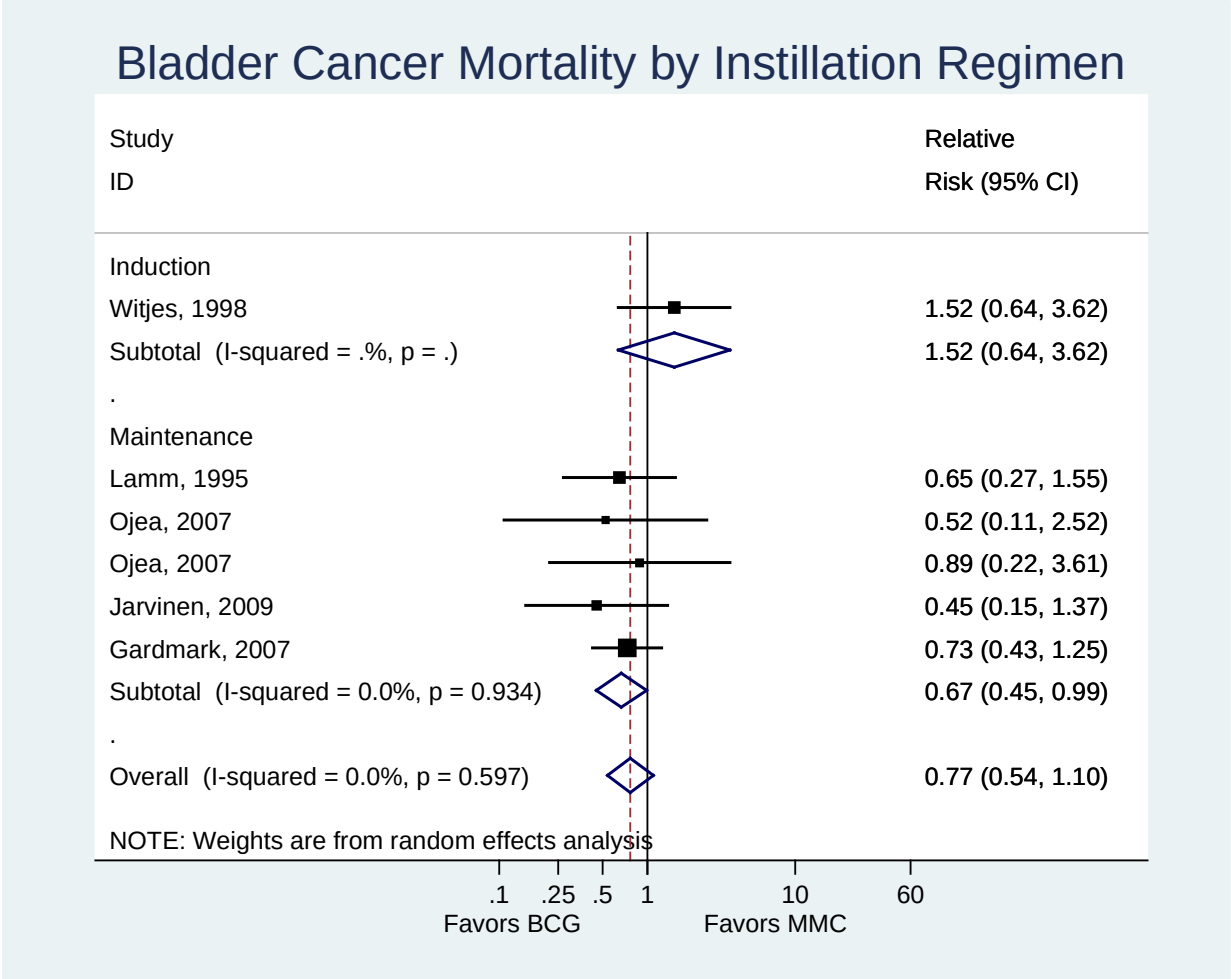
BCG = bacillus Calmette-Guérin; CI = confidence interval; MMC = Mitomycin C
Note: Witjes, 1996 and Ojea, 2007 each reported effects for two different regimens.

Figure 20. Meta-analysis of bacillus Calmette-Guérin versus MMC: Risk of mortality



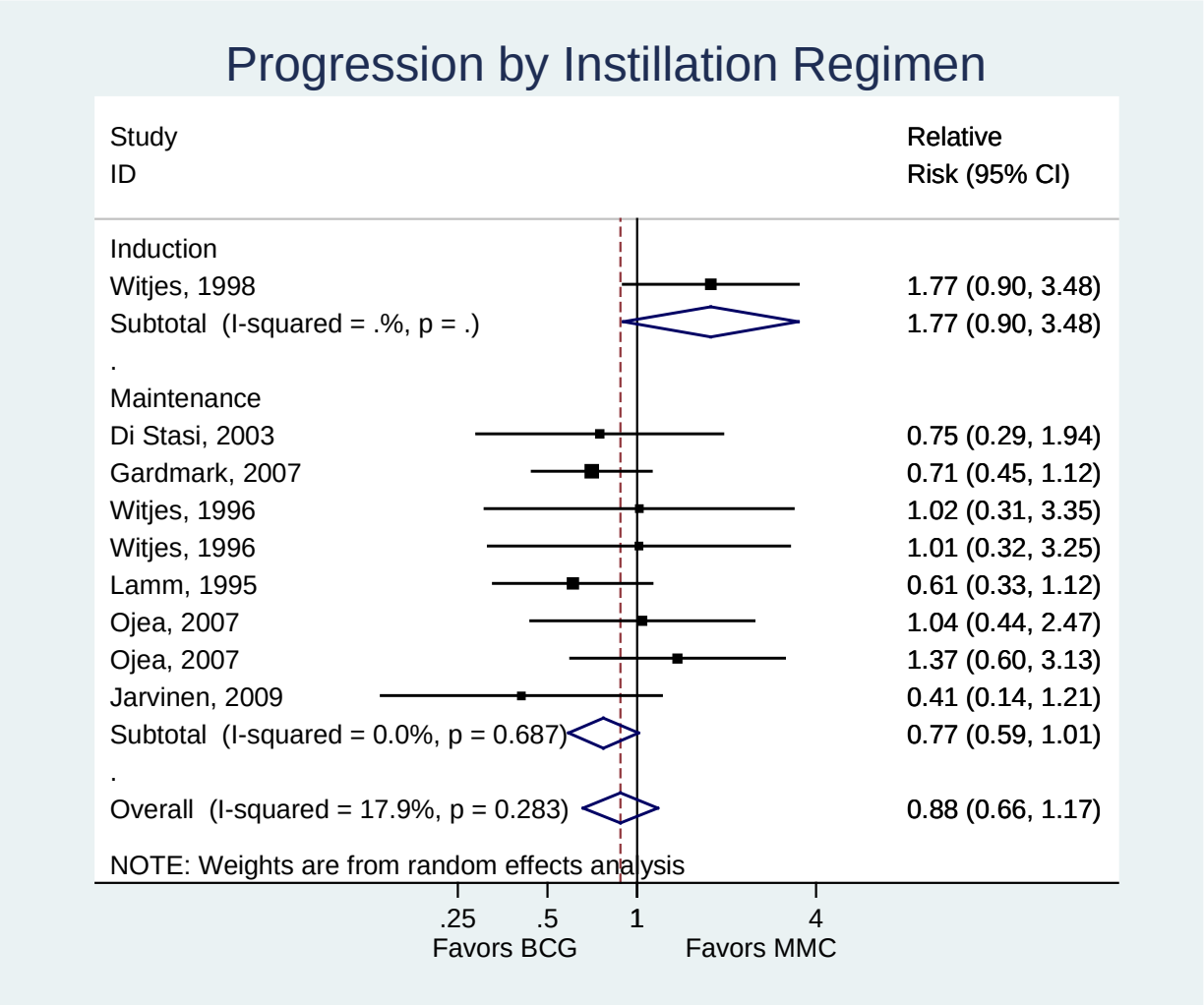
BCG = bacillus Calmette-Guérin; CI = confidence interval; MMC = Mitomycin C
Note: Ojea, 2007 reported effects for two different regimens.

Figure 21. Meta-analysis of bacillus Calmette–Guérin versus MMC: Risk of bladder cancer–specific mortality



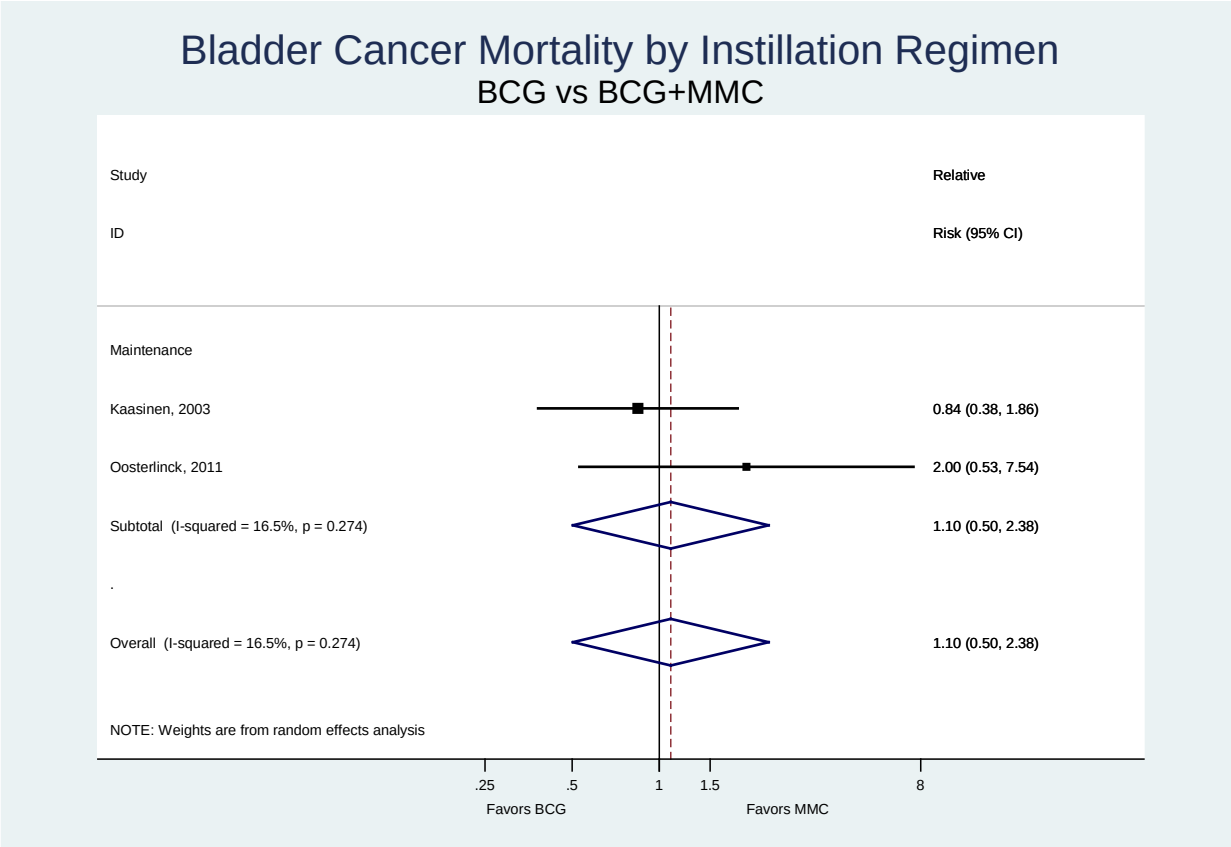
BCG = bacillus Calmette-Guérin; CI = confidence interval; MMC = Mitomycin C
Note: Ojea, 2007 reported effects for two different regimens.

Figure 22. Meta-analysis of bacillus Calmette-Guérin versus MMC: Risk of progression



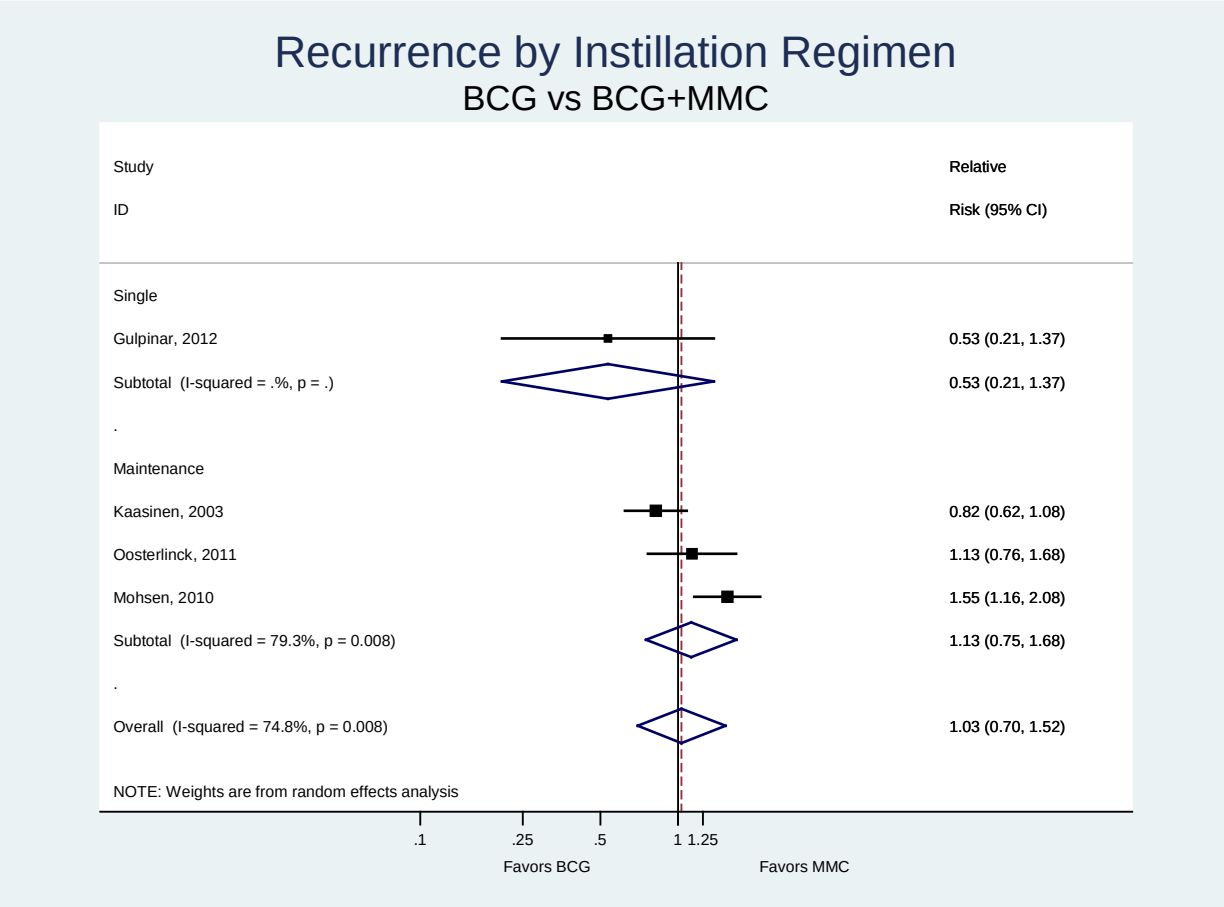
BCG = bacillus Calmette-Guérin; CI = confidence interval; MMC = Mitomycin C
Note: Witjes, 1996 and Ojea, 2007 each reported effects for two different regimens.

Figure 23. Meta-analysis of bacillus Calmette-Guérin versus bacillus Calmette–Guérin plus MMC: Risk of bladder cancer–specific mortality



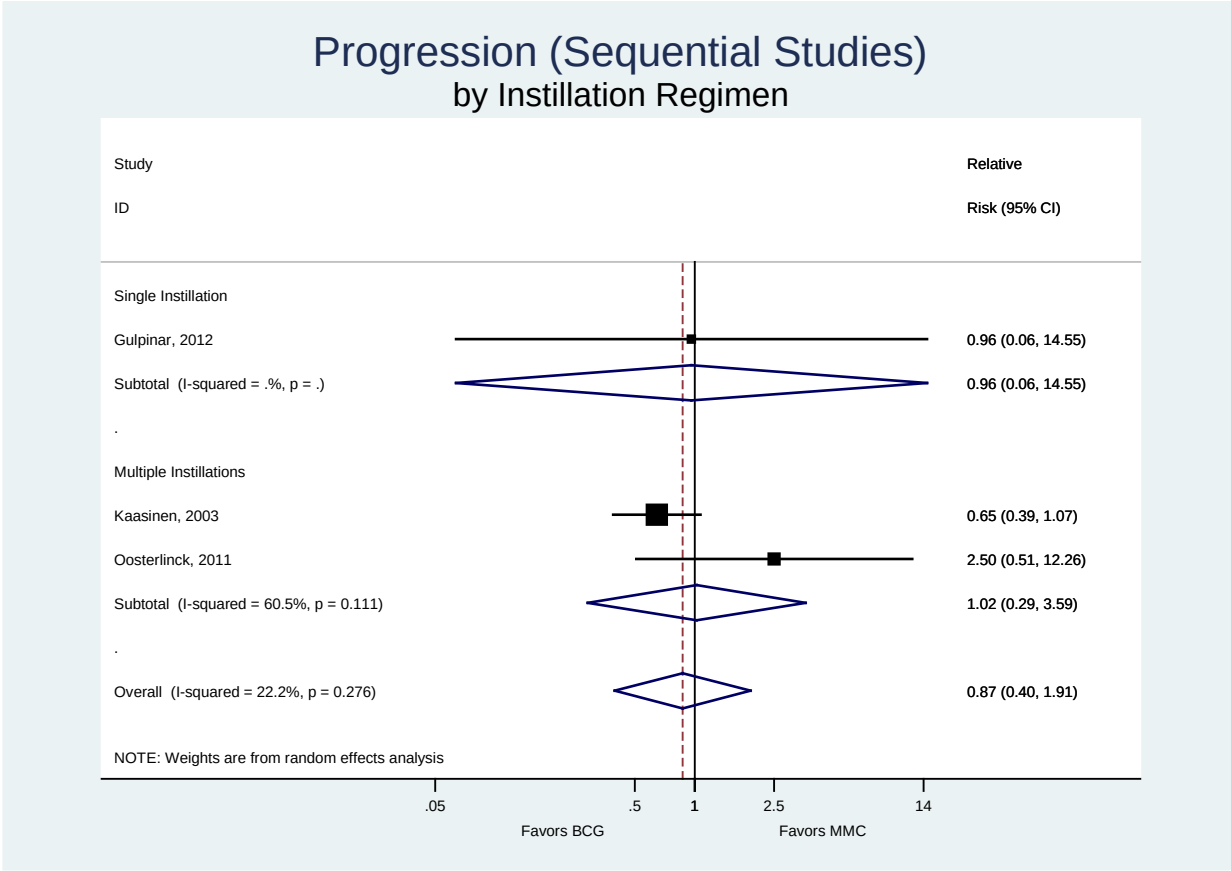
BCG = bacillus Calmette-Guérin; CI = confidence interval; MMC = Mitomycin C

Figure 24. Meta-analysis of bacillus Calmette-Guérin versus bacillus Calmette-Guérin plus MMC: Risk of recurrence



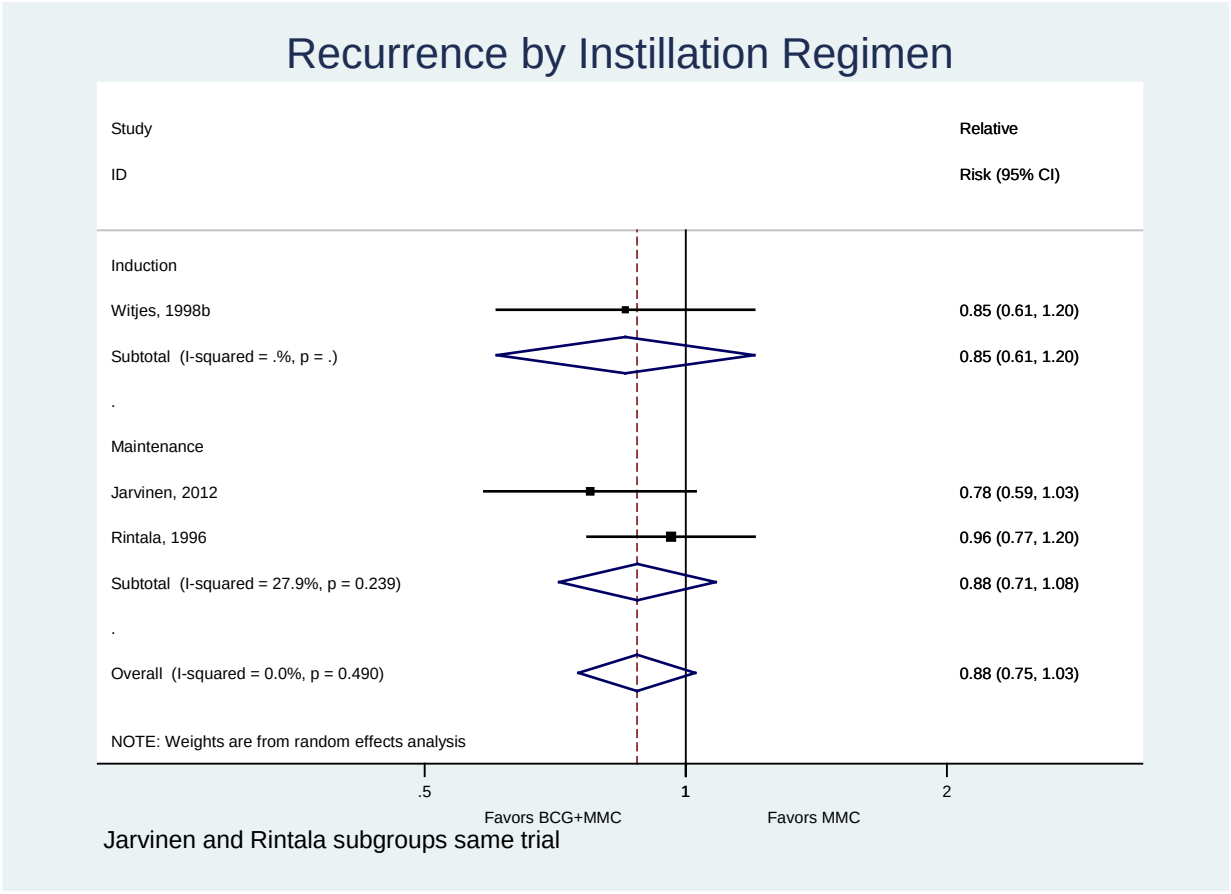
BCG = bacillus Calmette-Guérin; CI = confidence interval; MMC = Mitomycin C

Figure 25. Meta-analysis of bacillus Calmette-Guérin versus bacillus Calmette-Guérin plus MMC: Risk of progression



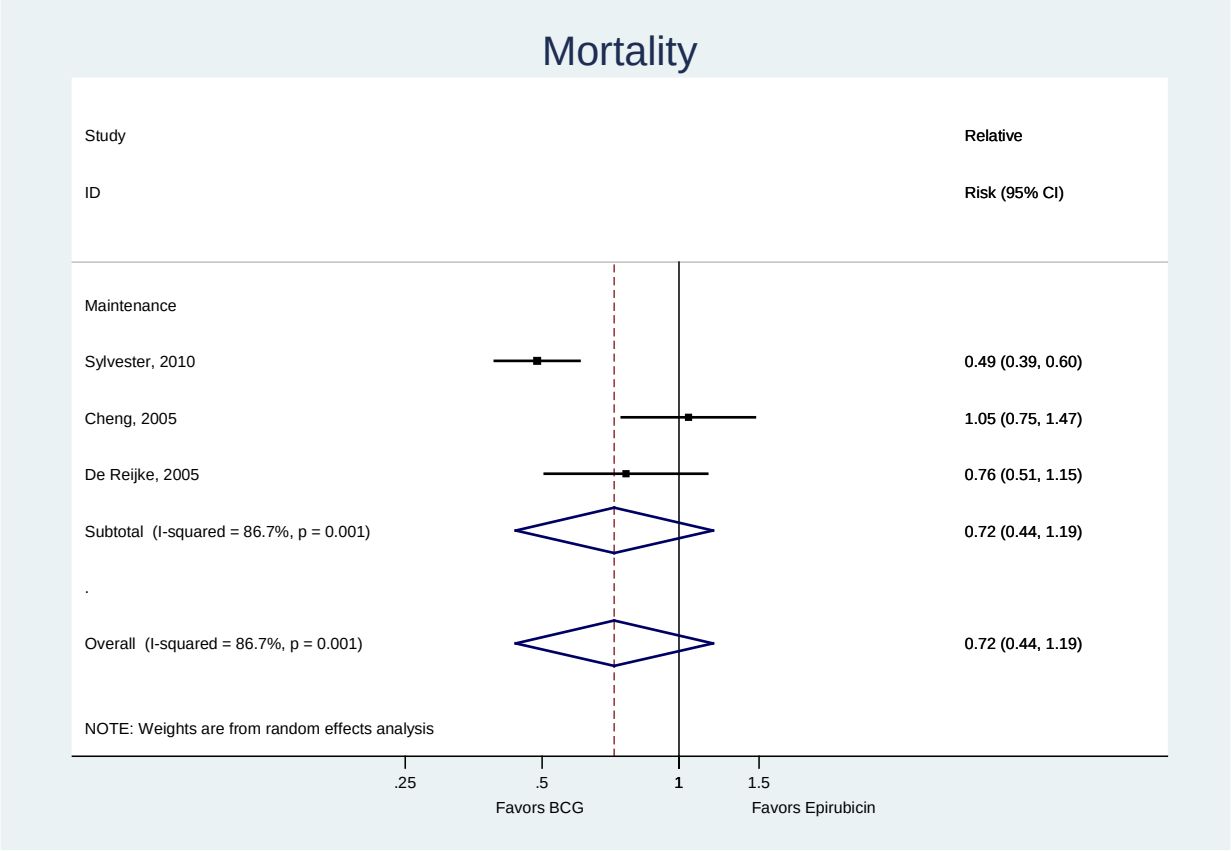
BCG = bacillus Calmette-Guérin; CI = confidence interval; MMC = Mitomycin C

Figure 26. Meta-analysis of bacillus Calmette-Guérin plus MMC versus MMC: Risk of recurrence



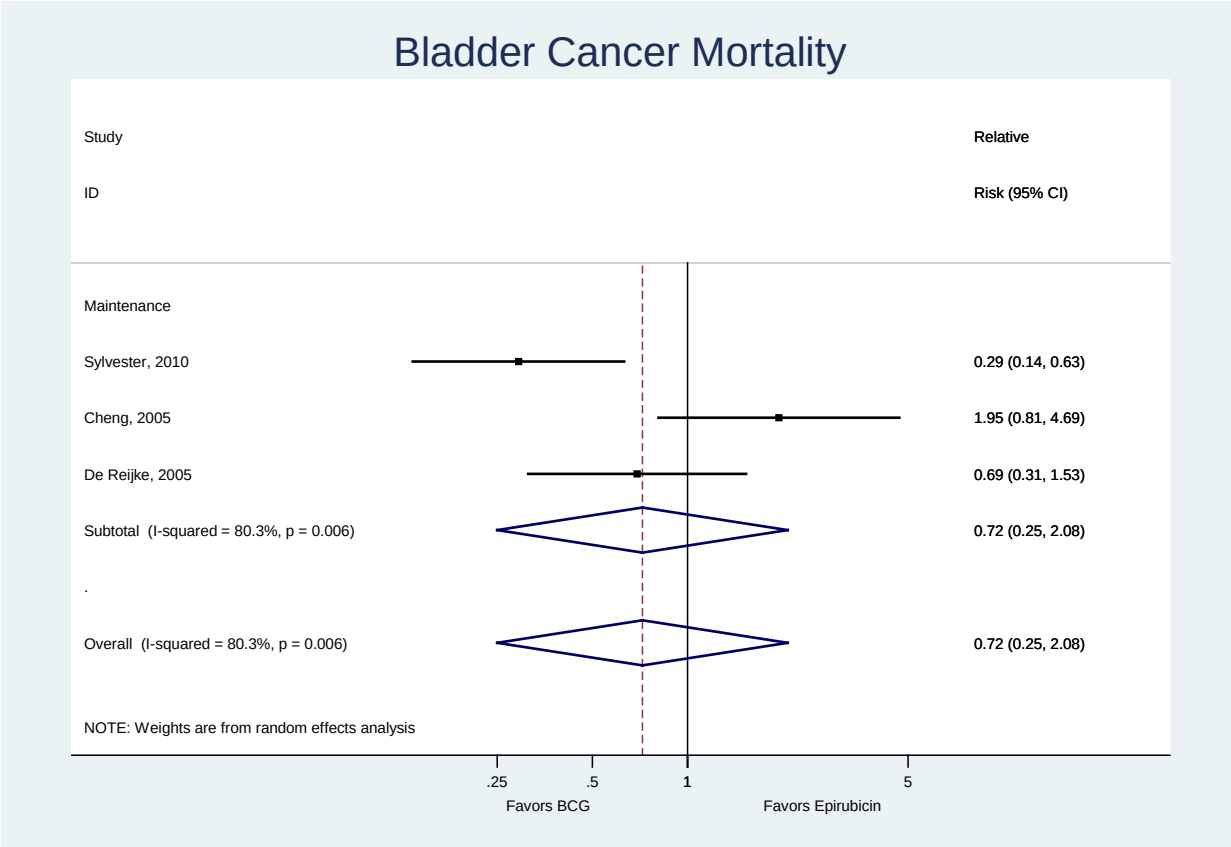
BCG = bacillus Calmette-Guérin; CI = confidence interval; MMC = Mitomycin C

Figure 27. Meta-analysis of bacillus Calmette-Guérin versus epirubicin: All-cause mortality



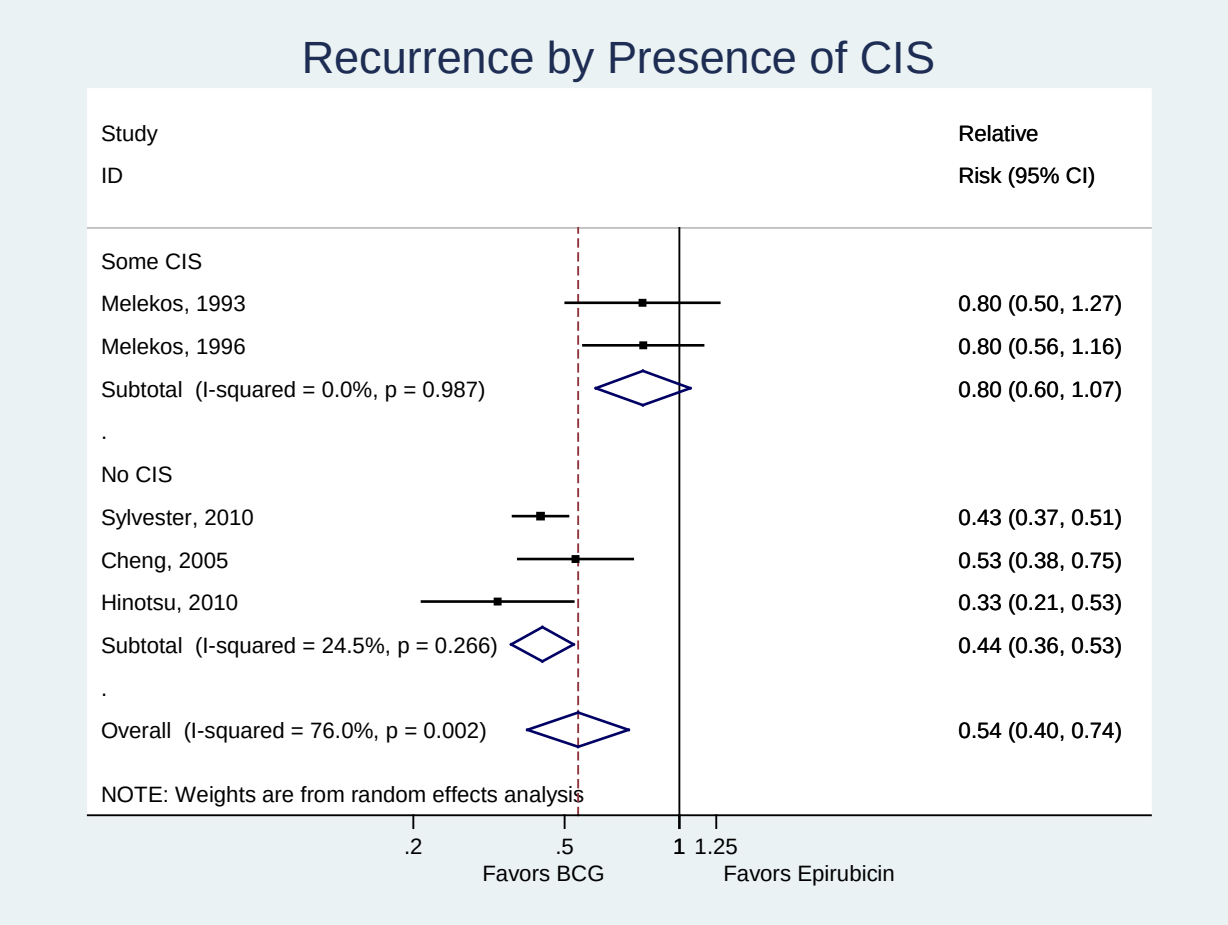
BCG = bacillus Calmette-Guérin; CI = confidence interval

Figure 28. Meta-analysis of bacillus Calmette-Guérin versus epirubicin: Bladder cancer–specific mortality



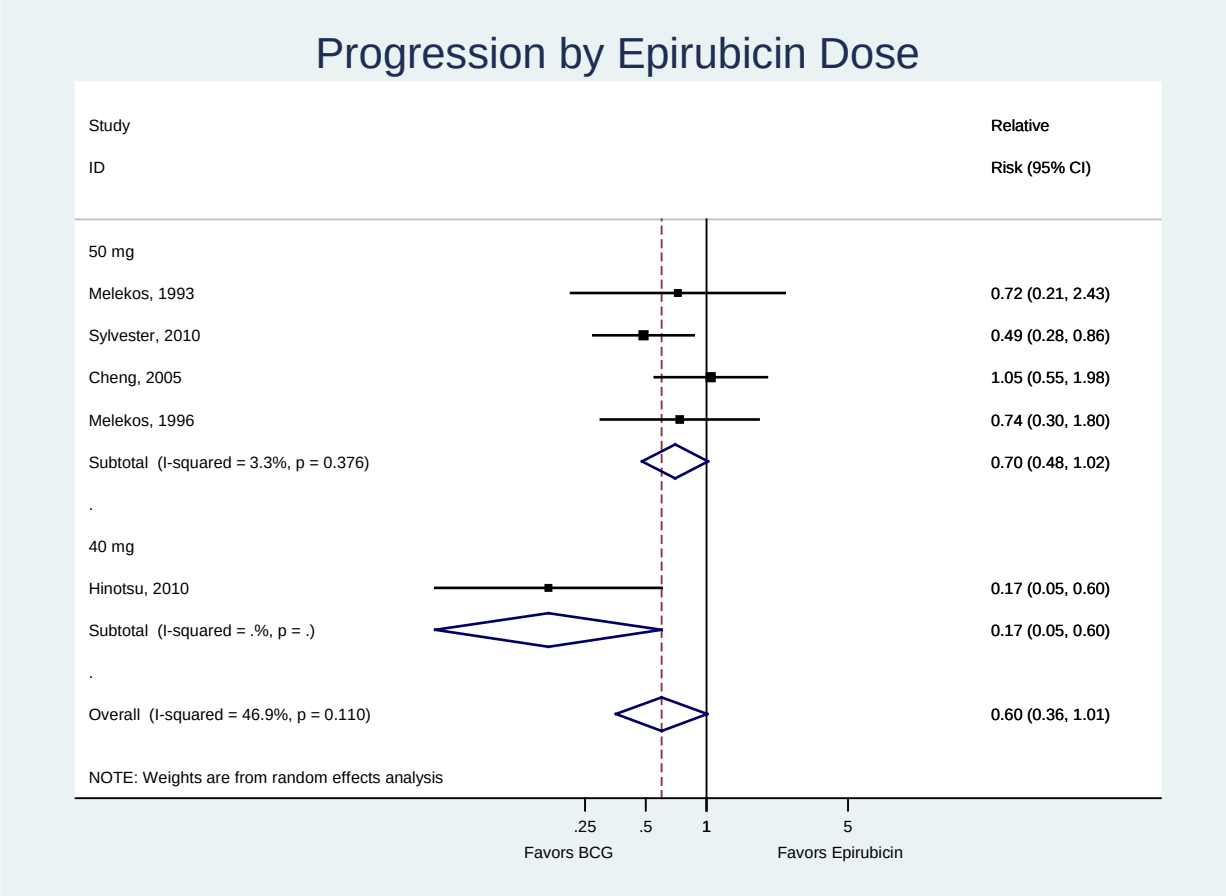
BCG = bacillus Calmette-Guérin; CI = confidence interval

Figure 29. Meta-analysis of bacillus Calmette-Guérin versus epirubicin: Risk of recurrence



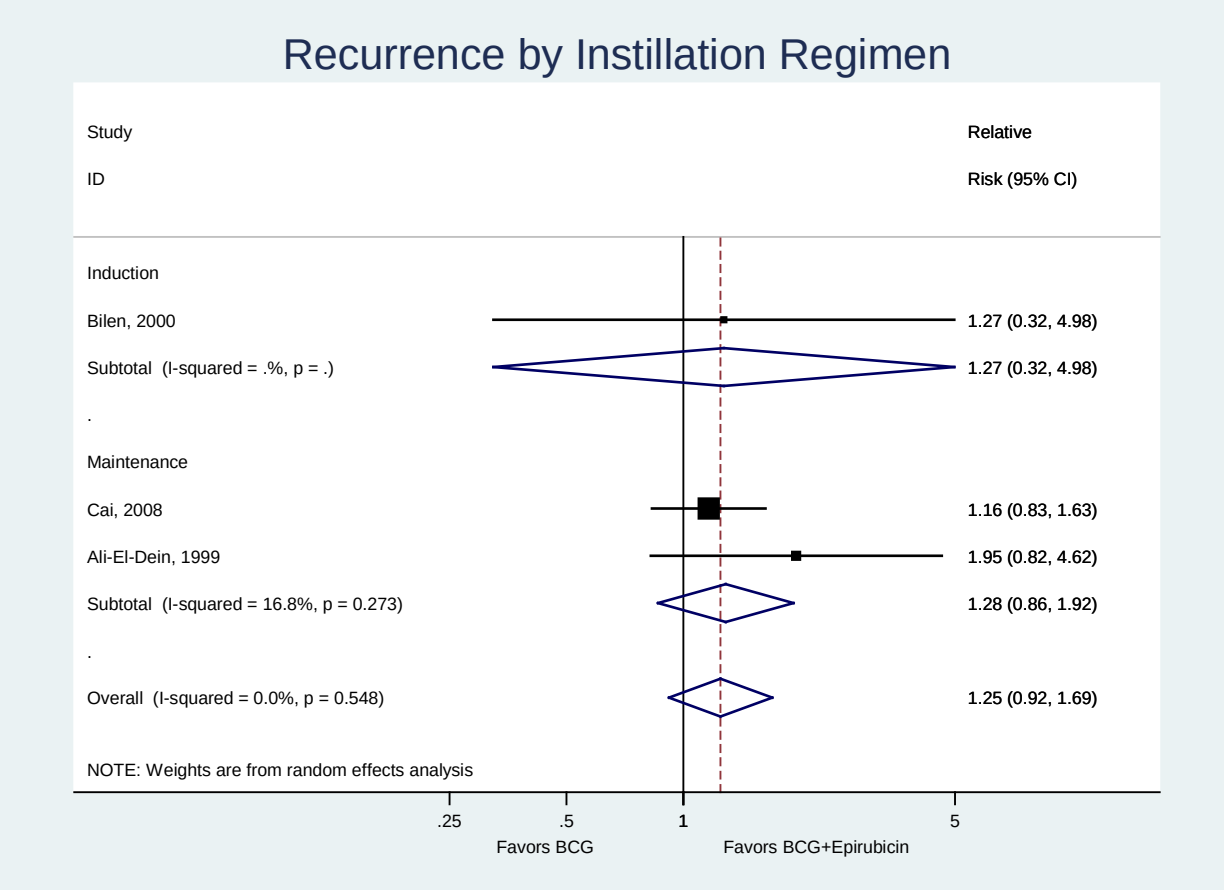
BCG = bacillus Calmette-Guérin; CI = confidence interval; CIS = carcinoma in situ

Figure 30. Meta-analysis of bacillus Calmette-Guérin versus epirubicin: Risk of progression



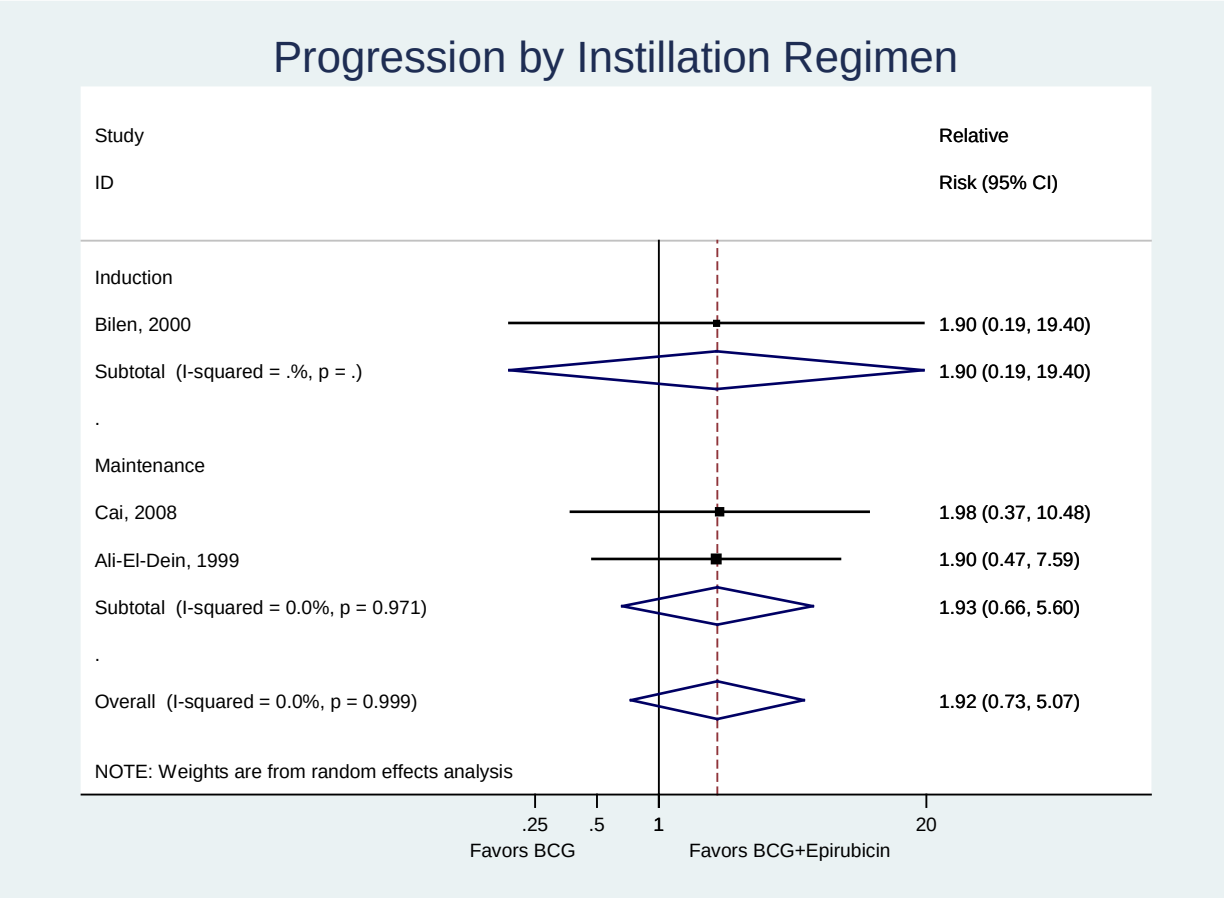
BCG = bacillus Calmette-Guérin; CI = confidence interval

Figure 31. Meta-analysis of bacillus Calmette-Guérin versus bacillus Calmette-Guérin plus epirubicin: Risk of recurrence



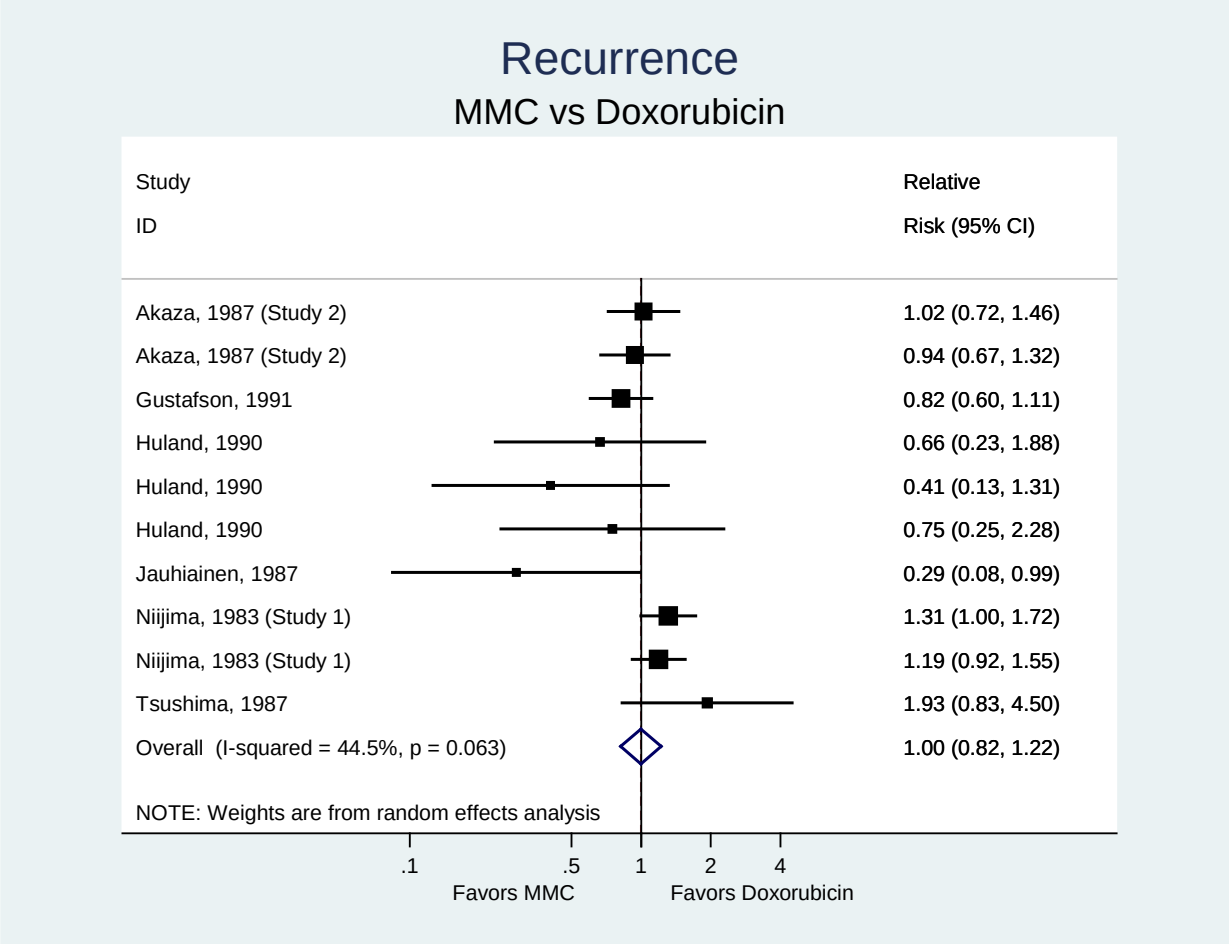
BCG = bacillus Calmette-Guérin; CI = confidence interval

Figure 32. Meta-analysis of bacillus Calmette-Guérin versus bacillus Calmette-Guérin plus epirubicin: Risk of progression



BCG = bacillus Calmette-Guérin; CI = confidence interval

Figure 33. Meta-analysis of MMC versus doxorubicin: Risk of recurrence



BCG = bacillus Calmette-Guérin; CI = confidence interval; MMC = Mitomycin C
Note: Akaza, 1987 (Study 2) and Niijima, 1983 (Study 1) each reported effects for two different regimens and Huland, 1990 reported effects for three different regimens.

Key Question 3b. Does the comparative effectiveness differ according to tumor characteristics, such as stage, grade, size, multiplicity, whether the tumor is primary or recurrent, or molecular/genetic markers?

Key Points

- There were no clear differences in estimates of effectiveness of intravesical therapies in subgroups defined by tumor stage, grade, size, multiplicity, recurrence status, or DNA policy (SOE: low for stage, grade, tumor multiplicity, primary versus recurrent DNA ploidy).

Detailed Synthesis

Evidence on how estimates of comparative effectiveness of intravesical therapies vary in subgroups defined by tumor characteristics was limited. There were no clear differences in

estimates of effectiveness in subgroups defined by tumor stage,[103,106,112,119,130,132,133,136,137,139,172,180,191,193-195] presence or absence of CIS,[152,159,171,172] tumor grade,[103,112,119,130,132,133,135-137,139,155,172,173,188,191,194,195] tumor multiplicity,[101,103,119,128,130,132,133,135,139,172,180,188,194,195] tumor size,[180,188,194] primary versus recurrent tumor,[100,103,112,119,122,124,128,130-133,135,180,191,194,195] or DNA ploidy.[180] The trials evaluated various intravesical therapies, comparisons, and outcomes (recurrence, progression, mortality). Risk estimates were generally similar across subgroups or were imprecise, with overlapping confidence intervals.

Key Question 3c. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, race/ethnicity, performance status, or medical comorbidities?

Key Points

- No trial evaluated how estimates of effectiveness of intravesical therapy vary in subgroups defined by patient characteristics such as age, sex, race/ethnicity, performance status, and comorbidities (SOE: insufficient).
- In patients with recurrence or progression following prior BCG therapy, one trial found maintenance therapy with gemcitabine associated with decreased risk of recurrence versus repeat treatment with BCG, and one trial found MMC maintenance therapy associated with lower likelihood of disease-free survival than gemcitabine; estimates for progression were imprecise (SOE: low).

No trial evaluated how estimates of effectiveness of intravesical therapy vary in subgroups defined by patient characteristics such as age, sex, race/ethnicity, performance status, and comorbidities. Most trials of patients with recurrent bladder cancer did not specify whether patients had received prior intravesical therapy or the type of intravesical therapy received.[109,149,165,168,179,180,188,189,196] One trial of patients with high-risk Ta or T1 NMIBC (based on the European Organization for Research and Treatment of Cancer Scoring System) who failed BCG therapy found a gemcitabine maintenance regimen with gemcitabine (2000 mg) associated with decreased risk of recurrence versus BCG-Connaught (81 mg) (53% vs. 88%, RR 0.60, 95% CI 0.44 to 0.82), though there was no difference in risk of progression (33% vs. 38%) and only one death was recorded.[184] Another trial (n=109) of patients with progression or relapse after intravesical therapy (83% BCG) found an MMC maintenance regimen associated with lower likelihood of disease-free survival (p=0.0021) than gemcitabine, though differences in recurrence rate (1.72 vs. 1.26 per 100 patient-months, p=0.31) and progression (18% vs. 11%, RR 1.64, 95% CI 0.64 to 4.19) were not statistically significant.[194]

Key Question 3d. Does the comparative effectiveness of various chemotherapeutic or immunotherapeutic agents differ according to dosing frequency, duration of treatment, and/or the timing of administration relative to TURBT?

Key Points

BCG

- Six trials found no clear differences between standard and lower doses of BCG in risk of recurrence, progression, or bladder cancer mortality, including in patients with higher-risk NMIBC, though there was some inconsistency between trials. Standard therapy was associated with increased risk of local and systemic adverse events versus lower dose BCG in most trials (SOE: low).
- Three trials of responders to BCG induction therapy found no clear differences between maintenance versus no maintenance therapy in risk of all-cause mortality (3 trials, RR 0.90, 95% CI 0.72 to 1.11) or bladder cancer mortality (2 trials, RR 1.14, 95% CI 0.24 to 5.40), though maintenance therapy was associated with decreased risk of recurrence (RR 0.76 [95% CI 0.65 to 0.88] and RR 0.16 [95% CI 0.02 to 1.21]) (SOE: low).
- Two of three trials found more prolonged courses of BCG associated with decreased risk of bladder cancer recurrence versus induction therapy in patients with higher-risk NMIIBC, but increased risk of adverse events (SOE: low).
- One trial found BCG TICE associated with lower likelihood of 5-year recurrence-free survival versus BCG Connaught (48% vs. 74%, p=0.01) and one trial found BCG TICE associated with lower likelihood of 5-year recurrence-free survival versus BCG RIVM (36% vs. 54%, p=0.07). Four trials that compared non-TICE BCG strains found no differences (SOE: low).

MMC

- One trial of patients with NMIBC (not selected for being at higher risk) found no clear differences between MMC 40 mg single instillation versus five instillations in risk of recurrence, progression, or mortality. The single instillation was associated with lower risk of local adverse events (SOE: low).
- One trial of patients with higher-risk NMIBC found MMC 20 mg induction therapy for 6 weeks associated with higher risk of recurrence than maintenance therapy. There were no clear differences in risk of adverse events (SOE: low).
- Two trials of MMC maintenance regimens in patients with NMIBC not selected for being at higher risk found some evidence that a higher total number of instillations and increased frequency during initial therapy were associated with lower risk of recurrence and progression, and might be associated with lower risk of local adverse events (SOE: low)
- One trial found no difference between “optimized” versus nonoptimizied administration of intravesical MMC in risk of recurrence in patients with low-risk NMIBC, but one other trial of patients with higher-risk NMIBC found optimized administration associated with lower risk of recurrence and increased risk of local adverse events (SOE: low).

Doxorubicin

- Two trials of patients with NMIBC not selected for being at higher risk found no differences between doxorubicin 30 mg and 20 mg given as short (8 week) or long (2 years) regimens in risk of recurrence or progression, with no differences in adverse events (SOE: low).
- Two trials of patients with NMIBC not selected for being at higher risk found no clear differences between doxorubicin induction therapy and induction plus maintenance in risk of recurrence, progression, or mortality, with no differences in adverse events (SOE: low).
- Two trials of doxorubicin found no clear benefits associated with administration prior to TURBT or multiple instillations immediately after TURBT, with some evidence of increased adverse events with multiple immediate post-TURBT instillations (SOE: low).

Epirubicin

- Three trials of epirubicin found no clear evidence that higher doses are associated with reduced risk of recurrence or progression versus lower doses, with no differences in adverse events (SOE: moderate).
- Three trials found no clear difference between single instillation epirubicin and multiple instillations in patients with low- or high-risk NMIBC in risk of recurrence, progression, or bladder cancer mortality, with some evidence of lower risk of local adverse events (SOE: moderate).
- Two trials found no clear differences between epirubicin maintenance therapy and induction without maintenance in risk of recurrence or progression, including one trial of patients with higher-risk NMIBC. There were no differences in risk of local adverse events (SOE: moderate).
- Five trials that evaluated different epirubicin regimens that included maintenance therapy found some evidence that more intensive therapy is associated with decreased risk of recurrence, but results were inconsistent. There was no difference in risk of adverse events (SOE: low).

Thiotepa

- Two trials found no clear differences between thiotepa 30 mg and 60 mg for maintenance or for treatment of incompletely resected NMIBC or CIS (SOE: low).

Interferon Alpha-2b

- Four trials found higher doses of interferon alfa-2b associated with improved outcomes related to recurrence, progression, or resolution of bladder cancer marker lesions versus lower doses, but most estimates were imprecise and did not reach statistical significance. There were no clear differences in risk of local or systemic adverse events (SOE: low).

Multiple Drugs

- One trial found no difference between initiation of intravesical therapy (9 instillations over 6 months) with MMC or doxorubicin 50 mg on the day of TURBT versus 1 to 2 weeks after TURBT in risk of recurrence, progression, or mortality; or between maintenance beyond 6 months versus no additional maintenance therapy. There were no clear differences in local or systemic adverse events (SOE: low).

Detailed Synthesis

Fifty-three trials in 57 publications of intravesical therapy compared different doses or instillation regimens of the same drug or different BCG strains (Tables 17, 18; Appendixes E4, F2).[112,113,116,118,119,123,126,134,136,140,148,151,154,156,157,176,191,192,197,198,200-236] Eleven trials in 12 publications evaluated comparisons involving BCG,[148,151,156,176,200,201,204-211,215,218,222,223,226,228,230,233,237] seven trials evaluated MMC,[118,154,191,197,198,212,213,232] five trials in six publications evaluated doxorubicin,[112,113,116,123,214,231,236] 13 trials evaluated epirubicin,[119,126,134,192,216,219,220,224,225,227,229,234,235] two trials in one publication evaluated thiotepa,[140] and three trials evaluated interferon alpha-2b.[136,203,217,221] Sample sizes ranged from 34 to 1,355 and duration of followup from 4 weeks to 9 years. Twenty-four trials were conducted in the United States or Europe.[118,136,140,148,151,154,156,191,197,212,214,216,217,221-224,228,230-232,234] Thirty-eight trials were rated medium risk of bias[112,113,116,118,119,123,126,134,136,140,148,151,154,156,176,191,192,197,212,214-217,219-225,227-229,231-236] and four trials high risk of bias.[198,218,226,230] No trial reported blinding of patients or care providers to the treatment regimen received. Only five trials[118,134,176,215,233] reported in adequate detail use of an appropriate randomization method and only one trial[221] reported assessment of outcomes blinded to the treatment received. Additional methodological shortcomings in the trials rated high risk of bias included use of sequential allocation[218,226] and reporting of only interim results.[230]

BCG

Comparisons of Different Doses

Seven trials (reported in eight publications) compared different doses of intravesical BCG.[151,218,222,223,226,228,230,237] The trials varied with regard to the BCG strain, dose comparisons, and populations evaluated. Most trials found no clear differences between standard and lower doses of BCG in risk of recurrence and other outcomes, though there was some inconsistency across studies.

Three trials compared different doses of intravesical Connaught strain BCG.[151,222,223] In all three trials, BCG was administered as 12 instillations over 5 to 6 months. One trial (n=499) found no differences between standard (81 mg) and reduced (27 mg) dose Connaught strain BCG in risk of recurrence (28% vs. 31%, RR 0.92, 95% CI 0.70 to 1.20), progression (12% vs. 13%, RR 0.86, 95% CI 0.54 to 1.37), or bladder cancer mortality (7.9% vs. 7.3%, RR 1.09, 95% CI 0.59 to 2.01) after a median of 69 months.[222] In the subgroup of patients with high-risk (T1G3, Tis, ≥2 prior relapses, multifocal, or ≥3 cm) tumors, there was a nonstatistically significant trend favoring standard (81 mg) dose therapy (30% vs. 37%, RR 0.80, 95% CI 0.60 to 1.08), but the estimate was imprecise and there were baseline differences in risk markers. In addition, a subsequent randomized trial (n=155) that focused on patients with higher-risk NMIBC (T1G3 and Tis) found no differences between standard dose versus 27 mg in risk of recurrence (39% vs. 45%, RR 0.86, 95% CI 0.60 to 1.25), progression (24% vs. 26%, RR 0.94, 95% CI 0.54 to 1.61), or bladder cancer mortality (12% vs. 15%, RR 0.81, 95% CI 0.36 to 1.79) after a median followup of 60 months.[223] The third trial, which enrolled patients with intermediate-risk (TaG2 or T1/G1-2 without CIS) tumors, found no statistically significant differences between one-third dose (27 mg) and one-sixth dose (13.5 mg) in risk of recurrence (27% vs. 36%, RR 0.74, 95% CI 0.52 to 1.06), progression (10% vs. 13%, RR 0.76, 95% CI 0.39 to 1.47), or bladder cancer mortality (2.1% vs. 3.6%, RR 0.59, 95% CI 0.14 to 2.41), though trends favored the higher dose group.[151]

Four trials evaluated dose comparisons involving other BCG strains.[218,226,228,230] One trial, which did not focus on high-risk NMIBC, found no differences between low (40 mg) versus standard (80 mg) dose Tokyo 172 strain BCG (6 instillations over 6 weeks) in risk of recurrence (28% vs. 16%, RR 1.71, 95% CI 0.66 to 4.40) or progression (5.0% vs. 6.4%, RR 0.78, 95% CI 0.12 to 5.20) after about 2 years followup.[218] The other three trials focused on treatment of higher-risk NMIBC. The largest trial (n=1805) enrolled patients with solitary T1G3 or multiple Ta-T1/G1-G3 tumors.[228] It found no differences between one third versus full dose OncoTICE strain BCG (administered as 15 instillations over 12 months or 27 instillations over 36 months) in the likelihood of remaining recurrence-free at 5 years (59% vs. 62%, p=0.09), progression, or mortality. However, the one-third dose/1 year regimen was associated with decreased likelihood of remaining disease-free versus the full dose/3 year regimen (HR 0.75, 95% CI 0.59 to 0.94). Benefits of three years of full-dose therapy were limited to high-risk patients (HR for recurrence 1.61, 95% CI 1.13 to 2.30). One trial (n=97) of patients with residual T1 or Tis tumors or a history of multiple recurrences found low-dose Armand Frappier BCG (60 mg) associated with lower likelihood of remaining recurrence-free (37% vs. 67%, RR 0.55, 95% CI 0.36 to 0.84) than standard dose therapy (each administered once weekly for 6 weeks) after a mean duration of followup of 21 months.[226] The other trial (n=183), which enrolled patients with multiple Ta/T1 tumors or CIS, found low-dose (75 mg) Pasteur strain BCG more effective than standard (150 mg) dose (6 weeks induction with 2 years maintenance) in time to recurrence (p=0.0009 overall), but there was no difference in risk of tumor progression (9% in both groups).[230] In addition, only interim results have been published from this trial.

In most trials, standard dose BCG therapy was consistently associated with increased risk of local and systemic adverse events versus reduced doses.[218,222,223,226] However, the largest trial found no clear differences between standard versus 1/3 dose BCG in local or systemic adverse events, or in risk of discontinuation due to adverse events.[228,237] One trial found no differences between 27 (1/3 dose) versus 13.5 mg (1/6 dose) in local or systemic adverse events.[151]

Comparisons of Different Instillation Regimens

Six trials (reported in seven publications) compared induction therapy with BCG for 6 to 8 weeks versus more prolonged courses.[176,200,205-207,209,215] Three trials randomized responders to BCG induction therapy (dose 80 to 81 mg) to maintenance therapy versus no maintenance therapy.[205-207,209] Maintenance therapy ranged from 3 additional instillations over 9 months to 21 additional instillations over 3 years. There was no difference between maintenance therapy versus no maintenance therapy in risk of all-cause mortality (3 trials, RR 0.90, 95% CI 0.72 to 1.11, I^2=0%),[205,206,209] bladder cancer mortality (2 trials, RR 1.14, 95% CI 0.24 to 5.40, I^2=0%),[205,209] or progression (2 trials, RR 0.85, 95% CI 0.69 to 1.04).[205,206] Two trials each found maintenance therapy associated with decreased risk of recurrence (RR 0.76 [95% CI 0.65 to 0.88][206] and RR 0.16 [95% CI 0.02 to 1.21][205]), but there was statistical heterogeneity and the pooled estimate was imprecise, with a nonstatistically significant effect (RR 0.49, 95% CI 0.12 to 1.93, I^2=56%). None of the trials reported risk of adverse events with maintenance therapy versus no maintenance therapy.

Three other trials randomized patients with high-risk (recurrent or multifocal) NMIBC to maintenance versus induction therapy with BCG, prior to determining response to induction therapy.[176,200,215] In one trial (n=83), maintenance therapy with Connaught strain BCG 81 mg (6 weeks induction followed by once weekly instillations for 3 weeks at 3, 6, 12, and 18 months) was associated with lower risk of recurrence (12% vs. 33%, RR 0.37, 95% CI 0.14 to 0.92) than

induction therapy alone after a median followup of 2 years.[176] In another trial (n=70), a 12-week course of Pasteur strain BCG 120 mg was associated with a trend towards decreased risk of recurrence versus a 6-week course after 2 years, but the difference was not statistically significant (30% vs. 45%, RR 0.67, 95% CI 0.35 to 1.27).[215] The third trial found no difference between monthly maintenance therapy with Pasteur strain BCG 120 mg versus a 6-week course of therapy in disease-free interval after a median followup of 22 months.[200] One trial[176] found no difference in risk of progression (0% vs. 6.1%, RR 0.15, 95% CI 0.01 to 2.7), one trial[215] found no differences in risk of mortality or radical cystectomy, and one trial reported no difference in risk of progression (there were no deaths),[200] but estimates were imprecise. Two trials reported risk of harms with maintenance versus induction therapy. In both trials, more prolonged courses of BCG therapy were associated with increased risk of local adverse events versus 6-week induction regimens, with no clear differences in systemic or serious adverse events.[176,215] In the trial of 18 months maintenance versus 6 weeks of induction therapy, rates of urinary frequency were 93 versus 71 percent (RR 1.3, 95% CI 1.1 to 1.6), dysuria 93 versus 69 percent (RR 1.3, 95% CI 1.1 to 1.7), hematuria 93 versus 71 percent (RR 1.3, 95% CI 1.1 to 1.6), and fever 43 versus 26 percent (RR 1.6, 95% CI 0.88 to 3.0).[176] In the trial of 12 versus 6 weeks of BCG, there were fewer adverse events and differences were not statistically significant.[215]

One trial of patients with solitary T1G3 or multiple Ta-T1/G1-G3 tumors found no difference between OncoTICE strain BCG (1/3 or full dose) administered as 15 instillations over 12 months versus 27 instillations over 36 months in the likelihood of remaining recurrence-free at 5 years (57% vs. 63%, p=0.06).[228] There were also no differences in risk of progression or mortality. There were no differences in risk of local or systemic adverse events.[228,237]

Comparisons of Different BCG Strains

Six trials (reported in eight publications) compared outcomes of 6 to 8 weeks of intravesical therapy with one BCG strain versus another.[148,156,201,204,208,210,211,233,238] The largest trial (n=437) found BCG TICE associated with lower likelihood of remaining recurrence-free after 5 years (36% vs. 54%, log-rank p=0.07) in patients with papillary NMIBC (not selected for being higher risk), though the difference was not statistically significant.[148,156,211] There was no difference in risk of progression (5% vs. 6%) or local or systemic side adverse events. The differences also were not statistically significant when analyses were restricted to patients with G3 tumors or CIS. Another trial (n=142) found BCG TICE associated with lower likelihood of 5-year recurrence-free survival versus BCG Connaught (48% vs. 74%, p=0.01) in higher-risk patients (high-grade tumors, low-grade tumor with multiple recurrences, or CIS), though there were no difference in progression-free or overall survival.[210] BCG TICE was also associated with higher risk of dysuria (30% vs. 13%, p=0.02), though there was no difference in risk of any harm.

Four other trials found no differences between non-TICE BCG strains.[201,204,208,233,238] Two trials focused on patients with multiple recurrent tumors and two included patients with CIS. One trial (n=129)[233] found no difference between BCG Tokyo versus BCG Connaught in likelihood of 5-year recurrence-free survival (62% vs. 56%, p=0.74). A smaller trial (n=38) also found no differences between low-dose BCG Tokyo versus regular dose BCG Connaught in likelihood of complete response (72% vs. 75%) at median followup of 16.5 months or in likelihood of 1-year recurrence-free survival (p=0.69).[204] One trial (n=94)[201] found no difference between BCG Evans versus BCG Pasteur in marker tumor clearance or development of new tumors after 3 months. Another trial found no difference between BCG Evans (Glaxo) versus BCG Pasteur in likelihood of a complete response at 1 year (42% vs. 44%), but enrolled a very small sample

(n=21).[208,238] There were no differences in risk of adverse events in any of these BCG comparisons.

MMC

Comparisons of Different Instillation Regimens

One trial (n=295) of patients with NMIBC (not selected for being at higher risk) found no clear differences between MMC 40 mg single instillation within 24 hours of TURBT versus 5 instillations in risk of recurrence at 24 months (42% vs. 31%, p=0.14), progression-free interval (HR 0.97, 95% CI 0.46 to 2.06), all-cause mortality (34% vs. 42%, RR 0.79, 95% CI 0.59 to 1.1), or bladder cancer mortality (5.4% vs. 5.5%, RR 0.98, 95% CI 0.38 to 2.5).[118] The single instillation was associated with lower risk of dysuria or frequency (0% vs. 6.2%, RR 0.05, 95% CI 0.003 to 0.88).

One trial (n=332) of patients with higher-risk NMIBC (based on higher stage, higher grade, multifocality, and recurrence) found MMC 20 mg induction therapy for 6 weeks associated with higher risk of recurrence than induction plus maintenance therapy for 3 years (26% vs. 10%, RR 2.5, 95% CI 1.5 to 4.2).[154] There were no clear difference in risk of adverse events.

Two trials compared MMC regimens that varied in both the number and frequency of instillations in patients with NMIBC who were not selected for being at higher risk. One trial (n=380) found that regimens of MMC 20 mg that involved more intensive induction (weekly for 8 weeks followed by maintenance for a total of 3 years or weekly for 20 weeks) were associated with lower risk of recurrence and progression than regimen involving less intensive (biweekly for 1 year, followed by maintenance for a total of 3 years) induction (18% and 20% vs. 24% for recurrence and 5.2% and 6.7% vs. 12% for progression, respectively).[232] Effects were more pronounced in patients with recurrent than with primary bladder cancer. Adverse events were not reported. Another trial found that a more intensive and prolonged course of MMC 20 mg (induction with 8 weekly instillations, with a total of 42 instillations over 3 years) was associated with lower risk of recurrence and stage progression than the same number of instillations over 3 years with a less intense induction (biweekly for the first year) or a course involving 20 weekly instillations (recurrence 9.4% vs. 15% and 17%; stage progression 1.0% vs. 2.9% and 5.3%), and a lower risk of chemical cystitis (12% vs. 25% and 18%).[191]

One trial (n=54) of MMC (40 mg) for patients with recurrent, single, small (<1.5 cm) NMIBC found 3 instillations per week for 2 weeks prior to TURBT associated with higher likelihood of complete response (absence of residual tumor) versus a once weekly instillation for 6 weeks prior to TURBT, though the difference was not statistically significant (70% vs. 44%, RR 1.58, 95% CI 0.97 to 2.56).[213] There were no cases of progression. There were no differences in risk of urinary frequency, chemical cystitis, or hematuria.

"Optimized" Versus Nonoptimized Administration

Two trials compared "optimized" administration of intravesical MMC (through alkalinization of urine) versus instillation without additional optimization.[197,198] One of the trials also optimized MMC administration by restricting fluids and emptying the bladder prior to instillation, and administering at a higher dose and concentration (40 mg in 20 mL versus 20 mg in 20 mL).[197] The first trial (n=26), which evaluated single-dose MMC for low-risk NMIBC (Ta, G1, solitary, <3 cm), found no difference between optimized and standard administration of a single dose of MMC, with no cases of recurrence in the standard therapy group after a median duration of

followup of 51 months.[198] However, a trial (n=201) of high-risk NMIBC found optimized therapy associated with lower risk of recurrence (51% vs. 66%; RR 0.78, 95% CI 0.63 to 0.97) and time to recurrence (median 29 vs. 12 months, p=0.005) after 5 years of followup. Benefits were not observed in patients with prior intravesical therapy, but were observed across other subgroups defined by tumor multifocality, stage, grade, and papillary lesion type. Optimized therapy was associated with increased risk of dysuria (33% vs. 18%, RR 1.86, 95% CI 1.15 to 3.02), with no difference in risk of other local or systemic adverse events and no difference in risk of discontinuation due to adverse events (1.8% vs. 1.9%).

Doxorubicin

Comparisons of Different Doses

Two trials found no differences between regimens involving doxorubicin 30 mg versus 20 mg in patients with NMIBC not selected for being at higher risk. One trial (n=368) of short-term therapy (eight instillations over 4 weeks) found no differences between doses in recurrence-free survival at 540 days (57% vs. 52% for 30 mg vs. 20 mg doses, respectively) or at 1800 days.[112,116] The other trial (n=345), which evaluated longer-term therapy (21 instillations over 2 years), found no difference in recurrence-free survival (62% vs. 59%) at 2 years.[112,113] In a subgroup of patients with long-term followup data (median 6.6 years) it also found no difference in risk of progression (43% vs. 31%) or recurrence rate (0.473 vs. 0.512 per year). In both trials, there were no clear differences in local adverse events and no systemic adverse events were reported.

Comparisons of Different Instillation Regimens

Two trials found no clear differences between doxorubicin induction therapy and induction plus maintenance in patients with NMIBC not selected for being at higher risk. One trial (n=146) found no difference between doxorubicin 50 mg maintenance therapy for 2 years versus induction therapy for 6 weeks without maintenance in risk of recurrence (47% vs. 42%, RR 1.1, 95% CI 0.78 to 1.6), progression (19% vs. 20%, RR 0.94, 95% CI 0.48 to 1.8), or bladder cancer mortality (13% vs. 13%, RR 0.95, 95% CI 0.41 to 2.2) after 5 years.[214] There were also no clear difference in risk of recurrence in subgroups stratified by primary or recurrent, solitary or multiple, or Ta vs. T1 cancers. Rates of local adverse events (chemical cystitis) were similar (13% vs. 12%). The other trial (n=220) found no differences between doxorubicin 50 mg given as 13 instillations over 6 weeks versus 28 instillations over 6 months in recurrence rate (25 vs. 2.3 per 100 patient-months), progression (16% vs. 11%, p>0.35), or bladder cancer mortality (5.3% vs. 1.8%).[231]

Two trials of doxorubicin involved comparisons regarding timing of therapy.[123] One trial (n=306) of patients with higher-risk NMIBC (multiple or recurrent lesions) found maintenance therapy with doxorubicin 20 mg (21 instillations over 2 years) associated with higher likelihood of remaining recurrence-free at 2 years (38% vs. 19%, p<0.05) than 6 instillations administered in the 2 weeks prior to TURBT, with no post-TURBT therapy.[123] There were no differences in risk of local adverse events. The other trial (n=187), which did not focus on higher-risk NMIBC, evaluated four regimens of doxorubicin 30 mg involving early initiation (two instillations in first 2 days, followed by 17 instillations over 1 year) versus no early instillation (17 instillations over 1 year, starting 7 days after TURBT), with or without 5-fluorouracil.[236] As no effects of 5-fluorouracil on outcomes were observed, these groups were combined for the analyses. The trial

found no overall difference between the early and delayed initiation groups in likelihood of remaining recurrence-free at 36 months (76% vs. 65%, p>0.05), though estimates favored the early initiation groups at some earlier time points and in patient subgroups with primary tumors, Ta, <1 cm lesions, G1 lesions, G2 lesions, and multiple tumors. Risk of bladder irritation was greater with the early instillation regimens (48-55% vs. 26%), but there was no difference in risk of bladder irritation resulting in withdrawal (5-8% vs. 2-3%).

Epirubicin

Comparisons of Different Doses

Three trials compared regimens involving different doses of intravesical epirubicin.[119,134,224] Overall there was no clear pattern that higher doses of epirubicin are associated with improved outcomes. One trial (n=132) of patients with higher-risk NMIBC found no statistically significant differences between epirubicin 50 mg vs. 80 mg, given as ~19 instillations over 1 year, in risk of recurrence (25% vs. 18%; RR 1.42, 95% CI 0.73 to 2.76), time to first recurrence (mean 16 vs. 15 months), or risk of progression (11% vs. 4.4%, RR 2.5, 95% CI 0.67 to 9.2) after a mean followup of 30 months, though trends favored higher-dose therapy.[126] Lower-dose therapy was associated with a higher recurrence rate (0.83 vs. 0.60 per 100 patient-months, p<0.05). Two other trials evaluated patients with NMIBC not selected for being at higher risk.[134,224] One trial (n=54) found no differences between epirubicin 50 mg vs. 100 mg (administered as 5 instillations over 1 year) in risk of recurrence (44% vs. 56%, HR 0.68, 95% CI 0.41 to 1.13) or recurrence rate (0.52 vs. 0.58 per patient-year, p>0.05) after mean followup of about 2 years.[224] The other trial (n=163) found no differences between epirubicin 20 mg vs. 50 mg (administered as 2 instillations, one immediately after TURBT and one the following day) in duration of recurrence-free survival (mean 24 vs. 38 months, p>0.05) or risk of progression (0% vs. 1.1%) after a median followup duration of 44 months.[134] One of the trials found lower-dose therapy associated with lower risk of bladder spasm (15% vs. 44%, RR 0.33, 95% CI 0.17 to 0.65);[224] otherwise there were no clear differences in risk of local or systemic adverse events.

Comparisons of Different Instillation Regimens

Three trials compared epirubicin single instillation therapy with multiple instillations.[119,192,235] One trial (n=143) of patients with low-risk NMIBC found no difference between a single instillation of epirubicin 100 mg within 6 hours of TURBT versus an additional instillation at 12 hours in risk of recurrence (15% vs. 21%, adjusted HR 0.67, 95% CI 0.30 to 1.51) or progression (1.5% vs. 4.0%, RR 0.37, 95% CI 0.04 to 3.45) after a mean followup duration of 16.9 months.[235] Another trial (n=44) of patients with Ta-T1/G1-G2 NMIBC found no differences between a single intravesical instillation of epirubicin 80 mg given within 6 hours of TURBT versus maintenance therapy with epirubicin 40 mg over about 1 year in risk or recurrence (36% vs. 33%, RR 1.07, 95% CI 0.39 to 2.92) or tumor-free survival (64% vs. 67%, RR 0.96, 95% CI 0.57 to 1.64) through 5 years.[192] Although the single instillation regimen was associated with lower risk of any side effect, there were no clear differences in risk of specific local adverse events and no systemic adverse events were recorded. The other trial (n=114), which evaluated patients with higher-risk NMIBC, found no difference between a single instillation of epirubicin 50 mg immediately after TURBT versus treatments initiated after 1 to 2 weeks and continued for 1 year (18 instillations) in risk of recurrence (24% vs. 25%), time to first recurrence (16 vs. 18 months), or risk of progression (5.5% vs. 3.4%) after a mean duration

of followup of 32 months.[119] There were also no clear differences in risk of recurrence in subgroups stratified by tumor stage, grade, or lesion size, though results favored delayed maintenance therapy for G3 lesions (53% vs. 20%, RR 2.63, 95% CI 0.88 to 7.89). There were no differences in risk of adverse events, including adverse events requiring temporary or permanent discontinuation of therapy.

Two trials evaluated epirubicin maintenance therapy versus induction without maintenance.[229,234] One trial (n=395) of patients with higher-risk, non-G3 NMIBC (multiple or recurrent tumors) found no clear differences between epirubicin 80 mg maintenance therapy (16 instillations over 1 year) versus induction without maintenance (6 instillations over 6 weeks) in remaining recurrence-free at 48 months (50% vs. 46%, p=0.26) or in risk of progression to MIBC (2.9% vs. 1.3%).[234] One trial (n=138) of patients with papillary NMIBC found no difference between epirubicin 40 mg induction therapy (6 instillations over 5 weeks) versus maintenance therapy (17 instillations over 1 year) in likelihood of remaining recurrence-free at 3 years (75% vs. 77%, p=0.62) or likelihood of progression (2.9% vs. 1.4%).[229] Both trials found no differences in risk of local adverse events.

Five trials compared different epirubicin regimens that included maintenance therapy.[216,219,220,225,227] One trial (n=269) of patients with multiple or recurrent Ta or T1 tumors or a solitary T1 tumor found no differences in likelihood of remaining recurrence- or progression-free at 5 years between epirubicin 50 mg administered as nine instillations over 6 months versus the same regimen plus an additional instillation within 48 hours of TURBT or the same regimen plus two additional maintenance instillations through 1 year.[216] One trial (n=150) of patients with Ta or T1 NMIBC (not selected for being at higher risk) found epirubicin 30 mg administered as 19 instillations over 1 year associated with lower risk of recurrence than nine instillations over 3 months (13% vs. 32%, HR 0.39, 95 % CI 0.18 to 0.82) after a median followup of 31 months.[219] A trial (n=125) of patients with Ta-T1/G1-G2 NMIBC found no difference between epirubicin 30 mg administered as 19 instillations over 1 year versus 12 instillations over 5 months in likelihood of remaining recurrence-free at 3 years (48% vs. 55%, p>0.05).[227] Another trial of patients with Ta-T1/G1-G2 NMIBC compared epirubicin 20 mg administered as 17 instillations over 12 months (total dose 340 mg), 30 mg given in 12 instillations over 7 months (total dose 360 mg), and 40 mg given in nine instillations over 4 months (total dose 360 mg).[220] The median time to recurrence was 688, 1007, and 1186 days, respectively (p=0.04 for dose/intensity response). There were no differences in mortality or bladder cancer mortality. A trial (n=69) of patients with Ta-T1/G1-G3 NMIBC compared four 12-week regimens involving epirubicin 30 mg that varied in the total dose administered (180 vs. 360 mg) and method of initiating therapy (once every 2 weeks starting 1 week after TURBT versus 3 instillations within the first 5-7 days after TURBT).[225] It found no difference between regimens based on the intensity of instillation, but the lower-dose regimens were associated with higher risk of recurrence at 12 months (42% vs. 29%, p=0.01). In all five trials, risk of local and systemic adverse events were similar across regimens.

Gemcitabine

Comparisons of Different Instillation Regimens

One small trial (n=32) of recurrent multiple Ta, G1 or G2 bladder cancers was too underpowered to determine if there were differences between gemcitabine 2000 mg once weekly

for 6 weeks, twice weekly for 3 weeks, or a single instillation in likelihood of experiencing a complete response (disappearance of marker lesion and no new tumor, 44% vs. 40% vs. 10%).[157]

Thiotepa

Comparisons of Different Doses

Two trials (reported in the same publication) compared different doses of thiotepa.[140] One trial (n=46) of patients with multifocal or recurrent NMIBC, or who had experienced a complete response to thiotepa, found no difference between maintenance therapy with thiotepa 30 mg versus 60 mg (once every 4 weeks for up to 2 years) in likelihood of being recurrence-free at 12 months (63% vs. 69%).[140] There were no differences in risk of adverse events. Another trial (n=95) of patients with incompletely resected NMIBC or CIS found no difference between thiotepa 30 mg versus 60 mg in likelihood of success (reduction in tumor or remission) following two courses of therapy (48% vs. 47%, RR 1.03, 95% CI 0.67 to 1.57).[140] There was no difference in risk of adverse events, though the lower-dose regimen was associated with a trend towards decreased risk of leukopenia (2.0% vs. 13%, RR 0.15, 95% CI 0.02 to 1.20).

Interferon Alpha-2b

Comparisons of Different Doses

Four trials compared different doses of intravesical interferon alpha-2b.[136,203,217,221] Two trials compared 100 MU versus 10 MU (once weekly for 10 or 12 weeks, then once monthly for a total of 1 year),[203,217] one trial compared 80, 50, and 40 MU (weekly for 12 weeks),[221] and one trial compared 80, 60, and 40 MU (once weekly for 2 months, then once every 2 weeks for 4 months, then once monthly).[136] One trial focused on patients with Tis lesions and the others included patients with Ta and T1 tumors.[203] Although the trials generally found higher doses of interferon alfa-2b associated with improved outcomes related to recurrence, progression, or resolution of bladder cancer marker lesions, most differences were not statistically significant, due to small sample sizes (n ranged from 24 to 89) with imprecise estimates. One trial found a statistically significant dose-dependent difference in recurrence rate with 80, 60, and 40 MU (1.19 vs. 0.88 vs. 0.63 per 100 patient-months, respectively).[136] The trial of patients with Tis found 100 MU associated with increased likelihood of a complete response (resolution of Tis, negative cytology, and no transitional cell carcinomas; 21% vs. 2.1% at 21 months, RR 10.0, 95% CI 1.33 to 75.0) and decreased risk of progression (13% vs. 37%, RR 0.35, 95% CI 0.15 to 0.82), with no difference in risk of cystectomy (15% vs. 18%, RR 0.81, 95% CI 0.31 to 2.10).[203] There were no clear differences in risk of local or systemic adverse events, including flu-like symptoms.[136,203,217,221]

Multiple Drugs

One trial found no difference between initiation of intravesical therapy (9 instillations over 6 months) with MMC 30 mg or doxorubicin 50 mg on the day of TURBT versus 1 to 2 weeks after TURBT in risk of recurrence (43% vs. 49% after 2.75 years, p=0.18), progression to invasive bladder cancer (11% vs. 10%), or mortality (19% vs. 21%, p=0.60).[212] The trial also randomized patients after 6 months to maintenance therapy for an additional 6 months or no maintenance. It found no differences in risk of recurrence (43% vs. 50% after 3 years, p=0.20), progression (9% vs. 8%), or mortality (17% vs. 20%). However, in a multivariate model that adjusted for

prognostic factors, patients who received delayed therapy and no maintenance had a higher rate of recurrence than the other patients. Rates of local and systemic side effects were low, with no clear differences between regimens.

One trial of responders to 5-week induction therapy with sequential mitomycin and doxorubicin found maintenance therapy through 12 months associated with decreased risk of recurrence versus no maintenance therapy that was of borderline statistical significance (36% vs. 65%, RR 0.55, 95% CI 0.30 to 1.0).[202] The estimate for risk of progression was very imprecise (RR 3.12, 95% CI 0.35 to 28.0).

Key Question 4. For patients with high-risk non–muscle-invasive bladder cancer treated with TURBT, what is the effectiveness of external beam radiation therapy (either alone or with systemic chemotherapy/ immunotherapy) for decreasing mortality or improving other outcomes compared with intravesical chemotherapy/immunotherapy alone or cystectomy?

Key Points

- One randomized trial of patients with T1G3 bladder cancer found no effects of radiation therapy versus no radiotherapy (unifocal disease and no CIS) or radiation therapy versus intravesical therapy (multifocal disease or CIS) in recurrence-free survival (HR 0.94, 95% CI 0.67 to 1.30), progression-free interval (HR 1.07, 95% CI 0.65 to 1.74), progression-free survival (HR 1.35, 95% CI 0.92 to 1.98), or overall survival (HR 1.32, 95% CI 0.86 to 2.04) after 5 years (SOE: low).

Detailed Synthesis

One randomized trial (rated medium risk of bias) compared external beam radiation therapy versus no radiation therapy in patients with NMIBC (Appendixes E5, F2).[239] Patients with T1G3 lesions and unifocal disease without CIS were randomized to radiation therapy (60 Gy in 30 fractions during 6 weeks or equivalent) versus no radiotherapy (group 1, n=77) and patients with multifocal disease or CIS were randomized to radiation therapy versus intravesical therapy (group 2, n=133). Radiation therapy was associated with no effects on recurrence-free survival (HR 0.94, 95% CI 0.67 to 1.30), progression-free interval (HR 1.07, 95% CI 0.65 to 1.74), progression-free survival (HR 1.35, 95% CI 0.92 to 1.98), or overall survival (HR 1.32, 95% CI 0.86 to 2.04) after 5 years. The rate of progression to muscle invasive disease was high (~32% overall). There was no evidence of an interaction between effects of radiotherapy and the patient group. Rates of cystectomy were similar (14% vs. 16%), and there was no clear difference in risk of long-term adverse events.

One cohort study of T1G3 patients found that patients who underwent radiotherapy plus TURBT had lower likelihood of progression than those who underwent TURBT alone, but there was no difference compared with TURBT + intravesical therapy, and the study did not attempt to adjust for potential confounders (Appendixes E5, F3).[240]

Key Question 5. In surveillance of patients treated for non–muscle-invasive bladder cancer, what is the effectiveness of various urinary biomarkers to decrease mortality or improve other outcomes compared with other urinary biomarkers or standard diagnostic methods (cystoscopy, cytology, and imaging)?

Key Points

- No study evaluated the effectiveness of urinary biomarkers to decrease mortality or improve other outcomes compared with standard diagnostic methods or other urinary biomarkers (SOE: insufficient).

Detailed Synthesis

No study evaluated the effectiveness of urinary biomarkers to decrease mortality or improve other outcomes compared with standard diagnostic methods or other urinary biomarkers.

Key Question 5a. Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?

Key Points

- No evidence (SOE: insufficient).

Key Question 5b. Does the comparative effectiveness differ according to the treatment used (i.e., specific chemotherapeutic or immunotherapeutic agents and/or TURBT)?

Key Points

- No evidence (SOE: insufficient).

Key Question 5c. Does the comparative effectiveness differ according to the length of surveillance intervals?

Key Points

- No evidence (SOE: insufficient).

Key Question 5d. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, or race/ethnicity?

Key Points

- No evidence (SOE: insufficient).

Key Question 6. For initial diagnosis or surveillance of patients treated for non–muscle-invasive bladder cancer, what is the effectiveness of blue light or other methods of augmented cystoscopy compared with standard cystoscopy for recurrence rates, progression of bladder cancer, mortality, or other clinical outcomes?

Key Points

- There was no difference between fluorescent versus white light cystoscopy in risk of mortality (3 trials, RR 1.28, 95% CI 0.55 to 2.95, I^2=41%) (SOE: low).
- Fluorescent cystoscopy with 5-ALA or hexaminolevulinate (HAL) was associated with decreased risk of bladder cancer recurrence versus white light cystoscopy at short-term (<3 months, 9 trials, RR 0.58, 95% CI 0.36 to 0.94, I^2=75%), intermediate-term (3 months to <1 year, 5 trials, RR 0.67, 95% CI 0.51 to 0.88, I^2=35%), and long-term followup (≥1 year, 11 trials, RR 0.81, 95% CI 0.68 to 0.98, I^2=64%), but findings were inconsistent and potentially susceptible to performance bias (due to failure to blind the initial cystoscopy) and publication bias (SOE: low).
- There was no difference between fluorescent versus white light cystoscopy in risk of progression to muscle invasive bladder cancer (9 trials, RR 0.78, 95% CI 0.55 to 1.12, I^2=0%) (SOE: moderate).
- Narrow band imaging was associated with lower risk of bladder cancer recurrence at 3 months (3.9% vs. 17%, OR 0.62, 95% CI 0.41 to 0.92) and at 12 months (OR 0.24, 95% 0.07 to 0.81) in one trial (SOE: low).

Detailed Synthesis

Fourteen trials (reported in 19 publications) evaluated clinical outcomes of augmented (fluorescent or narrow band imaging) cystoscopy versus standard white light cystoscopy (Table 19; Appendix E6).[241-259] Thirteen trials evaluated fluorescent cystoscopy following instillation of the photosensitizer 5-ALA, which is not commercially available (6 studies),[241,246,252,256,257,259] or HAL (7 studies).[245,247,248,250,251,255,258] One trial evaluated narrow band imaging.[254] Sample sizes ranged from 44 to 551 and duration of followup from 6 weeks to 60 months. Mean age of participants ranged from 60 to 70 years of age and participants were predominantly male, except in the trial of narrow band imaging (~80% female). One trial was conducted in the United States, Canada, and Europe;[249,258] the remainder were conducted in Europe. One trial restricted enrolment to patients with new bladder cancer;[255] the other trials included patients with either new or recurrent bladder cancer or did not specify whether patients had new or recurrent bladder cancer. In all studies, patients underwent TURBT and intravesical therapy protocols varied. Followup analyses were restricted to patients with NMIBC (Ta, T1, and in some cases CIS) on initial cystoscopy. Followup was performed with fluorescent light cystoscopy in one trial;[256] in the other trials followup was performed with white light cystoscopy or the method was not reported. Three trials were rated high risk of bias and the other 11 medium risk of bias (Appendix F2). Only one trial described an adequate randomization method,[254] four trials reported adequate allocation concealment,[247,248,255,257] and four trials reported followup cystoscopic examinations blinded to initial cystoscopy method.[247,248,257,259] All trials except for one used an unblinded design. It evaluated cystoscopic examination with white light and fluorescent cystoscopy blinded to instillation of fluorescent photosensitizer versus placebo,

which could reduce performance bias.[259] In one other trial, patients were initially randomized to no HAL versus HAL and all underwent white light cystoscopy; the HAL group subsequently underwent a second randomization to fluorescent cystoscopy versus no fluorescent cystoscopy.[258] Although this design may reduce performance bias related to performance of the initial white light cystoscopy, the second cystoscopic examination was still unblinded. Four trials reported high attrition[252,257-259] and one trial did not report attrition.

Fluorescent cystoscopy was associated with decreased risk of bladder cancer recurrence versus white light cystoscopy at short-term (<3 months, 9 trials, RR 0.58, 95% CI 0.36 to 0.94, I^2=75%, Figure 34),[241,245,247,248,251,252,255,256,259] intermediate-term (3 months to <1 year, 5 trials, RR 0.67, 95% CI 0.51 to 0.88, I^2=35%, Figure 35),[245,248,250,256,258] and long-term followup (≥1 year, 11 trials, RR 0.81, 95% CI 0.68 to 0.98, I^2=64%, Figure 36) (Table 20).[241,245,246,248,250,251,255-259] Estimates were similar in sensitivity analysis using the profile likelihood method. Statistical heterogeneity was not reduced and estimates were similar when trials were stratified according to the photosensitizer used (5-ALA or HAL), risk of bias (medium or high), or masking of followup cystoscopy to the initial cystoscopy method. Results were also similar in an analysis restricted to recurrence assessed at around 1 year (9 to 16 months) (9 trials, RR 0.80, 95% CI 0.63 to 1.02, I^2=69%).[241,245,248,250,251,255,257-259] For short-term recurrence, two outlier trials reported point estimates that favored white light cystoscopy. One of the trials was the only one in which the initial cystoscopy was blinded to use of a photosensitizer (patients randomized to identical 5-ALA and placebo solutions and all underwent cystoscopy using fluorescent light) (RR 1.37, 95% CI 0.90 to 2.09).[259] It also reported an estimate that favored white-light cystoscopy for long-term recurrence (RR 1.20, 95% 0.94 to 1.52). The other trial was the only one that restricted inclusion to patients with new bladder cancer (RR 1.16, 95% CI 0.61 to 2.19).[255] Although all patients in this trial, including those with low-risk lesions, received single-shot intravesical MMC, other trials that reported more favorable effects of fluorescent cystoscopy on risk of recurrence also administered intravesical therapy in patients with low-risk lesions.[241,245-247,256]

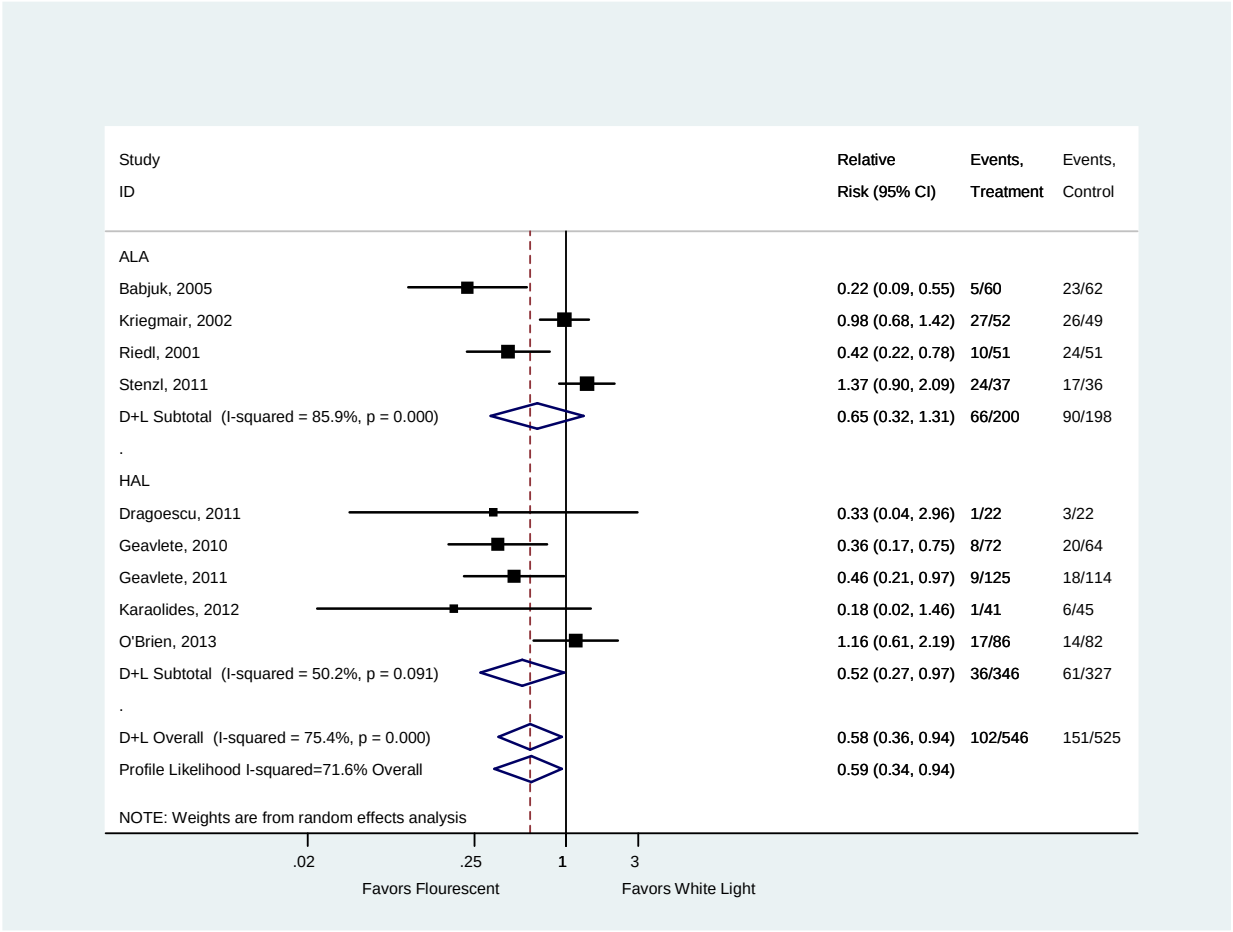
One other trial (n=604) did not meet inclusion criteria because it was published only as an abstract, but also reported results inconsistent with overall pooled estimates.[260] It found no differences between fluorescent versus white light cystoscopy in risk for recurrence at short-term (29% vs. 29%) or long-term (24-month) followup (18% vs. 19%). Followup was performed with fluorescent cystoscopy.

There was no difference between fluorescent versus white light cystoscopy in risk of progression to muscle-invasive bladder cancer (9 trials, RR 0.78, 95% CI 0.55 to 1.12, I^2=0%, Figure 37).[241,245,246,248,251,256-259] Estimates were similar in analyses stratified by the photosensitizer used, risk of bias, masking of the followup cystoscopy to the initial cystoscopy method, or duration of followup (9-18 months versus >24 months). Results were also similar when the one trial that performed followup using fluorescent cystoscopy was excluded.[256]

There was no difference between fluorescent versus white light cystoscopy in risk of mortality, though this outcome was only reported in three trials and the estimate was imprecise (RR 1.28, 95% CI 0.55 to 2.95, I^2=41%, Figure 38).[255,257,258] Stratification by the photosensitizer used, the duration of followup, and risk of bias did not reduce statistical heterogeneity. There was also no difference between fluorescent versus white light cystoscopy in risk of mortality when the one trial[256] that performed followup using fluorescent cystoscopy was excluded, or when the analysis was performed using the profile likelihood method.

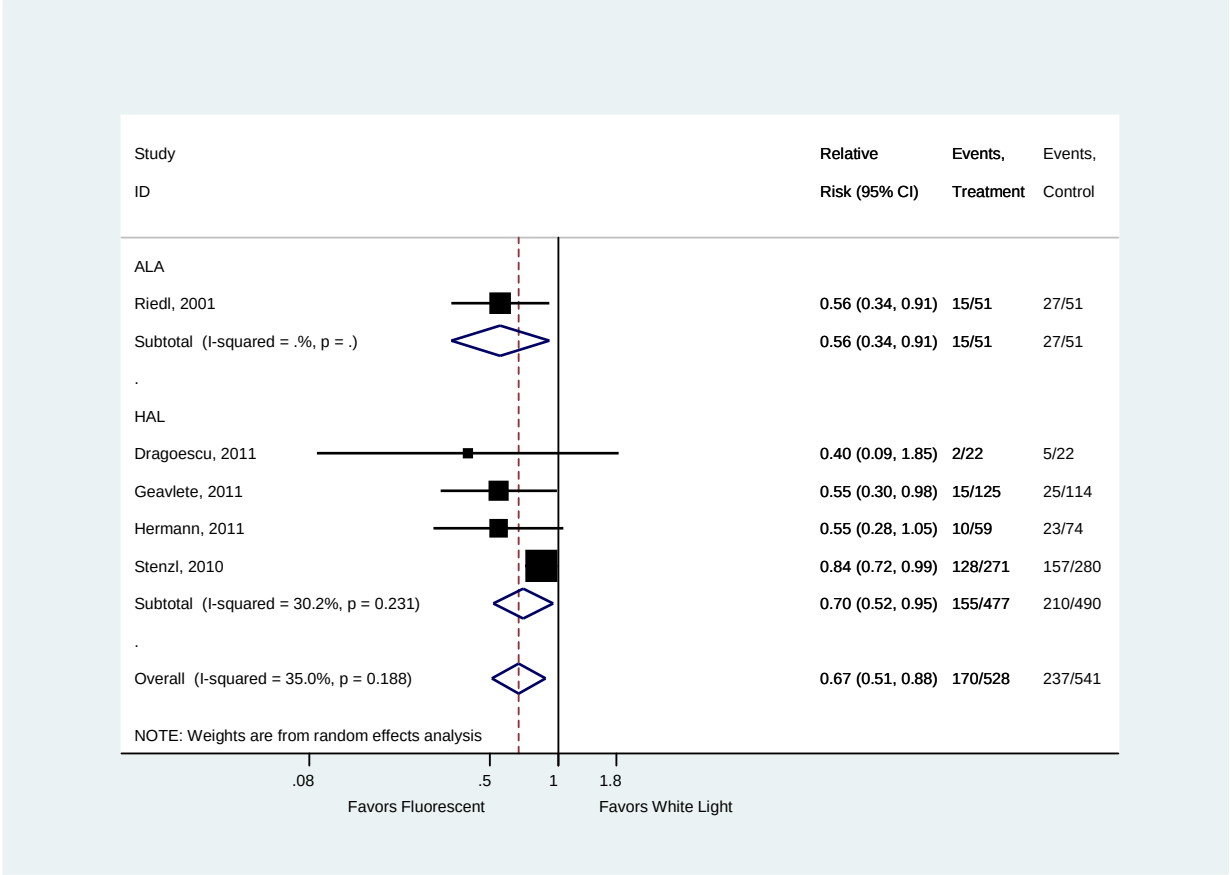
One trial evaluated outcomes following use of narrow band imaging versus white light cystoscopy. It found narrow band imaging associated with lower risk of bladder cancer recurrence at 3 months (3.9% vs. 17%, OR 0.62, 95% CI 0.41 to 0.92) and at 12 months (OR 0.24, 95% 0.07 to 0.81).[254] It did not report effects of narrow band imaging on risk of bladder cancer progression or mortality.

Figure 34. Meta-analysis of fluorescent cystoscopy versus white light cystoscopy: Risk of bladder cancer recurrence at short term (<3 months) followup



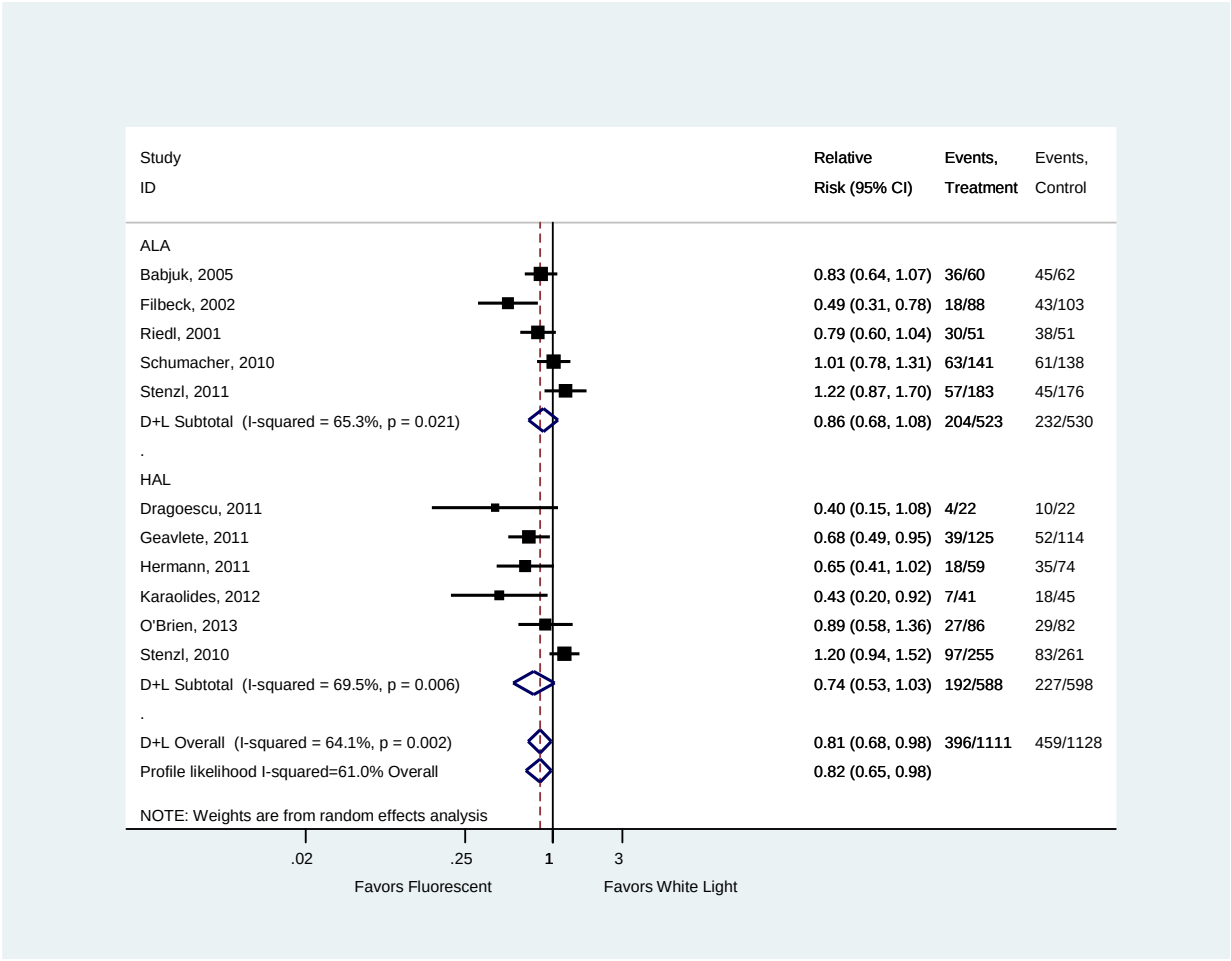
ALA = aminolevulinic acid; CI = confidence interval; HAL = hexaminolevulinate

Figure 35. Meta-analysis of fluorescent cystoscopy versus white light cystoscopy: Risk of bladder cancer recurrence at intermediate term (3 months to <1 year)



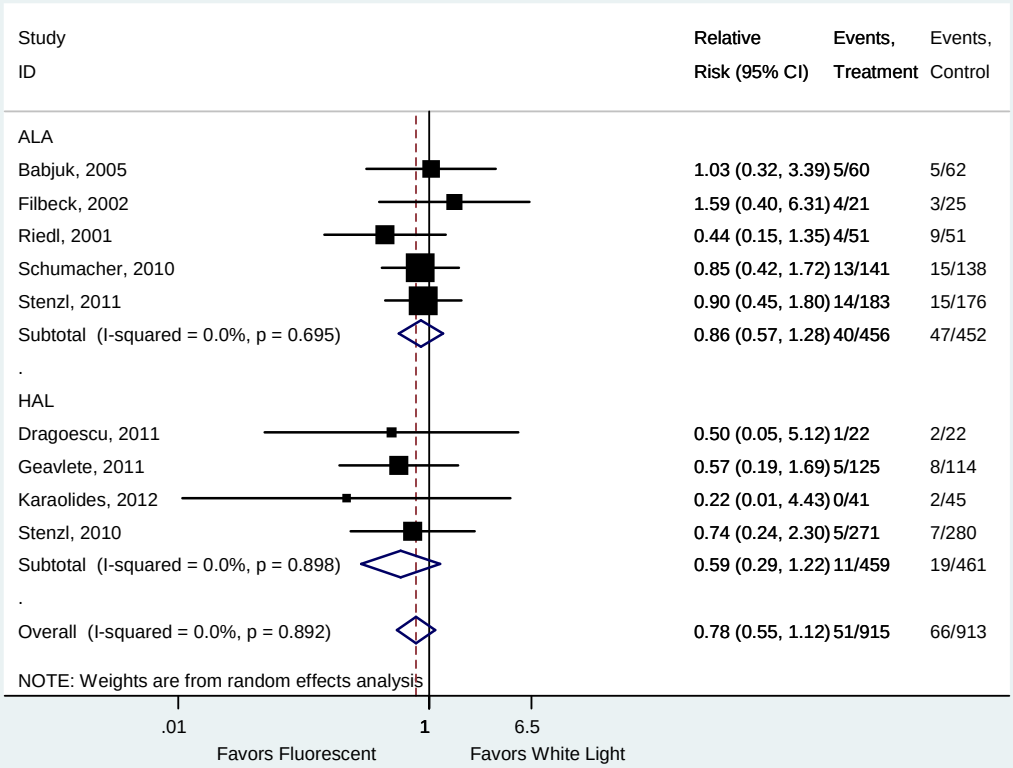
CI = confidence interval; HAL = hexaminolevulinate

Figure 36. Meta-analysis of fluorescent cystoscopy versus white light cystoscopy: Risk of bladder cancer recurrence at long term (≥1 year)



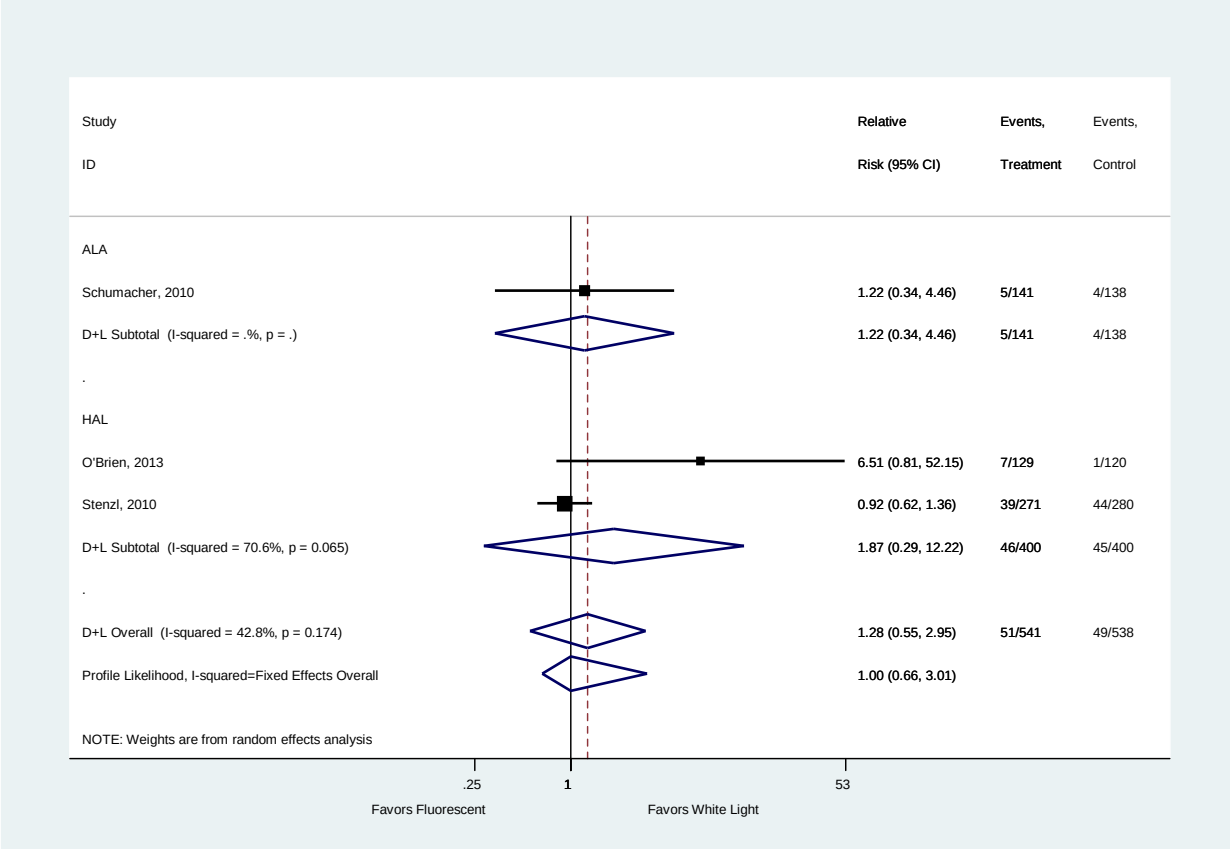
ALA = aminolevulinic acid; CI = confidence interval; HAL = hexaminolevulinate

Figure 37. Meta-analysis of fluorescent cystoscopy versus white light cystoscopy: Risk of progression to muscle-invasive bladder cancer



ALA = aminolevulinic acid; CI = confidence interval; HAL = hexaminolevulinate

Figure 38. Meta-analysis of fluorescent cystoscopy versus white light cystoscopy: Risk of mortality



ALA = aminolevulinic acid; CI = confidence interval; HAL = hexaminolevulinate

Key Question 7. What are the comparative adverse effects of various tests for diagnosis and post-treatment surveillance of bladder cancer, including urinary biomarkers, cytology, and cystoscopy?

Key Points

- Urinary biomarkers miss 23 to 42 percent of patients with bladder cancer and are incorrectly positive in 11 to 28 percent of patients without bladder cancer, but no study directly measured effects of inaccurate diagnosis on clinical outcomes (SOE: insufficient).
- There were no clear differences between fluorescent cystoscopy versus white light cystoscopy in risk of false-positives in two trials (SOE: low).
- There were no clear differences between fluorescent cystoscopy versus white light cystoscopy in risk of renal and genitourinary adverse events in two trials (SOE: low).

Detailed Synthesis

Urinary biomarkers are associated with potential harms as a result of false-negative tests (which could result in a failure to perform cystoscopy and diagnosis bladder cancer when it is present) or false-positive tests (which could result in unnecessary cystoscopy when bladder cancer is absent). As presented in Key Question 1, the sensitivity of urinary biomarkers ranged from 0.58 to 0.77, meaning that 23 to 42 percent of cancers were missed, and the specificity ranged from 0.72 to 0.89, meaning that 11 to 28 percent of patients without bladder cancer had incorrectly positive tests. However, no study directly measured the clinical consequences of false-negative or false-positives in terms of clinical outcomes such as morbidity, mortality, quality of life due to delayed diagnosis, or complications related to unnecessary cystoscopy.

Harms were not well reported in 13 trials of fluorescent cystoscopy versus white light cystoscopy. Seven trials did not report adverse events at all; two others reported no complications associated with intravesical instillation of the photosensitizer HAL but did not describe methods used to identify adverse events.[248,255] Two trials found no clear difference in risk of false-positives with HAL fluorescent cystoscopy versus white light cystoscopy (25% vs. 16%, RR 1.51, 95% CI 0.88 to 2.57 and 10% vs. 12%, RR 0.80, 95% CI 0.62 to 1.04).[250,258] There were also no clear differences between fluorescent cystoscopy versus white light cystoscopy in risk of renal and genitourinary adverse events[257,258] or serious adverse events.[258,259] One trial found no difference between narrow band imaging versus white light cystoscopy in risk of false-positives.[254]

Key Question 8. What are the comparative adverse effects of various treatments for non–muscle-invasive bladder cancer, including intravesical chemotherapeutic or immunotherapeutic agents and TURBT?

Key Points

Intravesical Therapy Versus No Intravesical Therapy

- Four trials of BCG vs. no intravesical therapy reported granulomatous cystitis or irritative symptoms in 27 to 84 percent of patients, macroscopic hematuria in 21 to 72 percent, and fever in 27 to 44 percent. Harms were not reported in patients who did not receive intravesical therapy (SOE: low).
- Evidence on harms associated with non-BCG intravesical therapies versus no intravesical therapy was very limited, though some trials reported an increased risk of local adverse events. Evidence was insufficient to determine effects of non-BCG intravesical therapies versus no intravesical therapy on risk of systemic adverse events (SOE: low for local adverse events, insufficient for systemic adverse events).

BCG Versus MMC

- BCG was associated with increased risk of any local adverse event (2 trials, RR 2.01, 95% CI 1.59 to 2.54, I^2=0%), granulomatous cystitis (5 trials, RR 1.71, 95% CI 1.22 to 2.41, I^2=58%), dysuria (3 trials, 48% vs. 32%, RR 1.23, 95% CI 1.03 to 1.46, I^2=34%), and hematuria (6 trials, RR 1.78, 95% CI 1.24 to 2.56, I^2=62%) versus MMC (SOE: low for local adverse events and dysuria; moderate for granulomatous cystitis and hematuria).

- BCG was associated with increased risk of any systemic adverse event (2 trials, RR 2.01, 95% CI 1.59 to 2.54, I^2=0%) and fever (4 trials, RR 4.51, 95% CI 2.31 to 8.82, I^2=25%) versus MMC (SOE: low for systemic adverse events and fever).
- There was no difference between BCG versus MMC in risk of discontinuation of instillations (4 trials, RR 1.26, 95% CI 0.39 to 4.01, I^2=70%) (SOE: low).
- BCG was associated with increased risk of discontinuation of instillations versus BCG plus MMC given sequentially (1 trial, RR 4.06, 95% CI 2.09 to 7.86) (SOE: low).

BCG Plus MMC Versus MMC

- There was no difference between sequentially administered BCG plus MMC and MMC alone in local adverse events (1 trial, RR 1.36, 95% CI 0.60 to 3.08) or risk of cystitis (1 trial, RR 1.30, 95% CI 0.88 to 1.93) (SOE: low for local adverse events and cystitis).
- There was no difference between BCG and MMC given sequentially and MMC used alone in systemic adverse events (1 trial, RR 1.07, 95% CI 0.63 to 1.84) but BCG plus MMC was associated with increased risk of fever (1 trial, 12% vs. 3%, RR 3.75, 95% CI 1.08 to 13) (SOE: low for systemic adverse events and fever).
- There was no difference between alternating BCG plus MMC and MMC alone in risk of discontinuation of instillations in patients with CIS (1 trial, RR 0.54, 95% CI 0.16 to 1.84) or in patients with Ta or T1 tumors (1 trial, RR 0.93, 95% CI 0.52 to 1.65) (SOE: low).

BCG Versus Doxorubicin

- BCG was associated with increased risk of cystitis versus doxorubicin (1 trial, RR 17, 95% CI 1 to 289), but there was insufficient evidence to determine effects on dysuria (3 trials, data not pooled) and hematuria (2 trials, data not pooled) due to small numbers of trials with inconsistent results (SOE: low for cystitis; insufficient for dysuria and hematuria).

BCG Versus Epirubicin

- BCG was associated with increased risk of local side effects (1 trial, RR 3.28, 95% CI 1.26 to 8.53), granulomatous cystitis (4 trials, RR 1.86, 95% CI 1.35 to 2.56, I^2=65%), dysuria (1 trial, RR 2.43, 95% CI 1.13 to 5.24), hematuria (4 trials, RR 1.77, 95% CI 1.41 to 2.22, I^2=0%) and fever (2 trials, RR 9.73, 95% CI 2.72 to 35,I^2=0%) versus epirubicin alone, but results were mixed for discontinuation of intravesical therapy (2 trials, data not pooled) (SOE: low for local side effects, dysuria; granulomatous cystitis, hematuria, and fever; insufficient for discontinuation of instillations).
- BCG was associated with increased risk of systemic adverse events (1 trial, RR 5.97, 95% CI 2.18 to 16), granulomatous cystitis (1 trial, RR 2.28, 95% CI 1.46 to 3.54) and discontinuation of instillations (1 trial, RR 4.56, 95% CI 1.35 to 15) versus sequentially administered BCG and epirubicin, but there was no difference in risk of dysuria (1 trial, RR 1.22, 95% CI 0.56 to 2.66), hematuria (2 trials, RR 2.27, 95% CI 0.86 to 6.00, I^2=0%) or fever (2 trials, RR 2.09, 95% CI 0.48 to 9.02, I^2=0%) (SOE: low for systemic adverse events, granulomatous cystitis, discontinuation of instillations, dysuria, hematuria, and fever).

BCG Versus Gemcitabine

- There were no differences between BCG and gemcitabine in risk of local adverse events requiring postponement or discontinuation of intravesical therapy (1 trial, RR 1.33, 95% CI 0.32 to 5.49), systemic adverse events (1 trial, RR 0.50, 95% CI 0.10 to 2.5), dysuria (2 trials, RR 1.51, 95% CI 0.92 to 2.50, I^2=0%), or hematuria (2 trials, RR 4.62, 95% CI 0.78 to 27, I^2=29%), but BCG was associated with increased risk of fever (2 trials, RR 6.24, 95% CI 1.03 to 38, I^2=5%) (SOE: low for local and systemic adverse events, dysuria, hematuria, and fever).
- One trial found no difference between BCG versus BCG plus gemcitabine given sequentially in risk of dysuria (RR 0.92, 95% CI 0.52 to 1.65) or hematuria (RR 0.30, 95% CI 0.08 to 1.09) (SOE: low).

BCG Versus Interferon

- BCG was associated with increased risk of dysuria versus interferon alpha-2a (1 trial, RR 84, 95% CI 5.29 to 1319) but no difference in risk of fever (1 trial, RR 4.82, 95% CI 0.25 to 94) (SOE: low for dysuria and fever).
- BCG was associated with increased risk of constitutional symptoms (1 trial, RR 1.63, 95% CI 1.12 to 2.38) and fever (1 trial, RR 2.26, 95% CI 1.30 to 3.95) versus coadministration of BCG and interferon alpha-2b (SOE: low for constitutional symptoms and fever).

BCG Versus Thiotepa

- BCG was associated with increased risk of bladder irritability (1 trial, RR 2.93, 95% CI 1.45 to 5.90), cystitis (1 trial, RR 18, 95% CI 1.11 to 306), and fever (1 trial, RR 8.36, 95% CI 0.47 to 150) versus thiotepa (SOE: low for dysuria, cystitis and fever).

MMC Versus Doxorubicin

- Evidence was insufficient to determine effects of MMC versus doxorubicin on risk of local adverse events, based on inconsistent results from six trials (SOE: insufficient).

MMC Versus Epirubicin

- One small trial found no difference between MMC versus epirubicin 80 mg in risk of urinary symptoms (SOE: low).

MMC Versus Interferon Alpha

- One trial found MMC associated with greater risk of hematuria versus interferon alpha (RR 2.00, 95% CI 1.09 to 3.65), decreased risk of fever (RR 0.13, 95% CI 0.03 to 0.55), and no difference in risk of dysuria or urinary frequency (SOE: low).

MMC Versus Gemcitabine

- One trial found MMC associated with increased risk of chemical cystitis versus gemcitabine (RR 3.93, 95% CI 1.17 to 13.14), with no difference in risk of dysuria or hematuria. (SOE: low).

Doxorubicin Versus Epirubicin

- Doxorubicin was associated with increased risk of chemical cystitis versus epirubicin (1 trial, RR 1.85, 95% CI 1.13 to 3.03), with no clear difference in risk of dysuria or urinary frequency (2 trials) or hematuria (3 trials, RR 1.53, 95% CI 0.50 to 4.66, I^2=0%) (SOE: low for chemical cystitis, urinary frequency, and hematuria).

Doxorubicin Versus Thiotepa

- One trial found no difference between doxorubicin versus thiotepa in risk of bladder irritability (RR 0.92, 95% CI 0.36 to 2.37) (SOE: low).

Epirubicin Versus Interferon Alpha

- One trial found no difference between epirubicin versus interferon alpha in risk of dysuria or fever (SOE: low).

Detailed Synthesis

Intravesical Drugs Versus No Intravesical Therapy

Eight trials evaluated harms of intravesical therapy versus no intravesical therapy.[117,131,133,135-138,140] One trial evaluated MMC,[117] two trials epirubicin,[131,133] two trials interferon alpha,[136,137] one trial interferon-gamma,[138] one trial thiotepa,[140] and one trial gemcitabine.[135] Reporting of harms was suboptimal and focused primarily on local adverse events.

BCG

Trials of BCG versus no intravesical therapy only reported harms in patients receiving BCG. Granulomatous cystitis or irritative vesical symptoms were reported in 27[110] to 84 percent[104] of patients, macroscopic hematuria in 21[104] to 72 percent,[205] and fever from 27[104] to 44 percent.[109]

MMC

One trial (n=121) found no difference between a single instillation of MMC 40 mg versus TURBT alone in risk of chemical cystitis [3.5% (2/57) vs. 1.6% (1/64)].[117]

Doxorubicin

No study evaluated harms of doxorubicin versus no intravesical therapy.

Epirubicin

One trial found single instillation epirubicin 80 mg (up to 4 repeat instillations for recurrence) associated with increased risk of chemical cystitis versus placebo (12% vs. 1.9%; RR 6.29, 95% CI 2.22 to 17.8).[131] A second trial of single instillation epirubicin 100 mg versus no intravesical therapy also reported imprecise estimates and no statistically significant differences in risk of dysuria (5.9% [4/68] vs. 0.0% [0/66]; RR 8.74, 95% CI 0.48 to 159) or fever (0.0% [0/68] vs. 0.9% [1/66]; RR 0.32, 95% CI 0.01 to 7.80).[133]

Gemcitabine

One trial (n=328) found no difference between a single instillation of gemcitabine 2000 mg versus placebo risk of experiencing at least one adverse event (30% vs. 26%; RR 1.11, 95% CI 0.79 to 1.57) or fever (1.2% [2/166] vs. 0.6% [1/162]).[135]

Interferon Alpha

One trial (n=78) found no difference between interferon alpha versus no intravesical therapy in risk of urinary tract infection (23.3% vs. 16.7%, p=NS).[137] Another trial (n=89) of maintenance therapy with three different doses of interferon alpha (40, 60, and 80 MU) versus no intravesical therapy reported high fever related to urinary tract infections in five patients, but did not specify treatment groups.[136]

Interferon Gamma

One trial (n=54) of induction therapy with interferon-gamma 21 MU (8 instillations over 8 weeks) versus no intravesical therapy reported no withdrawals from treatment due to adverse events, though harms were otherwise poorly reported.[138]

Thiotepa

One trial (n=93) evaluated a maintenance regimen with thiotepa 60 or 30 mg versus no intravesical therapy.[140] Urinary tract symptoms were reported in 17 percent (4/23) of patients randomized to thiotepa 60 mg (2 patients with UTI and 2 with dysuria and urinary frequency) but no patients in the other groups (0% [0/23] vs. 0% [0/47]).[140]

Intravesical Drugs Versus Intravesical Drugs

Fifteen trials evaluated harms of one drug administered for intravesical therapy versus another. Six trials evaluated MMC vs. doxorubicin,[101,112,115,116,144,191] one trial MMC vs. epirubicin,[192] two trials MMC vs. interferon alpha,[193,221] one trial MMC vs. gemcitabine,[194] three trials doxorubicin vs. epirubicin,[119,195,196] one trial doxorubicin vs. thiotepa,[172] and one trial epirubicin vs. interferon alpha.[133] Evaluation of harms was generally suboptimal and inconsistently reported.

BCG Versus MMC

BCG was associated with increased risk of any local adverse event versus MMC when each was administered alone (2 trials, 40% vs. 20%, RR 2.01, 95% CI 1.59 to 2.54, I^2=0%).[151,156] Regarding specific local adverse events, BCG was also associated with increased risk of granulomatous cystitis (5 trials, 31% vs. 19%, RR 1.71, 95% CI 1.22 to 2.41, I^2=58%),[111,153,155,156,160] dysuria (3 trials, 48% vs. 32%, RR 1.23, 95% CI 1.03 to 1.46, I^2=34%),[147,152,154] and hematuria (36% vs. 18%, 6 trials, RR 1.78, 95% CI 1.24 to 2.56, I^2=62%).[111,147,152-154,155] Estimates were similar using the profile likelihood method. For granulomatous cystitis, excluding one trial[160] that administered nine instillations of MMC (versus 12 to 38 instillations in the other trials) reduced statistical heterogeneity, though the pooled estimate was similar (4 trials, RR 2.01, 95% CI 1.56 to 2.59, I^2=0%). Other sensitivity and subgroup analyses had little effect on findings.

BCG was also associated with increased risk of any systemic adverse event (3 trials, 14% vs. 4%, RR 2.93, 95% CI 1.80 to 4.78, I^2=0%)[151,156,160] and fever (4 trials, 18% vs. 3%, RR 4.51, 95% CI 2.31 to 8.82,I^2=25%).[147,152,153,155]

There was no difference between BCG versus MMC alone in risk of discontinuation of further bladder instillations (4 trials, RR 1.26, 95% CI 0.39 to 4.01, I^2=70%), though statistical heterogeneity was present.[149,152,153,160] BCG was associated with reduced risk of discontinuation in one trial that did not include patients with grade 3 tumors,(4% vs. 24%, RR 0.18, 95% CI 0.04 to 0.78)[153] but was associated with increased risk of discontinuation in the three trials that included patients with grade 3 tumors (9% vs. 4%, RR 1.88, 95% CI 1.05 to 3.38, I^2=0%).[149,152,160]

No trial of BCG versus sequential BCG plus MMC evaluated risk of local or systemic adverse events. One trial (n=304) found BCG associated with increased risk of discontinuation of bladder instillations versus sequential BCG plus MMC (26% vs. 6%, RR 4.06, 95% CI 2.09 to 7.86)[163]

BCG Plus MMC Versus MMC

One trial (n=182) found no difference between BCG plus MMC administered sequentially versus MMC alone in risk of experiencing any local adverse event (RR 1.36, 95% CI 0.60 to 3.08) or granulomatous cystitis (RR 1.30, 95% CI 0.88 to 1.93).[166] There was also no difference in risk of any systemic adverse event (1 trial, RR 1.07, 95% CI 0.63 to 1.84). Although BCG plus MMC was associated with increased risk of fever (1 trial, 12% vs. 3%, RR 3.75, 95% CI 1.08 to 13), the estimate was very imprecise.

One other trial (n=256) found no difference between alternating BCG plus MMC versus MMC alone in risk of discontinuation of intravesical therapy in patients with CIS (RR 0.54, 95% CI 0.16 to 1.84)[169] or in patients with Ta or T1 tumors (RR 0.93, 95% CI 0.52 to 1.65).[168]

BCG Versus Doxorubicin

One trial found BCG associated with increased risk of cystitis versus doxorubicin, but the estimate was very imprecise (RR 17, 95% CI 1 to 289).[172] Findings for dysuria were mixed, with one trial finding decreased risk with BCG (RR 0.49, 95% CI 0.30 to 0.82),[170] one trial finding increased risk with BCG (RR 3.16, 95% CI 1.50 to 6.67),[172] and one trial finding no difference (RR 1.24, 95% CI 0.99 to 1.56).[171] The three trials differed in the dose of BCG (80 mg to 150 mg) and doxorubicin administered (20 mg to 50 mg). The trial that found BCG associated with decreased risk of dysuria used the lowest doses of both BCG and doxorubicin.

Effects on risk of systemic adverse events were also inconsistent. One trial found BCG associated with decreased risk of hematuria versus doxorubicin (RR 0.50, 95% CI 0.43 to 0.85),[170] but a second trial found no difference (RR 1.36, 95% CI 0.95 to 1.95).[171] One trial found BCG associated with increased risk of fever versus doxorubicin (RR 5.03, 95% CI 2.75 to 9.19),[171] but a second trial found no difference (RR 0.82, 95% CI 0.64 to 1.05).[170]

BCG Versus Epirubicin

One trial found BCG associated with increased risk of any local side effect versus epirubicin when each was administered alone (20% vs. 6%, RR 3.28, 95% CI 1.26 to 8.53).[177] BCG was also associated with increased risk of granulomatous cystitis (4 trials, 48% vs. 28%, RR 1.86, 95% CI 1.35 to 2.56, I^2=65%),[103,175,177,178] dysuria (1 trial, 24% vs. 10%, RR 2.43, 95% CI 1.13 to 5.24),[177] and hematuria (4 trials, 33% vs. 19%, RR 1.77, 95% CI 1.41 to 2.22, I^2=0%).[103,175,177,178] For granulomatous cystitis, the estimate was similar using the profile likelihood method and subgroup analyses did not impact findings.

BCG was associated with increased risk of fever versus epirubicin when each was administered alone (2 trials, 16% vs. 1%, RR 9.73, 95% CI 2.72 to 35, I^2=0%).[103,177] One trial found BCG associated with increased risk of discontinuation of intravesical therapy (32% vs. 10%, RR 3.29, 95% CI 1.58 to 6.83),[177] though another trial found no difference (RR 0.95, 95% CI 0.85 to 1.05).[178]

BCG was associated with increased risk of granulomatous cystitis versus sequentially-administered BCG plus epirubicin (1 trial, 62% vs. 27%, RR 2.28, 95% CI 1.46 to 3.54),[180] but there was no difference in risk of dysuria (1 trial, RR 1.22, 95% CI 0.56 to 2.66)[181] or hematuria (2 trials, RR 2.27, 95% CI 0.86 to 6.00, I^2=0%).[180,181]

BCG was associated with increased risk of any systemic adverse event versus alternating BCG plus epirubicin (1 trial, 36% vs. 6%, RR 5.97, 95% CI 2.18 to 16),[180] but there was no difference in risk of fever (2 trials, RR 2.09, 95% CI 0.48 to 9.02, I^2=0%).[180,181] One trial found BCG associated with increased risk of discontinuation of intravesical therapy versus alternating BCG plus epirubicin (21% vs. 5%, RR 4.56, 95% CI 1.35 to 15).[180]

BCG Versus Epirubicin Plus Interferon

One trial found BCG associated with increased likelihood of discontinuation of intravesical therapy versus the combination of epirubicin plus interferon, but the estimate was imprecise (9% vs. 2%, RR 5.41, 95% CI 1.23 to 24).[182] There was no difference in frequency of subjective urinary problems (specific adverse events and rates not reported).

BCG Versus Gemcitabine

One trial found no difference between BCG versus gemcitabine in risk of local adverse events requiring postponement or discontinuation of intravesical therapy (RR 1.33, 95% CI 0.32 to 5.49).[185] Two trials found no difference between BCG versus gemcitabine in risk of dysuria (RR 1.51, 95% CI 0.92 to 2.50, I^2=0%) or hematuria (RR 4.62, 95% CI 0.78 to 27, I^2=29%).[184,186] No trial reported risk of granulomatous cystitis.

One trial found no difference between BCG versus gemcitabine in risk of any systemic adverse event (RR 0.50, 95% CI 0.10 to 2.5).[185] Two trials found BCG associated with increased risk of fever, though the estimate was imprecise (RR 6.24, 95% CI 1.03 to 38, I^2=5%).[184,186]

One trial found no difference between BCG versus BCG plus gemcitabine given sequentially in risk of dysuria (RR 0.92, 95% CI 0.52 to 1.65) or hematuria (RR 0.30, 95% CI 0.08 to 1.09).[187] No cases of fever were reported.[187]

BCG Versus Interferon

One trial of BCG versus interferon alpha-2a found BCG associated with increased risk of dysuria (85% vs. 0%, RR 84, 95% CI 5.29 to 1319) and fever, but estimates were extremely imprecise (RR 4.82, 95% CI 0.25 to 94).[188]

One trial found BCG associated with increased risk of constitutional symptoms (18% vs. 11%, RR 1.63, 95% CI 1.12 to 2.38) and fever (11% vs. 5%, RR 2.26, 95% CI 1.30 to 3.95) versus BCG coadministered with interferon alpha-2b.[190]

BCG Versus Thiotepa

One trial found BCG was associated with increased risk of bladder irritability (42% vs. 13%, RR 2.93, 95% CI 1.45 to 5.90), cystitis (16% vs. 0%, RR 18, 95% CI 1.11 to 306), and fever (7%

vs. 0%, RR 8.36, 95% CI 0.47 to 150) versus thiotepa.[172] No patient randomized to thiotepa reported cystitis or fever, resulting in very wide confidence intervals.

MMC Versus Doxorubicin

Six trials reported inconsistent effects of MMC versus doxorubicin administered as induction or maintenance therapy in risk of dysuria or chemical cystitis.[101,112,115,116,144,191] Two trials found MMC was associated with decreased risk of chemical cystitis versus doxorubicin (8.9% vs. 22%, RR 0.41 [95% CI 0.22 to 0.75][116] and 21% vs. 48%, RR 0.31 [95% CI 0.23 to 0.42]),[191] but one trial found MMC associated with a nonstatistcially significant increased risk of chemical cystitis (19% vs. 13%, RR 1.44, 95% CI 0.32 to 6.54).[144] Three trials found no statistically significant differences in risk of dysuria or urinary frequency,[112,115,116] three trials found no difference in risk of hematuria,[112,116,144] and one trial found no difference in risk of bladder irritability.[144] Data were not poolable because event rates and sample sizes were not reported in all trials.

MMC Versus Epirubicin

One small trial (n=44) found no difference between maintenance therapy with MMC 40 mg and a single instillation or maintenance therapy with epirubicin 80 mg in risk of urinary symptoms (13% [2/15] vs. 7% [1/14] vs. 13% [2/15], respectively).[192]

MMC Versus Interferon Alpha

One trial (n=287) found induction therapy with MMC 40 mg associated with higher risk of hematuria versus interferon alpha (19% vs. 9.8%; RR 2.00, 95% CI 1.09 to 3.65).[193] There were no statistically significant differences in risk of dysuria (46% vs. 43%) or urinary frequency (47% vs. 41%). MMC was associated with lower risk of fever (1.4% vs. 11% ; RR 0.13, 95% CI 0.03 to 0.55). No patient in either group had to be withdrawn due to adverse effects. Another trial of induction regimens found no difference between MMC versus interferon alpha in risk of bladder pain (10% vs. 15%), though MMC was associated with increased risk of urinary frequency (28% vs. 11%, p not reported).[221] There were no clear differences in risk of withdrawal due to adverse events.

MMC Versus Interferon Gamma

No study evaluated harms of MMC versus interferon-gamma.

MMC Versus Gemcitabine

One trial (n=109) found induction therapy with MMC associated with increased risk of chemical cystitis versus gemcitabine (21% vs. 6%; RR 3.93, 95% CI 1.17 to 13.14).[194] There were no statistically significant differences in risk of dysuria (20% vs. 9%) or hematuria (7% vs. 4%). Treatment was delayed due to local adverse effects (not specified) in 10 percent of MMC patients and 5 percent of gemcitabine patients.

Doxorubicin Versus Epirubicin

One trial found maintenance therapy with doxorubicin associated with increased risk of chemical cystitis versus epirubicin (35% vs. 19%; RR 1.85, 95% CI 1.13 to 3.03).[119] Three patients (5%) in the doxorubicin group experienced systemic side effects (one case each of thrombocytopenia, hypersensitivity reaction, and fever). Two trials of maintenance therapy

found no clear differences in disk of dysuria, or urinary frequency.[195] There was also no difference in risk of hematuria (3 trials, RR 1.53, 95% CI 0.50 to 4.66; I^2=0.0).[119,195,196]

Doxorubicin Versus Thiotepa

One trial (n=109) found no difference between maintenance therapy with doxorubicin versus thiotepa in risk of bladder irritability (13% vs. 14%; RR 0.92, 95% CI 0.36 to 2.37).[172] Other harms were not reported

Epirubicin Versus Interferon Alpha

One trial (n=134) found no difference between a single instillation of epirubicin versus interferon alpha in risk of dysuria (5.9% [4/68] vs. 1.5% [1/66]) or fever (0.0% [0/68] vs. 6.1% [4/66]).[133] Other harms were not reported.

Key Question 8a. How do adverse effects of treatment vary by patient characteristics, such as age, sex, race/ethnicity, performance status, or medical comorbidities such as chronic kidney disease?

Key Points

- No study evaluated how harms of treatment vary in subgroups defined by patient characteristics such as age, sex, race/ethnicity, performance status, or medical comorbidities (SOE: insufficient).

Table 2. Biomarker study characteristics

Author, Year Country	Biomarker	Method of Data Collection	Reason for Testing: Evaluation of Symptoms, Surveillance, or Mixed	Subject Characteristics	Proportion with Bladder Cancer, Bladder Cancer Stage and Grade
Cha, 2012[74] Germany	ImmunoCyt	Prospective	Evaluation of symptoms	Median age: 65 years Male: 78% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: 68% microscopic hematuria and 32% macroscopic hematuria Prior bladder cancer stage/grade: None with prior bladder cancer	202/1182 (21%) Tumor stage: 160 Ta, 44 T1, 26 T2-T4 Tumor grade: 138 low grade, 97 high grade

Table 2. Biomarker study characteristics (continued)

Author, Year Country	Biomarker	Method of Data Collection	Reason for Testing: Evaluation of Symptoms, Surveillance, or Mixed	Subject Characteristics	Proportion with Bladder Cancer, Bladder Cancer Stage and Grade
Chahal, 2001[30] United Kingdom	NMP22 (quantitative)	Prospective	Mixed	Age: Not reported Sex: Not reported Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported	16/96 (17%) Primary tumor stage: 7 Ta, 5 T1, 3 T2, 1 T1 Tumor grade: 6 G1, 3 G2, 7 G3 17/115 Recurrent tumor stage: 15 Ta, 2 T1 Tumor grade: 13 G1, 3 G2, 1 G3
Feil, 2003[31] Germany	ImmunoCyt	Unclear	Mixed	Mean age: 62 years Male: 82% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported	26/113 (23%) Tumor stage: 11 Ta, 8 T1, 7 T2 Tumor grade: 7 G1, 19 G2/G3
Friedrich, 2002[32] Germany	BTA stat NMP22 (quantitative)	Unclear	Mixed	Age: Not reported Sex: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: 30 Ta, 15 T1	54/115 (47%) Tumor stage 25 Ta, 20 T1, 8 ≥T2, 1 CIS Tumor grade: 7 G1, 31 G2, 16 G3

Table 2. Biomarker study characteristics (continued)

Author, Year Country	Biomarker	Method of Data Collection	Reason for Testing: Evaluation of Symptoms, Surveillance, or Mixed	Subject Characteristics	Proportion with Bladder Cancer, Bladder Cancer Stage and Grade
Giannopoulos, 2001[33] Greece	NMP22 (quantitative, Bladderchek) BTA stat	Unclear	Mixed	Mean age: 66 years Male: 85% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported	118/234 (50%) Tumor stage: 57 Ta, 32 T1, 20 T2-4, 6 CIS, 3 Tx Tumor grade: 30 G1, 45 G2, 43 G3
Gibanel, 2002[34] Spain	BTA TRAK	Unclear	Mixed	Age: Not reported Sex: Not reported Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Previous bladder cancer stage/grade: Not reported	21/65 (32%) Tumor stage: 2 Tis, 12 Ta, 2 T1, 5 T2-4 Tumor grade: 9 G1, 4 G2, 6 G3
Grossman, 2005[35] United States (also Lotan 2009[47])	NMP22 (qualitative, BladderChek)	Prospective	Evaluation of symptoms	Mean age: 59 years Male: 57%Race/ethnicity: 82% White, non-Hispanic; 9% Smoker: Not reported Signs or symptoms: Not reported	79/1331 (5.9%) Tumor stage: 30 Ta, 27 T1, 6 T2 or T2a, 4 T3a or T3b, 7 Tx, 5 CIS Tumor grade: 27 well differentiated, 18 moderately differentiated, 25 poorly differentiated, 9 grade unknown
Grossman, 2006[36] United States	NMP22 (qualitative, BladderChek)	Prospective	Surveillance	Mean age: 71 years Male: 75% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported	103/668 (15%) Tumor stage: 50 Ta, 17 T1, 8 T2, 1 T3, 2 T4, 8 CIS, 17 Tx Tumor grade: 38 well differentiated, 16 moderately differentiated, 32 poorly differentiated

Table 2. Biomarker study characteristics (continued)

Author, Year Country	Biomarker	Method of Data Collection	Reason for Testing: Evaluation of Symptoms, Surveillance, or Mixed	Subject Characteristics	Proportion with Bladder Cancer, Bladder Cancer Stage and Grade
Gudjonsson, 2008[37] Sweden	FISH (UroVysion)	Prospective	Surveillance	Mean age: Not reported Sex: Not reported Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: All Ta, T1, or CIS; otherwise not reported	27/152 (18%) Tumor stage/grade: 1 low malignant potential, 16 TaG1-G2, 1 TaG1 + CIS, 5 Tis, 4 T1G2-G3
Gupta, 2009[38] India	NMP22 (qualitative, BladderChek)	Prospective	Surveillance	Mean age: 57 years Male: 87% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: 91 Ta, 45 T1, 9 CIS; 18 low malignant potential, 83 low grade, 44 high grade	56/145 (39%) Tumor stage: 31 Ta, 13 T1, 3 CIS Tumor grade: 6 low malignant potential, 27 low grade, 14 high grade
Gutierrez Banos, 2001[39] Spain	NMP22 (quantitative) BTA stat	Unclear	Mixed	Mean age: 68 years Sex: Not reported Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms (n=64): 88% macroscopic hematuria, 6.2% irritative symptoms, 6.2% other Prior bladder cancer stage/grade: Not reported	76/150 (51%) Tumor stage: 16 Ta, 46 T1, 14 T2-T4 Tumor grade: 16 G1, 29 G2, 31 G3

Table 2. Biomarker study characteristics (continued)

Author, Year Country	Biomarker	Method of Data Collection	Reason for Testing: Evaluation of Symptoms, Surveillance, or Mixed	Subject Characteristics	Proportion with Bladder Cancer, Bladder Cancer Stage and Grade
Halling, 2002[40] United States	BTA statFISH (UroVysion)	Unclear	Mixed	Mean age: 70 yearsMale: 75%Race/ethnicity: Not reportedSmoker: Not reportedSigns and symptoms: Not reportedPrior bladder cancer stage/grade: Not reported	75/265 (28%)Tumor stage: 38 Ta, 19 T1-T4, 17 CISTumor grade: 12 G1, 25 G2, 37 G3
Horstmann, 2009[75] Germany	NMP22 (quantitative) ImmunoCyt FISH (UroVysion)	Unclear	Surveillance	Mean age: 77 years Male: 82% Race/ethnicity: Not reported Smoker: Not reported Signs and symptoms: Not reported Prior bladder cancer stage/grade: Not reported	113/221 (51%) Tumor stage: 69 Ta, 15 T1, 11 T2-T4, 18 CIS Tumor grade: 32 G1, 53 G2, 28 G3
Ianari, 1997[41] Italy	BTA stat	Prospective	Surveillance	Median age: 66 years Male: 83% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported	13/75 (17%) Tumor stage: 18 Ta, 4 T1 and CIS, 13 T2, 4 T3, 1 T4, 3 CIS Tumor grade: 1 G1, 2 G2, 3 G3, 7 Gx
Irani, 1999[42] France	BTA stat BTA TRAK	Prospective	Evaluation of symptoms	Mean age: Not reported Male: 83% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported	49/81 (60%) Tumor stage: 28 Ta, 11 T1, 10 ≥T2 Tumor grade: 19 G1, 18 G2, 12 G3

Table 2. Biomarker study characteristics (continued)

Author, Year Country	Biomarker	Method of Data Collection	Reason for Testing: Evaluation of Symptoms, Surveillance, or Mixed	Subject Characteristics	Proportion with Bladder Cancer, Bladder Cancer Stage and Grade
Junker, 2006[76] Germany	FISH (UroVysion)	Unclear	Mixed	Mean age: Not reported Male: Not reported Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported	112/141 (79%) Tumor stage: 76 Ta, 24 T1, 11 T2-T3, 1 CIS Tumor grade: Not reported
Karnwal, 2010[43] United States	FISH (UroVysion)	Retrospective	Surveillance	Mean age: 56 years Male: 68% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: 33 Ta, 22 T1, 2 T1 and CIS; 23 G1, 20 G2, 16 G3	48/59 (81%) Tumor grade: 23 G1 or G2, 25 G3
Leyh, 1997a[44] Germany, UK, and France	BTA stat	Prospective	Mixed	Mean age: 60 yearsMale: 64%Race/ethnicity: Not reportedSmoker: Not reportedSigns or symptoms (n=413): 122 macroscopic hematuria, 323 microscopic hematuria, 75 dysuria, 148 bladder irritability, 77 urinary urgency, 39 flank pain, 44 suspicious cystoscopy, 21 abnormal intravenous urographyPrior bladder cancer stage/grade: Not reported	71/414 (17%)Tumor stage: 28 Ta, 23 T1, 18 ≥T2, 4 CISTumor grade: 6 G1, 36 G2, 25 G3

Table 2. Biomarker study characteristics (continued)

Author, Year Country	Biomarker	Method of Data Collection	Reason for Testing: Evaluation of Symptoms, Surveillance, or Mixed	Subject Characteristics	Proportion with Bladder Cancer, Bladder Cancer Stage and Grade
Leyh, 1997b[45] Germany and France	BTA stat	Prospective	Surveillance	Mean age: 67 years Male: 77% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported	39/164 (24%) Tumor stage: 15 Ta, 10 T1, 10 ≥T2 Tumor grade: 10 G1, 16 G2, 12 G3
Leyh, 1999[77] Austria, France, Germany, and Italy	BTA stat	Prospective	Evaluation of symptoms	Mean age: 64 years Male: 72% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported	107/231 (46%) Tumor stage: 58 Ta, 27 T1, 17 T2-T4, 5 CIS Tumor grade: 26 G1, 45 G2, 36 G3
Lodde, 2003[46] Italy	uCyt+ (ImmunoCyt)	Prospective	Mixed	Mean age: Not reported Sex: Not reported Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported	51/91 (56%) primary Tumor stage: 29 Ta, 13 T1, 6 ≥T2, 3 CIS Tumor grade: 20 G1, 18 G2, 13 G3 51/134 (38%) recurrent Tumor stage: 33 Ta, 3 t1, 5 ≥T2, 10 CIS Tumor grade: 23 G1, 10 G2, 18 G3

Table 2. Biomarker study characteristics (continued)

Author, Year Country	Biomarker	Method of Data Collection	Reason for Testing: Evaluation of Symptoms, Surveillance, or Mixed	Subject Characteristics	Proportion with Bladder Cancer, Bladder Cancer Stage and Grade
Messing, 2005[48] United States	ImmunoCyt	Unclear	Surveillance	Age: Not reported Sex: Not reported Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: All T1 or less; no other data provided	61/327 (19%) Tumor stage: 35 Ta, 8 T1, 2 T2, 5 CIS, 9 Tx Tumor grade: 28 G1, 10 G2, 6 G3
Mian, 1999[50] Italy	ImmunoCyt	Prospective	Mixed	Mean age: 66 yearsMale: 77%Race/ethnicity: Not reportedSmoker: Not reportedSigns or symptoms: Not reportedPrior bladder cancer stage/grade: Not reported	56/142 (39%) primary, 23/107 (21%) recurrentTumor stage: 43 Ta, 20 T1, 12 ≥T2, 4 CISTumor grade: 25 G1, 25 G2, 29 G3
Mian, 2000[49] Italy and Austria	BTA stat	Retrospective	Mixed	Mean age: 66 years Sex: Not reported Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported	53/180 (29%) Tumor stage: 28 Ta, 13 T1, 7 ≥T2, 1 CIS Tumor grade: 18 G1, 19 G2, 16 G3
Nasuti, 1999[51] United States	BTA stat	Unclear	Evaluation of symptoms	Age: Not reported Sex: Not reported Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported	3/100 (3%) Tumor stage: 2 noninvasive, 1 invasive Tumor grade: 2 G2, 1 G3

Table 2. Biomarker study characteristics (continued)

Author, Year Country	Biomarker	Method of Data Collection	Reason for Testing: Evaluation of Symptoms, Surveillance, or Mixed	Subject Characteristics	Proportion with Bladder Cancer, Bladder Cancer Stage and Grade
Olsson, 2001[78] Sweden	ImmunoCyt	Unclear	Mixed	Mean age: 68 years Male: 79% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: 50% with hematuria Prior bladder cancer stage/grade: Not reported	31/114 (27%) Tumor stage: 18 Ta, 7 T1, 4 T2, 2 CIS Tumor grade: 8 G1, 14 G2, 8 G3
O'Sullivan, 2012[52] New Zealand	CxBladder NMP22 (qualitative, Bladderchek) NMP22 (quantitative)	Prospective	Evaluation of symptoms	Median age: 69 years Male: 80% Race/ethnicity: 87% European, 6.8% Maori Smoker: 16% current, 44% ex-smoker, 40% never smoker Signs or symptoms: 100% macroscopic hematuria	66/485 (14%) Tumor stage: 38 Ta, 16 T1, 9 T2, 2 ≥T3, 2 CIS Tumor grade: 3 G1, 38 G2, 24, G3 (WHO 1973); 32 low, 4 mixed, 29 high (WHO ISUP 1998)
Paoluzzi, 1999[53] Italy	NMP22 (quantitative)	Unclear	Evaluation of symptoms	Age: Not reported Male: 85% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: 100% macroscopic or microscopic hematuria	32/90 (36%) Tumor stage: Not reported Tumor grade: Not reported
Piaton, 2003[79] Pfister, 2003[54] France	ImmunoCyt	Prospective	Mixed	Mean age: 66 years Male: 79% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported	57/236 (24%) primary; 85/458 (19%) recurrent Tumor stage: 75 Ta, 28 T1, 28 T2 or greater, 8 CIS Tumor grade: 31 G1, 40 G2, 68 G3

Table 2. Biomarker study characteristics (continued)

Author, Year Country	Biomarker	Method of Data Collection	Reason for Testing: Evaluation of Symptoms, Surveillance, or Mixed	Subject Characteristics	Proportion with Bladder Cancer, Bladder Cancer Stage and Grade
Placer, 2002[55] Spain	FISH (UroVysion)	Unclear	Mixed	Mean age: 70 years Male: 88% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported	47/86 (55%)Tumor stage: 26 Ta, 12 T1, 9 T2-T4Tumor grade: 16 G1, 12 G2, 19 G3
Pode, 1999[56] Israel	BTA stat	Prospective	Mixed	Mean age: Not reported Male: 83% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms of bladder cancer: 88 with hematuria or irritative voiding symptoms, otherwise not reported Prior bladder cancer stage/grade: Not reported	71/88 (81%) primary; 57/162 (35%) recurrent Tumor stage: 72 Ta, 29 T1, 13 T2 or T3a, 14 T3b or higher Tumor grade: 25 G1, 58 G2, 45 G3
Ponsky, 2001[57] United States	NMP22 (quantitative)	Prospective	Mixed	Mean age: 70 years in patients with cancer 61 years in patients without cancer 72% male Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: 143 macroscopic hematuria, 226 microscopic hematuria, 239 urinary frequency or dysuria Prior bladder cancer stage: Not reported	52/608 (8.6%) Tumor stage and grade: 30 Ta and grade 1 to 2, 12 T1 and grade 2 to 3, 7 T2 and grade 3 or greater, 3 Tis

Table 2. Biomarker study characteristics (continued)

Author, Year Country	Biomarker	Method of Data Collection	Reason for Testing: Evaluation of Symptoms, Surveillance, or Mixed	Subject Characteristics	Proportion with Bladder Cancer, Bladder Cancer Stage and Grade
Quek, 2002[58] Singapore	BTA stat	Prospective	Mixed	Mean age: 54 years 68% male Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: 60 macroscopic hematuria, 29 microhematuria, 13 vesical irritability Prior bladder cancer stage: Not reported	15% (16/106) primary; 31% (4/13) recurrent Tumor stage: 4 Ta, 10 T1, 6 T2-T4 Tumor grade: 7 G1, 6 G2, 7 G3
Raitanen, 2001a[59] and 2001b[80] Finland	BTA stat	Prospective	Surveillance	Mean age: 69 years79% male Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: 242 Ta, 187 T1, 20 CIS, 52 Tx; 220 G1, 215 G2, 52 G3, 14 Gx	131/501 (26%)Tumor stage: 56 Ta, 23 T1, 3 T2-3, 12 CIS, 37 TxTumor grade: 52 G1, 37 G2, 8 G3, 34 Gx
Saad, 2002[60] UK	NMP22 (quantitative) BTA stat	Prospective	Evaluation of symptoms	Mean age: 70 years Male: 83% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported	52/73 (71%) with bladder cancer Tumor stage: 23 Ta, 20 T1, 8 T2, 6 CIS Tumor grade: 13 G1, 22 G2, 17 G3
Sanchez-Carbayo, 2001[61] Spain	NMP22 (quantitative)	Prospective	Evaluation of symptoms	Mean age: 66 years 65% male Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: All had microscopic hematuria	43/112 (38%) Tumor stage: 5 Ta, 28 T1, 7 T2, 2 T3, 1 CIS Tumor grade: 11 G1, 15 G2, 17 G3

Table 2. Biomarker study characteristics (continued)

Author, Year Country	Biomarker	Method of Data Collection	Reason for Testing: Evaluation of Symptoms, Surveillance, or Mixed	Subject Characteristics	Proportion with Bladder Cancer, Bladder Cancer Stage and Grade
Sarosdy, 2002[62] United States	FISH (UroVysion) BTA stat	Prospective	Surveillance	Mean age: 71 years 75% male Nonwhite race/ethnicity: 13% Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: 118 Ta, 20 T1, 4 T2, 29 CIS, 5 Tx; 70 G1, 56 G2, 46 G3, 4 Gx	62/176 (35%) Tumor stage: 32 Ta, 6 T1, 3 T2, 7 CIS, 11 Tx Tumor grade: 22 G1, 9 G2, 18 G3
Sawczuk, 2000[63] United States	NMP22 (quantitative)	Unclear	Surveillance	Mean age: 69 years Sex: Not reported Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: 35 Ta, 14 T1, 2 T2, 5 T3-4; 31 G1 or G2, 25 G3 or G4 (7 with associated CIS)	34/56 (61%) Tumor stage: 27 Ta, 4 T1, 3 T3b or 4 Tumor grade: 22 G1-2, 12 G3-4

Table 2. Biomarker study characteristics (continued)

Author, Year Country	Biomarker	Method of Data Collection	Reason for Testing: Evaluation of Symptoms, Surveillance, or Mixed	Subject Characteristics	Proportion with Bladder Cancer, Bladder Cancer Stage and Grade
Schamhart, 1998[64] the Netherlands	BTA stat	Prospective	Mixed	Mean age: 66 years Sex: 81% male Nonwhite race/ethnicity: 0% Smoker: Not reported Signs and symptoms: 10% macroscopic hematuria, 4.7% microscopic hematuria, 0.5% flank pain, 2.6% dysuria, 4.7% dysuria, 2.6% urgency, 5.2% other symptoms Prior bladder cancer stage/grade: Not reported	62/149 (42%)Tumor stage: 42 Ta, 6 T1, 5 ≥T2, 3 CISTumor grade: 5 G1, 32 G2, 17 G3, 20 G3 + CIS
Schmitz-Drager, 2007a[82] Germany	ImmunoCyt	Unclear	Evaluation of symptoms	Mean age: 57 years Male: 77% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: All had painless microscopic hematuria Prior bladder cancer stage/grade: No prior bladder cancer	8/189 (4.2%) Tumor stage: 5 Ta, 1 T1, 2 T2-T3 Tumor grade: 5 low malignant potential, 3 high grade

Table 2. Biomarker study characteristics (continued)

Author, Year Country	Biomarker	Method of Data Collection	Reason for Testing: Evaluation of Symptoms, Surveillance, or Mixed	Subject Characteristics	Proportion with Bladder Cancer, Bladder Cancer Stage and Grade
Schmitz-Drager, 2007b[81] Germany	ImmunoCyt	Unclear	Evaluation of symptoms	Mean age: 58 years Male: 89% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: All had painless macroscopic hematuria Prior bladder cancer stage/grade: No prior bladder cancer	15/59 (25%) Tumor stage: 5 Ta, 3 T1, 6 T2-T4 Tumor grade: 5 low-grade, 9 high-grade
Serretta, 1998[65] Italy	NMP22 (quantitative)	Unclear	Surveillance	Mean age: 65 years Male: 89% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage and grade: 7 Tis, 49 Ta, 71 T1, 10 T2-3; 12 G1, 74 G2, 51 G3	42/137 (31%) Tumor stage: Not reported Tumor grade: Not reported
Serretta, 2000[83] Italy	NMP22 (quantitative) BTA Stat BTA TRAK	Unclear	Surveillance	Mean age: 65 years Male: 84% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage and grade: 53 Ta, 107 T1, 12 T2-3, 7 CIS, 16 G1, 93 G2, 70 G3	55/179 (31%) Tumor stage: 13 Ta, 27 T1, 12 T2-3, 3 CIS, 7 G1, 19 G2, 29 G3 Tumor grade: 7 G1, 19 G2, 29 G3

Table 2. Biomarker study characteristics (continued)

Author, Year Country	Biomarker	Method of Data Collection	Reason for Testing: Evaluation of Symptoms, Surveillance, or Mixed	Subject Characteristics	Proportion with Bladder Cancer, Bladder Cancer Stage and Grade
Shariat, 2006[66] United States, Europe, Japan, Canada	NMP22 (quantitative)	Prospective	Surveillance	Median age: 68 years Male: 76% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported	1045/2871 (36%) Tumor stage: 448 Ta, 276 T1, 220 ≥T2 Tumor grade: 233 G1, 420 G2, 329 G3
Sharma, 1999[67] United States	NMP22 (quantitative) BTA stat	Unclear	Mixed	Mean age: Not reported Sex: Not reported Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: 40% microscopic hematuria, 28% macroscopic hematuria, 32% chronic irritative voiding symptoms Prior bladder cancer stage/grade: Not reported	34/278 (12%) with bladder cancer; 6/199 (3.0%) in people without prior bladder cancer; 28/79 (35%) in people with prior cancer Tumor stage: Not reported Tumor grade: Not reported
Song, 2010[84] South Korea	FISH (UroVysion)	Prospective	Evaluation of symptoms	Mean age: 62 years Male: 82% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Hematuria Prior bladder cancer stage/grade: Not reported	95/602 (16%) Tumor stage: 38 Ta, 29 T1, 24 T2-T3, 4 CIS Tumor grade: 20 G1, 35 G2, 16 G3

Table 2. Biomarker study characteristics (continued)

Author, Year Country	Biomarker	Method of Data Collection	Reason for Testing: Evaluation of Symptoms, Surveillance, or Mixed	Subject Characteristics	Proportion with Bladder Cancer, Bladder Cancer Stage and Grade
Sullivan, 2009[85] USA	FISH (UroVysion) ImmunoCyt	Unclear	Surveillance	Mean age: Not reported Male: Not reported Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: All undergoing surveillance Prior bladder cancer stage/grade: Not reported	25/100 (12%) Tumor stage: 19 Ta, 4 T1, 2 T2 Tumor grade: 13 low grade, 11 high grade
Tetu, 2005[86] Canada	ImmunoCyt	Retrospective	Mixed	Mean age: Not reported Male: Not reported Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported	136/870 (16%) Tumor stage: 65 Ta, 6 T1, 19 T2-T4, 14 CIS Tumor grade: 31 low malignant potential, 33 low-grade papillary carcinoma, 40 high grade papillary carcinoma
Thomas, 1999[69] Europe	BTA TRAK	Prospective	Mixed	Mean age: 64 yearsMale: 70%Caucasian: 98%Smoker: Not reportedSigns or symptoms: Not reportedPrior bladder cancer stage/grade: Not reported	100/220 (45%) overall; 49/96 (51%) primary; 51/124 (41%) recurrent Tumor stage: 55 Ta, 24 T1, 16 T2-T4, 5 CISTumor grade: 25 G1, 41 G2, 34 G3
Toma, 2004[87] Germany	NMP22 (quantitative) ImmunoCyt BTA stat FISH (UroVysion)	Unclear	Mixed	Age: Not reported Sex: Not reported Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported	42/126 (33%) Tumor stage: 21 Ta, 15 T1, 6 T2-T4, 2 CIS Tumor grade: 7 G1, 23 G2, 12 G3

Table 2. Biomarker study characteristics (continued)

Author, Year Country	Biomarker	Method of Data Collection	Reason for Testing: Evaluation of Symptoms, Surveillance, or Mixed	Subject Characteristics	Proportion with Bladder Cancer, Bladder Cancer Stage and Grade
United Kingdom and Eire Bladder Tumour Antigen Study Group, 1997[68] UK	BTA stat	Prospective	Surveillance	Age: Not reported Sex: Not reported Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported	102/272 (38%) Tumor stage: Not reported Tumor grade: Not reported
van Der Poel, 1998[70] the Netherlands	BTA stat	Unclear	Surveillance	Age: Not reported Sex: Not reported Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported	58/103 (56%) Tumor stage: 40 Ta, 7 T1, 4 T2, 3 T3, 3 CIS Tumor grade: 7 G1, 27 G2, 20 G3
Varella-Garcia, 2004[71] United States	FISH (UroVysion)	Prospective	Surveillance	Mean age: 69 years Male: 84% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported	7/19 (37%) with bladder cancer Tumor stage: 3 Ta, 2 T1, 2 T2 Tumor grade: 2 G1, 3 G2, 2 G3
Vriesema, 2001[88] the Netherlands	ImmunoCyt	Prospective	Surveillance	Mean age: 68 years Male: 83% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: Not reported	22/86 (26%) with bladder cancer Tumor stage: 17 Ta, 3 T1, 1 T2-T4, 1 CIS Tumor grade: Not reported

Table 2. Biomarker study characteristics (continued)

Author, Year Country	Biomarker	Method of Data Collection	Reason for Testing: Evaluation of Symptoms, Surveillance, or Mixed	Subject Characteristics	Proportion with Bladder Cancer, Bladder Cancer Stage and Grade
Wiener, 1998[89] Austria	NMP22 (quantitative) BTA stat	Prospective	Mixed	Mean age: 65 years Male: 68% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: 65% Prior bladder cancer stage/grade: Not reported	91/291 (31%) with bladder cancer Tumor stage: 47 Ta, 25 T1, 19 T2-T4 Tumor grade: 23 G1, 38 G2, 30 G3
Witjes, 1998[72] the Netherlands	NMP22 (quantitative)	Unclear	Surveillance	Age: Not reported Sex: Not reported Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported Prior bladder cancer stage/grade: NMIBC, otherwise not reported	12/50 (24%) with bladder cancer Tumor stage: 2 Ta, 1 T1, 3 T2, 1 Tis, 5 not available Tumor grade: 1 G1, 3 G2, 2 G3, 5 not available
Zippe, 1999[73] United States	NMP22 (quantitative)	Unclear	Primary	Mean age: 64 years Male: 77% Race/ethnicity: Not reported Smoker: Not reported Signs or symptoms: Not reported	8/146 (5.5%) with bladder cancer Tumor stage: 3 Ta, 1 Ta/T1, 1 T1, 2 T2, 1 Tis Tumor grade: 2 G1, 1 G1/2, 2 G2, 1 G2/G3, 2 G3

BTA stat = bladder tumor antigen Polymedco rapid test; BTA TRAK = bladder tumor antigen quantitative immunoassay; FISH = fluorescence in situ hybridization; NMP22 = nuclear matrix protein-22; uCyt+ = ImmunoCyt assay.

Table 3. Test performance of urinary biomarkers for diagnosis of bladder cancer

Biomarker		Sensitivity (95% CI); τ^2 (p value)	Number of Studies	Specificity (95% CI); τ^2 (p value)	Number of Studies	LR+	LR-
NMP22 quantitative	Overall	0.69 (0.62 to 0.75); 0.33 (p=0.0005)	19	0.77 (0.70 to 0.83); 0.62 (p<0.0001)	19	3.05 (2.28 to 4.10)	0.40 (0.32 to 0.50)
	Excluding studies that didn't use cutoff of >10	0.70 (0.63 to 0.77); 0.35 (p=0.001)	17	0.77 (0.69 to 0.83); 0.66 (p=0.0001)	17	3.04 (2.19 to 4.20)	0.39 (0.30 to 0.50)
	Excluding high risk of bias studies	0.68 (0.61 to 0.75); 0.32 (p=0.001)	18	0.79 (0.72 to 0.84); 0.55 (p<0.0001)	18	3.18 (2.37 to 4.27)	0.40 (0.32 to 0.50)
	Prospective design	-0.63 (0.53 to 0.73); 0.29 (p=0.001)	8	0.85 (0.78 to 0.90); 0.41 (p<0.0001)	8	4.21 (2.70 to 6.55)	0.43 (0.32 to 0.57)
	United States or Europe	0.70 (0.63 to 0.76); 0.29 (p=0.001)	18	0.77 (0.69 to 0.83); 0.58 (p<0.0001)	18	2.99 (2.22 to 4.02)	0.77 (0.69 to 0.83)
	Prespecified threshold for positive test	0.72 (0.66 to 0.78); 0.23 (p=0.001)	16	0.75 (0.67 to 0.82); 0.53 (p<0.0001)	16	2.90 (2.14 to 3.94)	0.37 (0.29 to 0.47)
	Blinded interpretation of reference standard	0.73 (0.53 to 0.87); 0.34 (p=0.0005)	3	0.89 (0.78 to 0.95); 0.46 (p<0.0001)	3	6.73 (3.26 to 13.9)	0.30 (0.16 to 0.57)
	Evaluation of symptoms	0.67 (0.55 to 0.77); 0.34 (p=0.04)	9	0.84 (0.75 to 0.90); 0.45 (p=0.02)	7	4.20 (2.65 to 6.67)	0.40 (0.29 to 0.55)
	Surveillance	0.61 (0.49 to 0.71); 0.45 (p=0.04)	10	0.71 (0.60 to 0.81); 0.54 (p=0.01)	8	2.10 (1.58 to 2.80)	0.55 (0.44 to 0.69)
NMP22 qualitative	Overall	0.58 (0.39 to 0.75); 0.57 (p=0.14)	4	0.88 (0.78 to 0.94); 0.50 (p=0.13)	4	4.89 (3.23 to 7.40)	0.48 (0.33 to 0.71)
	Low risk of bias studies	0.53 (0.29 to 0.75); 0.46 (p=0.11)	2	0.87 (0.74 to 0.94); 0.35 (p=0.10)	2	3.91 (2.70 to 5.66)	0.55 (0.36 to 0.84)
	United States or Europe	0.53 (0.29 to 0.75); 0.46 (p=0.11)	2	0.87 (0.74 to 0.94); 0.35 (p=0.10)	2	3.91 (2.70 to 5.66)	0.55 (0.36 to 0.84)
	Blinded interpretation of reference standard	0.65 (0.45 to 0.81); 0.47 (p=0.26)	3	0.84 (0.80 to 0.88); 0.05 (p=0.36)	3	4.19 (3.40 to 5.16)	0.41 (0.25 to 0.69)
	Evaluation of symptoms	0.47 (0.33 to 0.61); 0.12 (p=0.38)	2	0.93 (0.81 to 0.97); 0.52 (p=0.31)	2	6.27 (2.98 to 13.2)	0.58 (0.46 to 0.72)
	Surveillance	0.70 (0.40 to 0.89); 0.74 (p=0.36)	2	0.83 (0.75 to 0.89); 0.74 (p=0.31)	2	4.20 (3.22 to 5.47)	0.36 (0.16 to 0.81)

Table 3. Test performance of urinary biomarkers for diagnosis of bladder cancer (continued)

Biomarker		Sensitivity (95% CI); τ^2 (p value)	Number of Studies	Specificity (95% CI); τ^2 (p value)	Number of Studies	LR+	LR-
Qualitative BTA	Overall	0.64 (0.58 to 0.69); 0.26 (p<0.0001)	22	0.77 (0.73 to 0.81); 0.27 (p<0.0001)	21	2.80 (2.31 to 3.39)	0.47 (0.30 to 0.55)
	Excluding high risk of bias studies	0.63 (0.57 to 0.69); 0.26 (p<0.0001)	19	0.79 (0.74 to 0.83); 0.22 (p<0.0001)	18	2.95 (2.42 to 3.61)	0.47 (0.40 to 0.56)
	Prospective design	0.62 (0.55 to 0.69); 0.25 (p<0.0001)	14	0.78 (0.72 to 0.83); 0.26 (p<0.0001)	13	2.84 (2.23 to 3.61)	0.48 (0.40 to 0.58)
	United States or Europe	0.63 (0.57 to 0.69); 0.26 (p<0.0001)	20	0.78 (0.74 to 0.82); 0.24 (p<0.0001)	19	2.91 (2.39 to 3.54)	0.47 (0.40 to 0.55)
	Blinded interpretation of reference standard	0.64 (0.48 to 0.77); 0.26 (p<0.0001)	3	0.85 (0.75 to 0.91); 0.23 (p<0.0001)	3	4.1 (2.49 to 6.85)	0.43 (0.29 to 0.64)
	Evaluation of symptoms	0.76 (0.67 to 0.83); 0.21 (p=0.05)	8	0.78 (0.66 to 0.87); 0.50 (p=0.02)	6	3.42 (2.04 to 5.74)	0.31 (0.21 to 0.46)
	Surveillance	0.60 (0.55 to 0.65); 0.02 (p=0.27)	11	0.76 (0.69 to 0.83); 0.26 (p=0.02)	8	2.53 (1.92 to 3.34)	0.52 (0.47 to 0.59)
Quantitative BTA	Overall	0.65 (0.54 to 0.75); 0.10 (p=0.32)	4	0.74 (0.64 to 0.82); 0.14 (p=0.27)	4	2.52 (1.86 to 3.41)	0.47 (0.37 to 0.61)
	Excluding high risk of bias studies	0.66 (0.53 to 0.77); 0.13 (p=0.42)	3	0.72 (0.59 to 0.83); 0.17 (p=0.41)	3	2.38 (1.69 to 3.35)	0.47 (0.36 to 0.62)
	Used threshold of >14 for positive test	0.69 (0.60 to 0.76); 0.02 (p=0.77)	3	0.71 (0.63 to 0.77); 0.02 (p=0.76)	3	2.35 (1.82 to 3.04)	0.44 (0.34 to 0.58)
	Evaluation of symptoms	0.76 (0.61 to 0.87)	1	0.53 (0.38 to 0.68)	1	1.61 (1.14 to 2.28)	0.46 (0.26 to 0.81)
	Surveillance	0.58 (0.46 to 0.69); <0.0001 (p=1.0)	2	0.79 (0.72 to 0.85); <0.0001 (p=1.0)	2	2.77 (1.66 to 4.61)	0.54 (0.39 to 0.76)
FISH	Overall	0.63 (0.50 to 0.75); 0.74 (p=0.01)	11	0.87 (0.79 to 0.93); 0.90 (p=0.003)	11	5.02 (2.93 to 8.60)	0.42 (0.30 to 0.59)
	Prospective design	0.60 (0.37 to 0.79); 0.72 (p=0.01)	4	0.91 (0.79 to 0.97); 0.83 (p=0.004)	4	7.00 (2.72 to 18.0)	0.44 (0.25 to 0.76)
	Excluding high risk of bias studies	0.61 (0.48 to 0.72); 0.57 (p=0.01)	10	0.86 (0.77 to 0.92); 0.74 (p=0.003)	10	4.24 (2.69 to 6.67)	0.46 (0.35 to 0.61)
	Blinded interpretation of reference standard	0.76 (0.43 to 0.93); 0.70 (p=0.01)	2	0.83 (0.50 to 0.96); 0.85 (p=0.005)	2	4.43 (1.20 to 16.4)	0.29 (0.10 to 0.86)
	Evaluation of symptoms	0.73 (0.50 to 0.88); 0.36 (p=0.40)	2	0.95 (0.87 to 0.98); <0.0001 (p=1.0)	1	14.2 (5.2 to 39)	0.29 (0.14 to 0.60)
	Surveillance	0.55 (0.36 to 0.72); 0.85 (p=0.03)	7	0.80 (0.66 to 0.89); 0.80 (p=0.03)	6	2.75 (1.95 to 3.89)	0.56 (0.42 to 0.76)

Table 3. Test performance of urinary biomarkers for diagnosis of bladder cancer (continued)

Biomarker		Sensitivity (95% CI); τ^2 (p value)	Number of Studies	Specificity (95% CI); τ^2 (p value)	Number of Studies	LR+	LR-
ImmunoCyt	Overall	0.78 (0.68 to 0.85); 0.71 (p=0.003)	14	0.78 (0.72 to 0.82); 0.25 (p=0.001)	14	3.49 (2.82 to 4.32)	0.29 (0.20 to 0.41)
	Excluding studies rated high risk of bias	0.78 (0.68 to 0.86); 0.70 (p=0.003)	13	0.79 (0.74 to 0.83); 0.18 (p=0.002)	13	3.73 (3.09 to 4.51)	0.28 (0.19 to 0.40)
	Prospective design	0.74 (0.54 TO 0.87); 0.70 (p=0.003)	4	0.80 (0.70 to 0.87); 0.24 (p=0.001)	4	3.68 (2.44 to 5.55)	0.32 (0.17 to 0.61)
	Evaluation of symptoms	0.85 (0.78 to 0.90); 0.10 (p=0.30)	6	0.83 (0.77 to 0.87); 0.11 (p=0.07)	7	4.89 (3.79 to 6.30)	0.18 (0.12 to 0.26)
	Surveillance	0.75 (0.64 to 0.83); 0.34 (p=0.05)	7	0.76 (0.70 to 0.81); 0.14 (p=0.04)	8	3.09 (2.56 to 3.72)	0.33 (0.24 to 0.46)
CxBladder	Evaluation of symptoms[a]	0.82 (0.70 to 0.90)	1	0.85 (0.81 to 0.88)	1	5.53 (4.28 to 7.15)	0.21 (0.13 to 0.36)

BTA = bladder tumor antigen; CI = confidence interval; FISH = fluorescence in situ hybridization; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; NMP22 = nuclear matrix protein-22

[a] Based on threshold selected for specificity of 0.85.

Table 4. Direct (within-study) comparisons of diagnostic accuracy of urinary biomarkers for diagnosis of bladder cancer

Biomarkers		Sensitivity A (95% CI)	Sensitivity B (95% CI)	Difference (95% CI); τ^2 (p value)	Number of Studies	Specificity A (95% CI)	Specificity B (95% CI)	Difference (95% CI); τ^2 (p value)	Number of Studies
Quantitative NMP22 (A) vs. qualitative BTA (B)	Restricted to NMP22 studies using a cutoff of >10 U/mL	0.69 (0.62 to 0.76)	0.66 (0.59 to 0.73)	0.03 (-0.04 to 0.10); 0.09 (p=0.04)	7	0.73 (0.62 to 0.82)	0.76 (0.66 to 0.84)	-0.03 (-0.08 to 0.01); 0.42 (p=0.02)	7
	Tumor stage Ta	0.54 (0.45 to 0.62)	0.53 (0.45 to 0.61)	0.01 (-0.11 to 0.13); <0.0001 (p=1.0)	5	No data	No data	--	--
	T1	0.81 (0.67 to 0.90)	0.77 (0.63 to 0.88)	0.03 (-0.07 to 0.13); 0.41 (p=0.08)	5	No data	No data	--	--
	Tumor grade G1	0.52 (0.40 to 0.63)	0.44 (0.33 to 0.56)	0.08 (-0.09 to 0.25); <0.0001 (p=1.0)	5	No data	No data	--	--
	G2	0.67 (0.57 to 0.76)	0.65 (0.55 to 0.74)	0.01 (-0.10 to 0.12); 0.08 (p=0.17)	5	No data	No data	--	--
	Evaluation of symptoms	0.66 (0.55 to 0.76)	0.64 (0.53 to 0.74)	0.02 (-0.09 to 0.14); 0.05 (p=0.44)	3	0.77 (0.61 to o.88)	0.75 (0.57 to 0.86)	0.03 (-0.06 to 0.11); 0.25 (p=0.33)	3
	Surveillance	0.60 (0.30 to 0.85)	0.51 (0.22 to 0.79)	0.10 (-0.10 to 0.29); 1.0 (p=0.28)	3	0.65 (0.54 to 0.75)	0.69 (0.58 to 0.78)	-0.04 (-0.15 to 0.08); 0.04 (p=0.47)	2
BTA qualitative (A) vs. FISH (B)	Overall	0.73 (0.62 to 0.82)	0.76 (0.65 to 0.84)	-0.03 (-0.14 to 0.09); 0.04 (p=0.52)	2	0.76 (0.69 to 0.82)	0.92 (0.87 to 0.96)	-0.16 (-0.24 to -0.08); 0.002 (p=0.83)	2
	Tumor stage Ta	0.57 (0.47 to 0.67)	0.64 (0.54 to 0.74)	-0.07 (-0.21 to 0.07); <0.0001 (p=1.0)	3	No data	No data	--	--
	T1	0.81 (0.59 to 0.93)	0.71 (0.49 to 0.87)	0.10 (-0.16 to 0.35); <0.0001 (p=1.0)	2	No data	No data	--	--
	Tumor grade G1	0.37 (0.23 to 0.52)	0.50 (0.35 to 0.65)	-0.13 (-0.35 to 0.08); <0.0001 (p=1.0)	3	No data	No data	--	--
	G2	0.72 (0.59 to 0.82)	0.70 (0.57 to 0.81)	0.02 (-0.15 to 0.18); <0.0001 (p=1.0)	3	No data	No data	--	--
BTA qualitative (A) vs. ImmunoCyt (B)	Overall	0.67 (0.52 to 0.81)	0.79 (0.66 to 0.91)	-0.12 (-0.31 to 0.07); (p=0.22)[a]	1	0.78 (0.69 to 0.87)	0.74 (0.65 to 0.84)	0.04 (-0.09 to 0.17); (p=0.57)[a]	1

Table 4. Direct (within-study) comparisons of diagnostic accuracy of urinary biomarkers for diagnosis of bladder cancer (continued)

Biomarkers		Sensitivity A (95% CI)	Sensitivity B (95% CI)	Difference (95% CI); τ^2 (p value)	Number of Studies	Specificity A (95% CI)	Specificity B (95% CI)	Difference (95% CI); τ^2 (p value)	Number of Studies
BTA qualitative (A) vs. BTA quantitative (B)	Overall	0.64 (0.52 to 0.74)	0.74 (0.62 to 0.83)	-0.10 (-0.25 to 0.05); <0.0001 (p=1.0)	2	0.67 (0.57 to 0.77)	0.73 (0.63 to 0.81)	-0.06 (-0.19 to 0.08); <0.0001 (p=1.0)	2
CxBladder (A) vs. NMP22 quantitative (B)	Evaluation of symptoms	0.82 (0.70 to 0.90)	0.50 (0.37 to 0.63)	0.32 (0.17 to 0.47); (p=0.0001)[a]	1	0.85 (0.81 to 0.88)	0.88 (0.85 to 0.91)	-0.03 (-0.07 to 0.02) (p=0.22)[a]	
CxBladder (A) vs. NMP22 qualitative (B)	Evaluation of symptoms	0.82 (0.70 to 0.90)	0.38 (0.26 to 0.51)	0.44 (0.29 to 0.59); (p<0.0001)[a]	1	0.85 (0.81 to 0.88)	0.96 (0.94 to 0.98)	-0.11 (-0.15 to -0.07); (p<0.0001)[a]	1
NMP22 quantitative (A) vs. NMP22 qualitative (B)	Evaluation of symptoms	0.50 (0.37 to 0.63)	0.38 (0.26 to 0.51)	0.12 (-0.05 to 0.29); (p=0.16)[a]	1	0.88 (0.85 to 0.91)	0.96 (0.94 to 0.98)	-0.08 (-0.12 to -0.05); (p<0.0001)[a]	1
NMP22 quantitative (A) vs. NMP22 qualitative (B)	Evaluation of symptoms	0.70 (0.50 to 0.90)	0.62 (0.39 to 0.86)	0.08 (-0.24 to 0.39); (p=0.64)[a]	1	0.56 (0.42 to 0.69)	0.79 (0.69 to 0.90)	-0.24 (-0.41 to -0.07); (p=0.01)[a]	1
NMP22 quantitative (A) vs. ImmunoCyt (B)	Evaluation of symptoms	0.69 (0.61 to 0.76)	0.75 (0.67 to 0.81)	-0.06 (-0.17 to 0.04); 0.001 (p=0.87)	2	0.56 (0.47 to 0.65)	0.72 (0.64 to 0.80)	-0.16 (-0.28 to -0.04); 0.02 (p=0.55)	2
	Tumor grade G1	0.59 (0.43 to 0.73)	0.67 (0.51 to 0.80)	-0.08 (-0.29 to 0.14); <0.0001 (p=1.0)	2	No data	No data	--	--
	G2	0.66 (0.54 to 0.76)	0.79 (0.68 to 0.87)	-0.13 (-0.27 to 0.01)	2	No data	No data	--	--

Table 4. Direct (within-study) comparisons of diagnostic accuracy of urinary biomarkers for diagnosis of bladder cancer (continued)

Biomarkers		Sensitivity A (95% CI)	Sensitivity B (95% CI)	Difference (95% CI); τ^2 (p value)	Number of Studies	Specificity A (95% CI)	Specificity B (95% CI)	Difference (95% CI); τ^2 (p value)	Number of Studies
NMP22 quantitative (A) vs. FISH (B)	Evaluation of symptoms	0.68 (0.60 to 0.75)	0.74 (0.66 to 0.80)	-0.06 (-0.16 to 0.04); 0.001 (p=0.85)	2	0.58 (0.40 to 0.74)	0.76 (0.60 to 0.87)	-0.18 (-0.28 to -0.08); 0.22 (p=0.33)	2
	Tumor grade G1	0.59 (0.43 to 0.73)	0.54 (0.38 to 0.69)	0.05 (-0.17 to 0.27); <0.0001 (p=1.0)	2	No data	No data	--	--
	G2	0.66 (0.54 to 0.76)	0.76 (0.66 to 0.85)	-0.11 (-0.25 to 0.04); <0.0001 (p=1.0)	2	No data	No data	--	--
ImmunoCyt (A) vs. FISH (B)	Evaluation of symptoms	0.71 (0.54 to 0.84)	0.61 (0.43 to 0.76)	0.11 (0.001 to 0.21); 0.31 (p=0.30)	3	0.71 (0.62 to 0.79)	0.79 (0.71 to 0.85)	-0.08 (-0.15 to -0.001); 0.07 (p=0.34)	3
	Tumor stage Ta	0.71 (0.46 to 0.87)	0.36 (0.17 to 0.61)	0.35 (0.13 to 0.56); 0.29 (p=0.40)	2	No data	No data	--	--
	T1	0.89 (0.66 to 0.97)	0.58 (0.36 to 0.77)	0.32 (0.05 to 0.58); <0.0001 (p=1.0)	2	No data	No data	--	--
	Low grade (G1 or low grade)	0.65 (0.47 to 0.80)	0.42 (0.25 to 0.60)	0.24 (0.05 to 0.24); 0.17 (p=0.40)	3	No data	No data	--	--
Biomarker + cytology (A) versus biomarker alone (B)	Overall	0.81 (0.75 to 0.86)	0.69 (0.61 to 0.76)	0.13 (0.08 to 0.17); 0.42 (p=0.0003)	16	0.74 (0.70 to 0.78)	0.75 (0.71 to 0.79)	-0.01 (-0.04 to 0.02); 0.12 (p=0.001)	13
	Tumor stage Ta	0.82 (0.75 to 0.87)	0.79 (0.72 to 0.85)	0.03 (-0.05 to 0.11); 0.01 (p=0.73)	5	No data	No data	--	--
	T1	0.87 (0.75 to 0.94)	0.85 (0.73 to 0.92)	0.02 (-0.11 to 0.15); <0.0001 (p=1.0)	5	No data	No data	--	--
	Low grade (G1, low grade, or low malignant potential)	0.74 (0.63 to 0.82)	0.73 (0.63 to 0.82)	-0.01 (-0.10 to 0.09)	6	No data	No data	--	--
ImmunoCyt + cytology (A) versus ImmunoCyt alone (B)		0.79 (0.68 to 0.87)	0.69 (0.56 to 0.80)	0.09 (0.03 to 0.16); 0.55 (p=0.01)	8	0.74 (0.68 to 0.79)	0.75 (0.70 to 0.80)	-0.02 (-0.05 to 0.01); 0.13 (p=0.01)	7

BTA = bladder tumor antigen; CI = confidence interval; CIS = carcinoma in situ; FISH = fluorescence in situ hybridization; NMP22 = nuclear matrix protein-22; U/mL = units per milliliter

[a] Based on Fisher's exact test

Table 5. Sensitivity of urinary biomarkers for bladder cancer according to tumor stage and grade

Biomarker		Sensitivity (95% CI); τ^2 (p value)	Number of Studies	Comparison	Difference in Sensitivity	Overall Difference Across Categories: p value for chi-square
NMP22 (quantitative)	Tumor stage Ta	0.48 (0.36 to 0.60); 0.46 (p=0.01)	10	T1 vs. Ta	0.23 (0.14 to 0.32)	p=0.002
	T1	0.72 (0.60 to 0.81)	11	≥T2 vs. T1	0.10 (0.01 to 0.20)	--
	≥T2	0.82 (0.70 to 0.89)	11	Ta vs. CIS	-0.18 (-0.43 to 0.07)	--
	CIS	0.66 (0.38 to 0.86)	6	--	--	--
	Tumor grade G1	0.44 (0.32 to 0.57); 0.44 (p=0.004)	12	G2 vs. G1	0.14 (0.05 to 0.24)	p<0.0001
	G2	0.58 (0.47 to 0.69)	12	G3 vs. G2	0.16 (0.09 to 0.24)	--
	G3	0.75 (0.65 to 0.83)	12	--	--	--
NMP22 (qualitative)	Tumor stage Ta	0.39 (0.30 to 0.49); 0.02 (p=0.57)	3	T1 vs. Ta	0.14 (-0.02 to 0.29)	p=0.37
	T1	0.53 (0.40 to 0.66)	3	≥T2 vs. T1	0.58 (-0.05 to 0.36)	--
	≥T2	0.69 (0.51 to 0.83)	3	Ta vs. CIS	-0.18 (-0.56 to 0.21)	--
	CIS	0.57 (0.22 to 0.86)	2	--	--	--
	Tumor grade G1	0.36 (0.23 to 0.51); 0.07 (p=0.36)	3	G2 vs. G1	0.06 (-0.12 to 0.25)	p=0.03
	G2	0.42 (0.29 to 0.56)	3	G3 vs. G2	0.30 (0.13 to 0.46)	--
	G3	0.65 (0.52 to 0.77)	3	--	--	--
FISH	Tumor stage Ta	0.49 (0.31 to 0.66); 0.89 (p=0.02)	8	T1 vs. Ta	0.30 (0.18 to 0.42)	p=0.002
	T1	0.79 (0.61 to 0.90)	7	≥T2 vs. T1	0.11 (-0.01 to 0.23)	--
	≥T2	0.89 (0.75 to 0.96)	7	Ta vs. CIS	-0.42 (-0.60 to -0.24)	--
	CIS	0.91 (0.66 to 0.98)	4	--	--	--
	Tumor grade G1	0.46 (0.34 to 0.59); 0.17 (p=0.07)	7	G2 vs. G1	0.28 (0.15 to 0.40)	p<0.0001
	G2	0.74 (0.63 to 0.82)	7	G3 vs. G2	0.21 (0.11 to 0.30)	
	G3	0.94 (0.88 to 0.98)	7	--	--	--
Quantitative BTA	Tumor stage Ta	0.53 (0.39 to 0.66); 0.04 (p=0.71)	4	T1 vs. Ta	0.29 (0.13 to 0.46)	p=0.11
	T1	0.82 (0.67 to 0.91)	4	≥T2 vs. T1	0.06 (-0.09 to 0.22)	--
	≥T2	0.88 (0.72 to 0.96)	4	Ta vs. CIS	-0.05 (-0.44 to 0.34)	--
	CIS	0.58 (0.23 to 0.86)	2	--	--	--
	Tumor grade G1	0.51 (0.36 to 0.67); 0.08 (p=0.42)	4	G2 vs. G1	0.12 (-0.06 to 0.29)	p=0.03
	G2	0.63 (0.47 to 0.76)	4	G3 vs. G2	0.23 (0.07 to 0.38)	--
	G3	0.86 (0.73 to 0.93)	4	--	--	--

Table 5. Sensitivity of urinary biomarkers for bladder cancer according to tumor stage and grade

Biomarker		Sensitivity (95% CI); τ^2 (p value)	Number of Studies	Comparison	Difference in Sensitivity	Overall Difference Across Categories: p value for chi-square
Qualitative BTA	Tumor stage Ta	0.49 (0.41 to 0.56); 0.28 (p=0.0003)	18	T1 vs. Ta	0.25 (0.18 to 0.32)	p<0.0001
	T1	0.74 (0.66 to 0.80)	17	≥T2 vs. T1	0.15 (0.08 to 0.22)	--
	≥T2	0.89 (0.83 to 0.93)	17	Ta vs. CIS	-0.20 (-0.34 to -0.06)	--
	CIS	0.68 (0.52 to 0.81)	10	--	--	--
	Tumor grade G1	0.39 (0.30 to 0.48); 0.40 (p=0.0001)	19	G2 vs. G1	0.24 (0.17 to 0.32)	p<0.0001
	G2	0.63 (0.54 to 0.71)	19	G3 vs. G2	0.18 (0.12 to 0.25)	--
	G3	0.81 (0.75 to 0.87)	19	--	--	--
ImmunoCyt	Tumor stage Ta	0.74 (0.63 to 0.83); 0.42 (p=0.01)	9	T1 vs. Ta	0.06 (-0.05 to 0.17)	p=0.60
	T1	0.81 (0.67 to 0.90)	9	≥T2 vs. T1	0.002 (-0.13 to 0.13)	--
	≥T2	0.81 (0.68 to 0.89)	10	Ta vs. CIS	-0.16 (-0.27 to -0.05)	--
	CIS	0.90 (0.76 to 0.96)	9	--	--	--
	Tumor grade G1	0.73 (0.63 to 0.81)	6	G2 vs. G1	0.10 (0.01 to 0.19)	p=0.20
	G2	0.83 (0.75 to 0.89)	6	G3 vs. G2	0.003 (-0.07 to 0.08)	--
	G3	0.83 (0.75 to 0.89)	6	--	--	--
	Low grade[a]	0.74 (0.66 to 0.80); 0.09 (p=0.05)	10	High vs. low grade	0.10 (0.03 to 0.17)	--
	High grade[a]	0.83 (0.78 to 0.88)	10	--	--	--

BTA = bladder tumor antigen; CI = confidence interval; CIS = carcinoma in situ; FISH = fluorescence in situ hybridization; NMP22 = nuclear matrix protein-22

[a]Low grade=G1, low grade, or low malignant potential, high grade=G2, G3, or high grade.

Table 6. Summary of bacillus Calmette-Guérin study characteristics and results

Comparison	Author, Year	Population	Intervention	Results/Followup
BCG vs. MMC; BCG vs. MMC+BCG; BCG+MMC vs. MMC	DeBruyne, 1992[160] Debruyne, 1988[150] Witjes, 1998[159]	Primary or recurrent superficial bladder cancer, including CIS, Ta, T1	A. BCG-RIVM (5 x 10^8 CFU) in 50 mL saline weekly for 6 weeks B. MMC 30 mg in 50 mL saline weekly for 4 weeks then monthly for 6 months	Recurrence: 42% vs. 36% 7 year followup: Recurrence 48% vs. 43% Progression 12% vs. 7% Mortality: 46 vs. 51 Malignant disease: 15 vs. 18 Median followup: 21 months
	Di Stassi, 2003[155]	Histologically proven multifocal carcinoma in situ of the bladder and most had concurrent pT1 papillary transitional cell carcinoma	A. BCG 81 mg, 6 weekly instillations then monthly instillations for 10 months B. MMC 40 mg, 6 weekly instillations then monthly instillations for 10 months C. MMC 40 mg (electromotive), 6 weekly instillations then monthly instillations for 10 months	Overall mortality: 11/36 vs. 12/36 vs. 9/36 Recurrence: 19/36 vs. 27/36 vs. 19/36 Progression: 6/36 vs. 8/36 vs. 6/36 Granulomatous cystitis: 24/36 vs. 9/36 vs. 13/36 Fever: 7/36 vs. 0/36 vs. 0/36 Hematuria: 26/36 vs. 6/36 vs. 8/36 Median followup: 43 vs. 42 vs. 45 months
	Friedrich, 2007[154]	Patients with primary transitional cell carcinoma of the bladder or tumor recurrence after TURBT without prior adjuvant therapy were eligible if pTaG1 tumor (size>3cm, recurrent or multifocal tumor) or pTaG2 up to pT1 tumor (G1-3). Patients with apT1G3 tumor were eligible in case of a unifocal small tumor (≤2.5 cm).	A. BCG RVIM, 6 weekly instillations B. MMC 20 mg, 6 weekly instillations C. MMC 20 mg, 6 weekly instillations followed by monthly instillations for 3 years	Recurrence: 41/163 vs. 46/179 vs. 16/153 Dysuria: 28/163 vs. 21/179 vs. 31/153 Hematuria: 19/163 vs. 1/179 vs. 14/153 Fever: 15/163 vs. 4/179 vs. 4/153 Median followup: 2.9 years

Table 6. Summary of bacillus Calmette-Guérin study characteristics and results (continued)

Comparison	Author, Year	Population	Intervention	Results/Followup
	Gardmark, 2007[157] Lundholm, 1996[152] Malmstrom, 1999[158]	Stage Ta, grades 1 to 3 or stage T1, grades 1 and 2 tumors were included provided there had been at least 3 tumor events during the prior 18 months. Patients with stage T1 grade 3 and those with primary or concomitant dysplasia or carcinoma in situ were included without having had prior tumor events	A. BCG 120 mg, 6 weekly instillations followed by monthly instillations for 1 year then quarterly for 1 year B. MMC 40 mg, 6 weekly instillations followed by monthly instillations for 1 year then quarterly for 1 year	Overall mortality: 68/125 vs. 72/125 Bladder cancer mortality: 19/125 vs. 26/125 Progression: 24/125 vs. 34/125 Fever: 29/125 vs. 7/125 DC instillations: 16/125 vs. 10/125 Dysuria: 100/125 vs. 87/125 Hematuria: 112/125 vs. 78/125 Median followup: 39 months; Also 10 year followup
	Gulpinar, 2012[162]	Patients with intermediate or high risk for recurrence and progression according to the EAU guidelines were included. Patients with stage pTaG1or pTaG2 tumors were included if tumor size>3cm or recurrent or multifocal tumors. Patients with CIS, pTaG3 tumors and all pT1 tumors were included	A. BCG $5x10^8$ CFU, 6 weekly instillations beginning at least 15 days from TURBT B. MMC 40, single dose at surgery followed by 6 weekly BCG instillations beginning at least 15 days from TURBT	Recurrence: 5/26 vs. 9/25 Progression: 1/26 vs. 1/25 Cystectomy: 1/26 vs. 1/25 Median followup: 41months
	Jarvinen, 2009[161] Rintala, 1991[149]	Frequently recurrent TaT1 tumors and/or CISTa-T1 cancers with a minimum of two episodes of recurrence during the preceding 1.5 years	A. BCG 75 mg, 5 weekly instillations beginning 2 weeks after TURBT then monthly instillations for 2 years B. MMC 30-40 mg, 5 weekly instillations beginning 2 weeks after TURBT then monthly instillations for 2 years	Overall mortality: 36/44 vs. 36/45 Bladder cancer mortality: 4/44 vs. 9/45 Recurrence: 26/44 vs. 36/45 Progression: 4/44 vs. 10/45 DC instillations: 10/44 vs. 5/45 Mean followup: 28 months; Also median followup 8.5 years

Table 6. Summary of bacillus Calmette-Guérin study characteristics and results (continued)

Comparison	Author, Year	Population	Intervention	Results/Followup
	Jarvinen, 2012[167] Rintala, 1995[169] (Jarvinen, 2012[167], Rintala, 1995[169] and Rintala, 1996[168] are part of same trial but results reported by subgroup)	Primary, secondary, or concomitant CIS	A. BCG 75 mg + MMC varied dose, 4 weekly instillations of MMC then MMC alternating with BCG monthly for 2 years B. MMC varied dose, 4 weekly doses followed by monthly doses for two years	Overall mortality: 20/28 vs. 30/40 Bladder cancer mortality: 8/28 vs. 12/40 Recurrence: 19/28 vs. 35/40 Progression: 8/28 vs. 14/40 Cystectomy: 1/28 vs. 7/40 Mean followup: 33 months; Also median followup 7.2 years
	Kaasinen, 2003[163]	High-grade primary, secondary, or concomitant (with pTa or pT1 tumor) carcinoma in situ of the urinary bladder	A. BCG 120 mg, 6 weekly instillations followed by monthly instillations up to one year B. MMC 40 mg, 6 weekly instillations followed monthly alternating instillations with BCG for up to 1 year	Bladder cancer mortality: 10/145 vs. 13/159 Recurrence: 53/145 vs. 71/159 Progression: 20/145 vs. 34/159 Cystectomy: 4/145 vs. 4/159 DC instillations: 37/145 vs. 10/159 Median followup: 56 months
	Krege, 1996[111]	Histological evidence of superficial bladder cancer (stage pTa/1 grades 1 to 3)	A. BCG 120 mg, 6 weekly instillation then monthly for 4 months B. MMC 20 mg, instillations every 2 weeks for 1 year then monthly for 1 year	Recurrence: 26/102 vs. 30/112 Cystitis: 35/102 vs. 18/112 Cystectomy: 1/102 vs. 0/112 Fever: 18/102 vs. 0/112 Hematuria: 6/102 vs. 3/112 Mean followup: 20 months
	Lamm, 1995[147]	Histologically proven, completely resected Ta (noninvasive) or T1 (lamina propria invasive) transitional cell carcinoma and at increased risk for tumor recurrence (2 occurrences of tumor within 56 weeks, stage T1 within 16 weeks of registration, or 3 or more tumors presenting simultaneously within 16 weeks)	A. BCG 50 mg, 6 weekly instillations then at 8 and 12 weeks, then monthly up to 1 year B. MMC 20 mg, 6 weekly instillations then at 8 and 12 weeks, then monthly up to 1 year	Overall mortality: 25/191 vs. 28/186 Bladder cancer mortality: 8/191 vs. 12/186 Recurrence: 77/191 vs. 101/186 Progression: 15/191 vs. 24/191 Fever: 38/222 vs. 8/220 Dysuria: 115/222 vs. 80/222 Hematuria: 85/222 vs. 57/220 Median followup: 913 days

Table 6. Summary of bacillus Calmette-Guérin study characteristics and results (continued)

Comparison	Author, Year	Population	Intervention	Results/Followup
	Mangiarotti, 2008[153]	Nonmuscle invasive bladder cancer not previously treated with any chemotherapeutic or immunotherapeutic agent	A. BCG 50 mg, 6 weekly instillations then monthly for up to 1 year B. MMC 40 mg, 8 weekly instillations then monthly for up to 1 year	Overall mortality: 1/46 vs. 0/46 Recurrence: 23/46 vs. 23/46 Granulomatous cystitis: 16/46 vs. 10/46 Fever: 2/46 vs. 2/46 DC instillations: 2/46 vs. 11/46 Hematuria: 0/46 vs. 2/46 Mean followup: 66 months
	Mohsen, 2010[165]	At least 2 histologically verified recurrent stage Ta or T1 during the preceding 1.5 years	A. BCG $5x10^8$ CFU, 6 weekly instillations 1 month after TURBT, then monthly for months 3-12 B. MMC 40 mg perioperatively, then 4 weekly instillations, then BCG monthly for months 2-13	Recurrence: 16/27 vs. 9/29 Cystectomy: 2/27 vs. 1/29 Mean followup: 24 months
	Ojea, 2007[151]	Intermediate risk with stages TaG2 and T1G1-2 superficial bladder tumors without carcinoma in situ	A. BCG 27 mg, 6 weekly instillations then 6 biweekly instillations B. BCG 13.5 mg, 6 weekly instillations then 6 biweekly instillations C. MMC 30 mg, 6 weekly instillations then 6 biweekly instillations	A vs. B vs. C Overall mortality: 13/142 vs. 17/139 vs. 27/149 Bladder cancer mortality: 3/142 vs. 5/139 vs. 7/149 Recurrence: 38/142 vs. 50/139 vs. 58/149 Progression: 14/142 vs. 18/139 vs. 14/149 Local side effects: 93/142 vs. 9/139 vs. 45/149 Systemic side effects: 16/142 vs. 15/139 vs. 7/149 Median followup: 57 vs. 61 vs. 53 months

Table 6. Summary of bacillus Calmette-Guérin study characteristics and results (continued)

Comparison	Author, Year	Population	Intervention	Results/Followup
	Oosterlinck, 2011[164]	Primary, concurrent, or recurrent biopsy-proven CIS	A. BCG $5x10^8$ CFU, 6 weekly instillations, then 3 weeks rest, then 3 weekly instillations, then 3 weekly instillations every 6 months up to 3 years B. MMC 40 mg, 6 weekly instillations then 6 weekly instillations of BCG then 3 weekly instillations (one MMC then 2 BCG) every 6 months up to 3 years	Overall mortality: 11/48 vs. 7/48 Bladder cancer mortality: 6/48 vs. 3/48 Recurrence: 26/48 vs. 23/48 Progression: 5/48 vs. 2/48 Cystectomy: 5/48 vs. 8/48 Median followup: 4.7 years
	Rintala, 1996[168] (Jarvinen, 2012[167], Rintala, 1995[169] and Rintala, 1996[168] are part of same trial but results reported by subgroup	recurrent stage Ta or T1 papillary transitional cell carcinoma; no CIS	4 weekly instillation of MMC then: A. BCG $5x10^8$ CFU + MMC 40 mg (alternating monthly) for two years B. MMC 40 monthly for two years	Recurrence: 57/92 vs. 58/90 DC instillations: 18/92 vs. 19/90 Mean followup: 34 months

Table 6. Summary of bacillus Calmette-Guérin study characteristics and results (continued)

Comparison	Author, Year	Population	Intervention	Results/Followup
	Sekine, 2001[145]	Tis with or without T1 bladder cancer	A: BCG, type of BCG, dose, and number and timing of instillations not reported B: MMC, 20 mg and doxorubicin, 30 mg sequential therapy, number and timing of instillations not reported	Compete response to initial therapy (no residual CIS and negative urine cytology for at least 4 weeks): 86% (18/21) vs. 81% (17/21), RR 1.06 (95% CI 0.81 to 1.39) within 2 months of completion of therapy Complete response, including crossover therapy: 90% (19/21) vs. 100% (21/21), RR 0.90 (95% CI 0.79 to 1.04) Recurrence after complete response: 11% (2/21) vs. 52% (11/21), RR 0.18 (95% CI 0.05 to 0.72) Progression: 14% (3/21) vs. 10% (2/21), RR 1.50 (95% CI 0.28 to 8.08) Bladder cancer mortality: 10% (2/19) vs. 4.8% (1/21), RR 2.21 (95% CI 0.22 to 22.5) Duration of followup: 47 months (range 3 to 143 months) Method of followup: cystoscopy and urine cytology every 3 months and urography every 12 months
	Witjes, 1996[156] Witjes, 1993[148] Vegt, 1995[211]	Histologically proven papillary pTa-pT1 transitional cell transitional cell carcinoma of the bladder with or without CIS	A. BCG TICE $5x10^8$ CFU, 6 weekly instillations with a B. BCG RIVM $5x10^8$, 6 weekly instillations C. MMC 30 mg, 4 weekly instillations then monthly for 5 months If recurrence then additional instillations in all groups	A vs. B vs. C Recurrence: 75/117 vs. 62/134 vs. 58/136 Progression: 7/117 vs. 8/134 vs. 8/136 Granulomatous cystitis: 38/140 vs. 34/149 vs. 27/148 Local side effects: 23/140 vs. 22/149 vs. 7/148 Systemic side effects: 38/140 vs. 27/149 vs. 6/148 Median followup: 32 months

Table 6. Summary of bacillus Calmette-Guérin study characteristics and results (continued)

Comparison	Author, Year	Population	Intervention	Results/Followup
	Witjes, 1998b[166]	Histologically proved primary multiple (more than 2 tumors) or recurrent multiple (2 or more tumors) stage pTa or pT1 transitional cell carcinoma, solitary or multiple grade III tumors and primary or concomitant CIS	A. BCG $5x10^8$ CFU + MMC 40 mg, 4 weekly instillations of MMC then 6 weekly instillations of BCG B. MMC 40, 10 weekly instillations	Overall mortality: 21/90 vs. 14/92 Bladder cancer mortality: 5/90 vs. 8/92 Recurrence: 35/90 vs. 42/92 Progression: 5/90 vs. 4/92 Local side effects: 12/90 vs. 9/92 Granulomatous cystitis: 37/90 vs. 29/92 Systemic side effects: 21/90 vs. 20/92 Fever: 11/90 vs. 3/92 Median followup: 32 months
BCG vs. Epirubicin; BCG vs. Epirubicin + BCG	Ali-El-Dein, 1999[180]	Grade 2 or 3, stage pT1 disease, rapid disease recurrence within 6 months of initial resection, multicentricity, aneuploid DNA pattern, tumor size equal to or not more than 3 cm, assoc carcinoma in situ or other dysplastic mucosal changes and/or positive postoperative urinary cytology	A. BCG $5x10^8$-$5x10^9$ CFU, 6 weekly then 10 monthly instillations B. Epirubicin 50 mg + BCG $5x10^8$-$5x10^9$ CFU, 6 weekly then 10 monthly instillations alternating BCG and epirubicin	Recurrence: 12/58 vs. 7/66 Progression: 5/58 vs. 3/66 Granulomatous cystitis: 36/58 vs. 18/66 Hematuria: 4/58 vs. 0/66 Fever: 3/58 vs. 0/66 DC instillations: 12/58 vs. 3/66 Systemic side effects: 21/58 vs. 4/66 Mean followup: 30 months
	Bilen, 2000[181]	Superficial transitional-cell carcinoma of the bladder; patients with pT1 who had an additional one of four prognostic factors (grade 3 tumors, multiple tumors, tumors greater than 40 mm, recurrent tumors) were included	A. BCG 81 mg, 6 weekly instillations B. Epirubicin 50 mg + BCG 81 mg, epirubicin given weeks 1-4 and week 12 and BCG given weeks 5-7, and 9-11	Recurrence: 4/21 vs. 3/20 Progression: 2/21 vs. 1/20 Hematuria: 8/21 vs. 4/20 Fever: 3/21 vs. 2/20 Dysuria: 9/21 vs. 7/20 Median followup: 18 months

Table 6. Summary of bacillus Calmette-Guérin study characteristics and results (continued)

Comparison	Author, Year	Population	Intervention	Results/Followup
	Cai, 2008[179]	High risk NMIBC patients with recurrent urothelial cancer and with tumor recurrence at same stage and grade of the initial tumor at diagnosis	A. BCG 5x10^8 CFU, 6 weekly instillations with boosters at 3, 6, 12, 18, 24, 30, and 36 months B. Epirubicin 80 mg + BCG 5x10^8 CFU, epirubicin given perioperatively then 6 weekly instillations of BCG with BCG boosters 3, 6, 12, 18, 24, 30, and 36 months	Recurrence: 40/81 vs. 34/80 Progression: 4/81 vs. 2/80 Median followup: 15 months
	Cheng, 2005[174]	Superficial bladder cancer (Ta or T1) with one or more of the following: stage>a, grade>1size>1cm or multiple or recurrent tumors	A. BCG 81 mg, 6 weekly instillations then 10 monthly instillations B. Epirubicin 50 mg, 4 weekly instillations then 5 monthly instillation then quarterly for 6 months	Overall mortality: 41/102 vs. 41/107 Bladder cancer mortality: 13/102 vs. 7/107 Recurrence: 30/102 vs. 59/107 Progression: 16/102 vs. 16/107 Median followup: 23 months for recurrence, 47 months for progression, 61 months for survival
	De Reijke, 2005[177]	Patients with biopsy proven primary, secondary or concurrent CIS of the bladder with or without primary urinary cytology.	A. BCG 81 mg, 6 weekly instillations then at months 3, 6, 12, 18, 24, 30, 36 B. Epirubicin 50 mg, 8 weekly instillations then at months 3, 6, 12, 18, 24, 30, 36	Overall mortality: 26/84 vs. 34/84 Bladder cancer mortality: 9/84 vs. 13/84 Granulomatous cystitis: 21/80 vs. 7/82 Hematuria: 33/80 vs. 23/82 Fever: 6/80 vs. 0/82 DC instillations: 26/81 vs. 8/82 Local side effects: 16/80 vs. 5/82 Dysuria: 19/80 vs. 8/82 Median followup: 67 months
	Melekos, 1993[103]	Histologically proven superficial transitional cell carcinoma of the bladder; primary or recurrent neoplasms	A. BCG 150 mg, 6 weekly instillations then quarterly for 2 years then semi-annually B. Epirubicin 50 mg, 6 weekly instillations then quarterly for 2 years then semi-annually	Recurrence: 20/62 vs. 27/67 Progression: 4/62 vs. 6/67 Granulomatous cystitis: 49/62 vs. 23/67 Hematuria: 14/62 vs. 10/67 Fever: 17/62 vs. 2/67 Total months of followup: 1784 vs. 1745 months

Table 6. Summary of bacillus Calmette-Guérin study characteristics and results (continued)

Comparison	Author, Year	Population	Intervention	Results/Followup
	Melekos, 1996[175]	Completely resectable recurrent (at least 2 recurrences in the most recent 12 months) or multiple (more than 2) papillary superficial bladder tumors Ta and T1 of any grade	A. BCG $5x10^8$ CFU, 6 weekly instillations then quarterly for 2 years then semiannually (if T1 or TaG2/G3 then 3 weekly doses at 6 months) B. Epirubicin 50 mg, 4 weekly instillations then quarterly for 2 years then semiannually (if T1 or TaG2/G3 then 3 weekly doses at 3 and 6 months)	Recurrence: 26/58 vs. 34/61 Progression: 7/58 vs. 10/61 Granulomatous cystitis: 39/58 vs. 23/61 Hematuria: 14/58 vs. 10/61 Median followup: 43 months
	Hinotsu, 2011[176]	Recurrent or multiple tumors with confirmed Ta or T1 transitional cell carcinoma; must have 1 of the following: (a) at least 3 tumors (b) recurrence is at least the third such event or (c) recurrence diagnosed within 12 months from previous TURBT for NMIBC	A. BCG 81 mg, 6 weekly instillations then 3 weekly instillations at months 3, 6, 12 and 18 B. BCG 81 mg, 6 weekly instillations B. Epirubicin 40 mg, 2 weekly instillations then biweekly times 7	A vs. B vs. C* Recurrence: 5/41 vs. 14/42 vs. 22/32 Progression: 0/41 vs. 3/42 vs. 7/32 *groups A and B combined in analysis Median followup: 2 years
	Sylvester, 2010[173] Van Der Meijden, 2001[178]	Intermediate or high risk superficial bladder tumors; single or multiple, primary or recurrent, completely resectable stages Ta-T1, G1 to G3, biopsy proven TCC	A. BCG $5x10^8$ CFU, 6 weekly instillations then 3 weekly instillations at months 3, 6, 12, 18, 24, 30 and 36 B. Epirubicin 50 mg, 6 weekly instillations then 3 weekly instillations at months 3, 6, 12, 18, 24, 30 and 36	Overall mortality: 84/281 vs. 106/173 Bladder cancer mortality: 41/102 vs. 41/107 Recurrence: 103/281 vs. 147/173 Progression: 19/281 vs. 24/173 Granulomatous cystitis: 111/263 vs. 82/265 Hematuria: 93/263 vs. 45/264 DC instillations: 190/265 vs. 201/265 Median followup: 4 years; Also median followup 9 years

Table 6. Summary of bacillus Calmette-Guérin study characteristics and results (continued)

Comparison	Author, Year	Population	Intervention	Results/Followup
BCG vs. Gemcitabine; BCG vs. BCG + Gemcitabine	Cho, 2009[187]	Patients with intermediate-risk (i.e., Ta, T1, G1-G2 multifocal, recurrent lesions>3 cm, or high-risk (T1, G3 lesions or CIS) were included	A. BCG 12.5 mg, 6 weekly instillations B. Gemcitabine 1000 mg first dose then 2000 mg at week 1, then BCG weekly for 6 weeks	Recurrence: 17/51 vs. 14/36 Progression: 5/51 vs. 3/36 Dysuria: 17/51 vs. 13/36 Hematuria: 3/51 vs. 7/36 Mean followup: 32 and 34 months
	Di Lorenzo, 2010[184]	Patients with high risk NMIBC based on the European Organization for Research and Treatment of Cancer Scoring System failing BCG therapy for whom radical cystectomy was indicated but not conducted because of refusal or ineligibility because of age or comorbidities and high anesthesiological risk	A. BCG 81 mg, 6 weekly instillations then 3 weekly instillations at 3, 6 and 12 months B. Gemcitabine 2000 mg twice weekly for 6 weeks then 3 weekly instillations at 3, 6 and 12 months	Overall mortality: 1/35 vs. 0/21 Recurrence: 35/40 vs. 21/40 Progression: 13/35 vs. 7/21 Dysuria: 8/40 vs. 6/40 Hematuria: 5/40 vs. 2/40 Fever: 3/40 vs. 1/40 Median followup: 15 months
	Gontero, 2013[186]	Intermediate risk NMIBC (namely Ta-1, G1-2, multifocal or unique and recurrent, more than 3 cm in diameter) were eligible	A. BCG 27 mg, 6 weekly instillations then 3 weekly instillations at 3, 6 and 12 months B. Gemcitabine 2000 mg , 6 weekly instillations then monthly instillations up to 1 year	Recurrence: 14/47 vs. 16/41 Progression: 3/47 vs. 5/41 Dysuria: 21/57 vs. 13/56 Hematuria: 9/57 vs. 0/56 Fever: 10/57 vs. 0/56 Followup 1 year
	Porena, 2010[185]	Superficial TCC; high risk superficial bladder cancer according to EAU guidelines	A. BCG $5x10^8$ CFU, 6 weekly instillations then instillations at 3, 6, 12, 18, 24, 30 and 36 months B. Gemcitabine 2000 mg, 6 weekly instillations then instillations at 3, 6, 12, 18, 24, 30 and 36 months	Recurrence: 9/32 vs. 17/32 Local toxicity: 4/32 vs. 3/32 Systemic toxicity: 2/32 vs. 4/32 Mean followup: 44 months

Table 6. Summary of bacillus Calmette-Guérin study characteristics and results (continued)

Comparison	Author, Year	Population	Intervention	Results/Followup
BCG vs. Interferon alpha-2a; BCG vs. Interferon alpha-2b + BCG	Jimenez-Cruz, 1997[188]	Recurrent histologically proved superficial transitional cell carcinoma of the bladder (Stage T1, grade 1 to 3)	A. BCG 150 mg, 4 weekly instillations then biweekly for 2 months then monthly for 9 months B. Interferon alpha-2a 54 MU, 4 weekly instillations then biweekly for 2 months then monthly for 9 months	Recurrence: 24/61 vs. 34/49 Progression: 6/61 vs. 7/49 Dysuria: 52/61 vs. 0/49 Fever: 3/61 vs. 0/49 Cystectomy: 3/61 vs. 0/49 Mean followup: 21 vs. 18 months
	Kaasinen, 2000[189]	At least 2 histologically verified recurrent stage Ta or T1 grade 1 to 2 tumors without concomitant CIS, Grade 3 tumors also included	All patients received 5 instillations of MMC 40 mg prior to randomization A. BCG $5x10^8$ CFU, 12 monthly instillations B. Interferon alpha-2b 50 MU + BCG $5x10^8$ CFU, 12 monthly instillations (alternating drugs)	Recurrence: 29/102 vs. 70/103 Progression: 3/102 vs. 4/103 Median followup: 56 months
	Nepple, 2010[190]	Histologically confirmed CIS, Ta, T1 urothelial cancer diagnosed within 8 weeks	A. BCG 50 mg then BCG 16.6 mg, 6 weekly instillations then 3 weekly instillations of BCG 16.6 mg at 4, 7, 13, 19, 25 and 37 months B. Interferon alpha-2b 50 MU + BCG 16.6 mg, 6 weekly instillations then 3 weekly instillations of BCG 16.6 mg at 4, 7, 13, 19, 25 and 37 months (Patients were also randomized to regular or mega-dose vitamins.)	Recurrence: 104/324 vs. 127/346 Constitutional symptoms: 58/324 vs. 38/346 Fever: 36/324 vs. 17/346 Followup 24 months

Table 6. Summary of bacillus Calmette-Guérin study characteristics and results (continued)

Comparison	Author, Year	Population	Intervention	Results/Followup
BCG vs. Doxorubicin	Hinotsu, 2006[170]	Histopathologically proven transitional cell carcinoma (Stage pTa or pT1 and grade 1 to 2)	A. BCG 80 mg, 6 weekly instillations B. Doxorubicin 20 mg, 2 weekly instillations then 7 biweekly followed by 8 monthly instillations	DC instillations: 1/41 vs. 2/42 Hematuria: 20/41 vs. 34/42 Fever: 28/41 vs. 35/42 Dysuria: 13/41 vs. 27/42 Median followup: 667 days
	Lamm, 1991[171]	Transitional-cell carcinoma with tumors at stage Ta or T1 of any grade with two or more recurrences in the most recent 12 months, CIS, or both	A. BCG 120 mg, 6 weekly instillations then single instillations at 3, 6, 12, 16 and 24 months B. Doxorubicin 50 mg, 4 weekly instillations then 11 monthly instillations	Overall mortality: 45/127 vs. 48/135 Recurrence: 78/127 vs. 110/135 Hematuria: 46/127 vs. 36/135 Fever: 52/127 vs. 11/135 Dysuria: 76/127 vs. 65/135
	Martinez-Pineiro, 1990[172]	Histologically proved superficial transitional cell carcinoma; Initially Ta or T1 tumors admitted, later only T1 cancer patients admitted	A. BCG 150 mg, 4 weekly instillations then 11 monthly instillations B. Doxorubicin 50 mg, 4 weekly instillations then 11 monthly instillations	Overall mortality: 0/67 vs. 1/53 Bladder cancer mortality: 0/67 vs. 1/53 Recurrence: 9/67 vs. 23/53 Progression: 1/67 vs. 4/53 Dysuria: 28/67 vs. 7/53 Cystectomy: 1/67 vs. 3/53 Cystitis: 11/67 vs. 0/53 Median followup: 3 years
BCG vs. Thiotepa	Brosman, 1982[142]	NMIBC patients with at least one tumor recurrence within the preceding four months	A: BCG: 6 x 10^9 TICE BCG in 60mL saline B: Thiotepa: 60mg in 60mL saline Both treatment groups were treated with weekly x 6 instillations, every 2 weeks for 3 months, then monthly until a total treatment period of 24 months.	Recurrence: 0/39 (includes 12 nonrandomized patients) vs. 9/19 (47%) Minimum followup: 24 months

Table 6. Summary of bacillus Calmette-Guérin study characteristics and results (continued)

Comparison	Author, Year	Population	Intervention	Results/Followup
	Martinez-Pineiro, 1990[172]	Histologically proved superficial transitional cell carcinoma; Initially Ta or T1 tumors admitted, later only T1 cancer patients admitted	A. BCG 150 mg, 4 weekly instillations then 11 monthly instillations B. Doxorubicin 50 mg, 4 weekly instillations then 11 monthly instillations	Overall mortality: 0/67 vs. 1/56 Bladder cancer mortality: 0/67 vs. 0/56 Recurrence: 9/67 vs. 20/56 Progression: 1/67 vs. 2/56 Dysuria: 28/67 vs. 8/56 Cystectomy: 1/67 vs. 0/56 Cystitis: 11/67 vs. 0/56 Median followup: 3 years
BCG vs. Epirubicin + Interferon alpha-2b	Duchek, 2010[182] Hemdan, 2014[183]	Patients with newly detected T1 G2-G3 urinary bladder cancer	A. BCG 2 mL OncoTice, 6 weekly instillations then 3 weekly instillations at 3, 6, 12, 18 and 24 months B. Epirubicin 50 mg + Interferon alpha-2b 10 MU, 6 weekly instillations then monthly at months 3-12 then at months 15, 18, 21 and 24	Disease-free survival favors BCG at 6 and 24 months (p=0.065; p=0.012, respectively) Bladder cancer mortality: 8/126 vs. 10/124 5-year Recurrence: 50/126 vs. 75/124 No difference in progression-free survival (p=not reported) Cystectomy: 9/126 vs. 13/124 DC instillations: 11/126 vs. 2/124 No difference in urinary symptoms (p=not reported) Followup 24 months; Also median followup 6.9 years
BCG vs. No intravesical therapy	Herr, 1995[102] Herr, 1988[106] Herr, 1997[107] Cookson, 1997[108] Pinsky, 1985[109]	Recurrent, superficial transitional-cell carcinoma of the bladder (Ta, T1, Tis)	A. BCG 120 mg, 6 weekly instillations B. Control	Bladder cancer mortality: 10/43 vs. 17/45 Progression: 23/43 vs. 41/43 Cystectomy: 11/43 vs. 18/43 Median followup: 72 months; Also median followup: 108 vs. 140 months
	Melekos, 1990[104]	Superficial bladder carcinoma (Ta and T1)	A. BCG 150 mg, 8 weekly instillations then every 3 months for 24 months B. Control	Recurrence: 22/67 vs. 19/33 Progression: 7/67 vs. 13/33 Mean followup: 29 vs. 30 months
	Melekos, 1993[103]	Histologically proven superficial transitional cell carcinoma of the bladder; primary or recurrent neoplasms	A. BCG 150 mg, 6 weekly instillations then quarterly for 2 years then semi-annually B. Control	Recurrence: 20/62 vs. 19/32 Progression: 4/62 vs. 7/32 Total months of followup: 1784 vs. 603

Table 6. Summary of bacillus Calmette-Guérin study characteristics and results (continued)

Comparison	Author, Year	Population	Intervention	Results/Followup
	Pagano, 1991[105] Pagano, 1990[110]	Patients followed for one year after the study or until recurrence or progression were included in the report. Multiple (>3 tumors at entry), superficial papillary and nonpapillary tumors	A. BCG 75 mg, 6 weekly instillations then monthly for 1 year then quarterly for 1 year B. Control	Progression: 3/70 vs. 11/63 Mean followup: 21 months

BCG = bacillus Calmette-Guérin; BCG (RIVM) = RIVM strain of bacillus Calmette-Guérin; CFU = colony forming unit; CIS = carcinoma in situ; DC = dendritic cells; EAU = European Association of Urology ; FISH = fluorescence in situ hybridization; FU = followup; G1 = Grade 1; G2 = Grade 2; G3 = Grade 3; MMC = Mitomycin C; MU = million units; NMIBC = non–muscle-invasive bladder cancer; NMP22 = nuclear matrix protein-22; pT1 = Tumor stage 1 determined by pathology; pTa = Tumor stage a determined by pathology; T1 = Tumor stage 1; Ta = Tumor stage a; TCC = transitional cell carcinoma; Tis = carcinoma in situ; TURBT = transurethral resection of bladder tumor

Table 7. Summary of MMC study characteristics

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Addeo, 2010[194]	Italy Multicenter 2003 – 2005	A: MMC, 40 mg (in 50 mL normal saline). Total 5 instillations: First within 2 days after TURBT, then 4 weekly treatments. (n=55) B: Gemcitabine, 2,000 mg (in 50 mL normal saline). "6-week induction course of infusion", dosing not otherwise specified. (n=54) A and B: Maintenance therapy of 10 monthly treatments for initial responders who remained free of recurrence.	Duration: 36 months (median) for each group Method: Not reported	Age (mean), years: 67.9 vs. 64.9 Age (median), years: 70 vs. 66.5 Male: 85.5% vs. 85.2% Race/ethnicity: Not reported Smoking status: Not reported Recurrent bladder cancer: 100% vs.100% (recurrent only) Stage: Ta: 63.6% vs.68.5%; T1: 36.4% vs. 31.5% Grade: G1: 25.5% vs. 20.4%; G2: 49.1% vs. 51.9%; G3: 25.5% vs. 27.8% Functional Status: Not reported
Akaza, 1987[112] Study One (followup of Niijima, 1983[116])	Japan Multicenter 1980 – 1985	A: Doxorubicin, 30 mg (in 30 mL saline). Total 8 instillations. (n=149) B: Doxorubicin, 20 mg (in 40 mL saline). Total 8 instillations. (n=148) C: MMC: 20 mg (in 40 mL saline). Total 8 instillations. (n=139) D: No adjuvant treatment. TURBT alone. (n=139) For A, B, and C: First instillation within 1 week of TURBT. Twice weekly X 4 weeks	Duration: 5 years (maximum), overall. Method: cystoscopy and urinary cytology.	Age (average), years: 62.3 vs. 62.9 vs. 62.9 vs. 62.9 Male: 82.6% vs. 75.7% vs. 74.8% vs. 74.1% Race/ethnicity: Not reported Smoking status: Not reported Recurrent bladder cancer: 29.5% vs. 31.1% vs. 33.8% vs. 35.3% Stage: Not reported Grade: Not reported Functional Status: Not reported Size: <1 cm: 40.3% vs. 37.2% vs. 43.9% vs. 46.0%; 1-3 cm: 43.0% vs. 52.7% vs. 38.8% vs. 48.2%; 3-5 cm: 14.8% vs. 74.3% vs. 12.2% vs. 5.0% Number of tumors: 1: 64.4% vs. 63.5% vs. 48.2% vs. 60.4%; 2-4: 26.2% vs. 25.7% vs. 39.6% vs. 30.2%; 5+: 80.5% vs. 10.8% vs. 11.5% vs. 9.4%

Table 7. Summary of MMC study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Akaza, 1987[112] Study Two	Japan Multicenter 1982 - 1985	A: Doxorubicin, 30 mg (in 30 mL saline). Total 21 instillations over 2 years. (n=151) B: Doxorubicin, 20 mg (in 40 mL saline). Total 21 instillations over 2 years. (n=158) C: MMC: 20 mg (in 40 mL saline). Total 21 instillations over 2 years. (n=150) D: No adjuvant treatment. TURBT alone. (n=148) For A, B, and C: First instillation within 1 week of TURBT. Once weekly X 2 weeks, then once every 2 weeks X 14 weeks, then once monthly X 8 months, then once every 3 month X 1 year	Duration: 3.5 years (maximum), overall. Method: cystoscopy and urinary cytology.	Age (average), years: 63.1 vs. 62.1 vs. 62.3 vs. 62.0 Male): 80.1% vs. 82.3% vs. 82.0% vs. 81.1% Race/ethnicity: Not reported Smoking status: Not reported Recurrent bladder cancer: None (primary only) Stage: Not reported Grade: Not reported Functional Status: Not reported Size: <1 cm: 31.8% vs. 30.4% vs. 36.0% vs. 38.5%; 1-3 cm: 51.0% vs. 53.2% vs. 44.0% vs. 49.3%; 3-5 cm: 14.6% vs. 11.4% vs. 11.3% vs. 6.8% Number of tumors: 1: 64.2% vs. 55.7% vs. 55.3% vs. 66.9%; 2-4: 29.8% vs. 30.4% vs. 33.3% vs. 23.6%; 5+: 6.0% vs. 12.7% vs. 10.7% vs. 8.1%

Table 7. Summary of MMC study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Akaza, 1992[113] Study Two (followup of sub-group of Akaza, 1987[112])	Japan Multicenter 1982 - 1990	A: Doxorubicin, 30 mg (in 30 mL saline). Total 21 instillations over 2 years. (n=44) B: Doxorubicin, 20 mg (in 40 mL saline). Total 21 instillations over 2 years. (n=42) C: MMC: 20 mg (in 40 mL saline). Total 21 instillations over 2 years. (n=41) D: No adjuvant treatment. TURBT alone. (n=31) For A, B, and C: First instillation within 1 week of TURBT. Once weekly X 2 weeks, then once every 2 weeks X 14 weeks, then once monthly X 8 months, then once every 3 month X 1 year	Duration: 6.6 years (median), overall. Method: with cystoscopy and urinary cytology.	Only reported overall; Not reported by treatment group Age ≤50 years: 13.3% Age ≤60 years: 17.7% Age <70 years: 35.4% Age ≥70 years: 33.5% Sex (male): 84.8% Race/ethnicity: Not reported Smoking status: Not reported Recurrent bladder cancer: None (primary only) Stage: Tis: 1.3%; Ta: 44.3%; T1: 40.5%; Ta or T1: 13.9% Grade: G1: 48.7% G2: 45.6%; G1 or G2: 5.7% Functional Status: Not reported
Boccardo, 1994[193]	Italy Multicenter 1987 - 1989	A: MMC, 40 mg (in 50 mL saline). Total 8 instillations: weekly dose X 8 weeks. (n=141) B: Interferon alfa-2b, 50 million units (in 50 mL normal saline). Total 8 instillations: weekly dose X 8 weeks. (n=146)	Duration: 42 months (maximum). Method: cystoscopy and urine cytology.	Age (median), years: 64 vs. 63 Male: 87.9% vs. 84.9% Race/ethnicity: Not reported Smoking status: Not reported Recurrent bladder cancer: None (primary only) Stage/Grade: pTa/G2: 55.3% vs. 53.4%; pT1/G1-G2: 45.7% vs. 45.6% Functional Status: Not reported Size: <3 cm: 75.2% vs. 78.1%; ≥3 cm: 24.1% vs. 21.9% Number of tumors: 1: 63.2% vs. 61.7%; 2: 14.9% vs. 17.1%; 3+: 20.5% vs. 21.2%

Table 7. Summary of MMC study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
De Nunzio, 2011[114]	Italy Single center 2000 - 2009	A: MMC, 40 mg (in 50 mL saline). Single instillation within 24 hours of TURBT. (n=97) B: TURBT only. No adjuvant therapy. (n=105)	Duration: 90 months vs. 85 months (median). Method: cystoscopy and urine cytology.	Age (median), years: 60.8 vs. 61.5 Male: 62.9% vs. 68.6% Race/ethnicity: Not reported Smoking status: Not reported Recurrent bladder cancer: None (primary only) Stage: Ta: 100% vs. 100% Grade: G1: 70.1% vs. 77.1%; G2: 29.9% vs. 22.9% Functional Status: Not reported
Flanigan, 1986[143]	USA Single center 1981-1984	A: MMC 40 mg in 40 cc sterile water, 8 weekly instillations, then monthly for 2 years (n=25) B: Thiotepa 60 mg in 60 cc sterile water, 8 weekly instillations, then monthly for 2 years (n=22, includes 7 cross-overs due to MMC toxicity)	Duration (mean): MMC: 13.5 months Thiotepa: not reported Method: Cystoscopy and cytology every 3 months for the first 2 years and every 6 months thereafter.	Age: Not reported Male: Not reported Race/ethnicity: Not reported Stage/grade: Ta, G1 or G2: 2 vs. 1 T1, G1: 6 vs. 8 T1, G2: 13 vs. 11 T1, G3: 3 vs. 2 Focal Tis: 1 vs. 0 Functional status: Not reported
Giannopoulos, 2003[141]	Greece Multicenter 1997 - 2001	A: Interferon-gamma 1b, 15 million units (in 50 mL normal saline). Total 20 instillations: First instillation 2 weeks after TURBT; then once a week X 7, then once biweekly X 4, then once monthly X 8. (n=60) B: MMC, 40 mg (in 50 mL normal saline). Total 20 instillations: First instillation 2 weeks after TURBT; then once a week X 7, then once biweekly X 4, then once monthly X 8. (n=63)	Duration: 26.5 months vs. 24 months (median). Method: Cystoscopy and urine cytology. Random cold cup biopsies at 6 months and 12 months.	Age (median), years: 68 vs. 60 Male: 80.0% vs. 88.9% Race/ethnicity: Not reported Smoking status: Not reported Recurrent bladder cancer: None (primary only) Stage: Ta: 66.7% vs. 60.3%; T1: 33.3% vs. 39.7% Grade: G2: 100% vs. 100% Functional Status: Not reported

Table 7. Summary of MMC study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Gustafson, 1991[115]	Sweden Single center Study years not reported	A: MMC. Dosages "varied according to individual patient's bladder capacity". Range: "5 mg in 20 mL" to "40 mg in 250 mL". Total 15 instillations: First instillation approximately 2 weeks after TURBT; instillations weekly X 4 weeks, then monthly X 11 months. (n=19) B: Doxorubicin. Dosages "varied according to individual patient's bladder capacity". Range: "10 mg in 20 mL" to "80 mg in 250 mL". Total 15 instillations: Same protocol as A. (n=20)C: TURBT only. No adjuvant therapy. (n=21)	Duration: 47 months vs. 45 months vs. 35 months (mean). Method: Cystoscopy	Age (mean), years: 67 (overall) Male: "Four to one", male/female (overall) Race/ethnicity: Not reported Smoking status: Not reported Recurrent bladder cancer: Not reported Stage: Ta: 89.5% vs. 90.0% vs. 95.2%; T1: 10.5% vs. 10.0% vs. 4.8% Grade: G1: 36.8% vs. 35% vs. 33.3%; G2: 63.2% vs. 65% vs. 61.9%; G3: 0.0% vs. 0.0% vs. 4.8% Functional Status: Not reported

Table 7. Summary of MMC study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Huland, 1990[191]	Germany Multicenter 1983 - 1985	A: MMC (20 mg/20 mL). Total 42 instillations: Every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year. (n=209) B: MMC (20 mg/20 mL). Total 42 instillations: Every week X 8 weeks, then every 4 weeks for rest of 1st year and 2 additional years. (n=96) C: MMC (20 mg/20 mL). Total 20 instillations: Every week X 20 weeks. (n=75) D: Doxorubicin (50 mg/50 mL). Total 42 instillations: Every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year. (n=39) For all groups: Instillations started 4 to 6 weeks after discharge from hospital.	Duration: 26.7 months vs. 27.4 months vs. 26.7 months vs. 30.2 months (mean). Method: Cystoscopy	Age (mean), men/women, years: 61.1/67.5 vs. 66.3/68.1 vs. 65.1/64.6 vs. .68.0/58.3 Male: 82.3% vs. 77.1% vs. 77.3% vs. 74.4% Race/ethnicity: Not reported Smoking status: Not reported Recurrent bladder cancer: 32.1% vs. 25.0% vs. 25.3% vs. 43.6% Stage: Ta: 73.7% vs. 78.1% vs. 76.0% vs. 59.0%; T1: 23.0% vs. 19.8% vs. 21.3% vs. 33.3%; Tis: 3.3% vs. 2.1% vs. 29.3% vs. 7.7% Grade: G1: 47.4% vs. 58.3% vs. 52.0% vs. 43.6%; G2: 47.7% vs. 35.4% vs. 37.3% vs. 38.5%; G3: 1.9% vs. 4.2% vs. 8.0% vs. 10.3%; CIS: 3.3% vs. 2.1% vs. 2.7% vs. 7.7% Functional Status: Not reported
Jauhiainen, 1987[144]	Finland Single center Study years not reported	A: MMC, range 20 mg to 40 mg. Dosages varied according to patient's bladder capacity. (n=26) B: Doxorubicin, range: 50 mg to 100 mg. Dosages varied according to patient's bladder capacity. (n=15) First instillation not less than 14 days after TURBT; 5 times weekly, then monthly.	Duration: Mean: 23.6 months vs. 23.3 months. Method: Followup with cystoscopy and biopsy cytology.	Age (mean): 68.1 vs. 65.2 Male: 84% (42/50) of a larger series, of which only 41 were randomized. Race/ethnicity: not reported Recurrent bladder cancer: 100% vs. 100% Stage: All Ta or T1, Functional Status: Not reported

Table 7. Summary of MMC study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Kim, 1989[97]	Korea Single center 1983-1986	A: MMC, 40 mg (in 50 mL saline). Weekly for 8 weeks. (n=21) B: TURBT alone.(n=22)	Duration, mean: 32 months vs. 31 months. Method: Cystoscopy and cytology every 3 to 4 months.	Age, mean: 51.6 vs. 57.0 Male: 90.5% vs. 86.4% Race/ethnicity: not reported Recurrent bladder cancer: 71.4% vs. 55.5% Stage: Ta: 23.8% vs. 27.3%; T1: 76.2% vs. 72.7% Functional Status: not reported
Krege, 1996[111]	Germany, Multicenter, number not reported 1985-1992	A. MMC 20 mg (in 50 mL saline). Total 38 instillations: First approximately 7 days after TURBT, then every 2 weeks during year 1 and monthly during year 2 (n=113) B. TURBT only. No adjuvant therapy. (n=122)	Duration: 20 months, overall (mean) Method not reported	Age (mean), years: 65 (not specified by group) Male: 84% vs. 75% Race/ethnicity: Not reported Smoking: Not reported Stage: Ta: 74% vs. 78%; T1: 26% vs. 22% Grade: G1: 39% vs. 39%; G2: 51% vs. 57%; G3: 11% vs. 5% Functional Status: Not reported
Liu, 2006[192]	China Multicenter 1997 - 1998	A: Epirubicin, 80 mg (in 40 mL normal saline). Single instillation within 6 hours of TURBT. (n=14) B: Epirubicin, 40 mg. Total 16 - 18 instillations: Every week for 6 ~ 8 weeks, then every month for 10 months. (n=15) C: MMC, 40 mg. Total 16 - 18 instillations: Every week for 6 ~ 8 weeks, then every month for 10 months. (n=15)	Duration: 5 years (all patients). Method: Cystoscopy and urine cytology.	Age (mean), years: 62.2 (overall) Male: Not reported Race/ethnicity: Not reported Smoking status: Not reported Recurrent bladder cancer: 23.4% (overall) Stage and Grade: TaG1: 6.3% vs. 0.0% vs. 0.0%; TaG2: 6.3% vs. 6.6% vs. 6.3%; T1G1: 12.5% vs. 26.7% vs. 12.5%; T1G2: 75.0% vs. 66.7% vs. 81.3% Functional Status: Not reported

Table 7. Summary of MMC study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Niijima, 1983[116] (see Akaza, 1987[112])	Japan Multicenter 1980 - 1985	A: Doxorubicin, 30 mg (in 30 mL saline). Total 8 instillations. (n=149) B: Doxorubicin, 20 mg (in 40 mL saline). Total 8 instillations. (n=148) C: MMC: 20 mg (in 40 mL saline). Total 8 instillations. (n=139) D: No adjuvant treatment. TURBT alone. (n=139) For A, B, and C: First instillation within 1 week of TURBT. Twice weekly X 4 weeks	Duration: 5 years (maximum), overall. Method: Cystoscopy and urinary cytology.	Age (average), years: 62.3 vs. 62.9 vs. 62.9 vs. 62.9 Male: 82.6% vs. 75.7% vs. 74.8% vs. 74.1% Race/ethnicity: Not reported Smoking status: Not reported Recurrent bladder cancer: 29.5% vs. 31.1% vs. 33.8% vs. 35.3% Stage: Not reported Grade: Not reported Functional Status: Not reported Size: <1 cm: 40.3% vs. 37.2% vs. 43.9% vs. 46.0%; 1-3 cm: 43.0% vs. 52.7% vs. 38.8% vs. 48.2%; 3-5 cm: 14.8% vs. 74.3% vs. 12.2% vs. 5.0% Number of tumors: 1: 64.4% vs. 63.5% vs. 48.2% vs. 60.4%; 2-4: 26.2% vs. 25.7% vs. 39.6% vs. 30.2%; 5+: 80.5% vs. 10.8% vs. 11.5% vs. 9.4%
Solsona, 1999[117]	Spain Single center 1988 - 1992	A: MMC, 30 mg (in 50 mL saline). Single intravesical dose, usually within 6 hours of TURBT. (n=57) B: TURBT only. No adjuvant therapy. (n=64)	Duration: 94 months vs. 93 months (median). Method: Cystoscopy and urine cytology.	Age (mean), years: 62.2 vs. 59.9 Male: 91.2% vs. 92.2% Race/ethnicity: Not reported Smoking status: Not reported Recurrent bladder cancer: 10.5% vs. 12.5% Stage Ta: 49.1% vs. 48.4% Stage T1: 50.9% vs. 51.6% Grade G1: 52.6% vs. 51.6% Grade G2: 47.4% vs. 48.4% Functional Status: All patients with WHO performance status ≤2.

Table 7. Summary of MMC study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Tolley, 1996[118] (followup Tolley, 1988[261])	United Kingdom Multicenter 1984 - 1986	A: MMC, 40 mg (in 40 mL water). Single instillation within 24 hours of TURBT. (n=149) B: MMC, 40 mg (in 40 mL water). Total 5 instillations: First within 24 hours of TURBT, then every 3 months x 1 year. (n=146) C: TURBT only. No adjuvant therapy. (n=157)	Duration: 7 years (median) for groups A and B; not reported for group C. Method: Cystoscopy	Age 24-50: 13% vs. 9% vs. 9% Age 51-60: 24% vs. 23% vs. 29% Age 61-70: 36% vs. 37% vs. 34% Age 71-80: 23% vs. 30% vs. 25% Age 81-100: 4% vs. 1% vs. 3% Male: Not reported Race/ethnicity: Not reported Smoking status: Not reported Recurrent bladder cancer: None (primary only) Stage Ta: 50% vs. 52% vs. 56% Stage T1: 48% vs. 50% vs. 43% Grade 1: 37% vs. 34% vs. 45% Grade 2: 52% vs. 55% vs. 46% Grade 3: 10% vs. 10% vs. 8% Functional Status: Not reported

Table 7. Summary of MMC study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Tsushima, 1987[101]	Japan Number of sites unclear 1981-unclear end date	A: Doxorubicin, 50 mg in 100 mL saline. B: MMC, 30 mg in 100 mL. C: TURBT or transurethral coagulation alone. For A and B: Six times in first 2 weeks after TURBT, then on 2 consecutive days every 4 weeks X 2 years. If recurrence, repeat TURBT or TUC and resume 2 consecutive days every 4 weeks until 2 years after initial treatment. For C: If recurrence, repeat TURBT or TUC x 2 recurrences, then removed from protocol.	Duration, median: 15 months vs. 21 months vs. 13 months. Method: Cystoscopy every 3 months.	Age (average), years: 66.1 Male: 84.8% vs. 81.1% vs. 81.8% Race/ethnicity: not reported Recurrent bladder cancer: 39.4% vs. 16.2% vs. 33.3% Stage: All Ta or T1 Functional Status: not reported
Zincke, 1985[146]	USA Single center Study years not reported	A. MMC 40 mg in 40 mL distilled water B. Thiotepa 60 mg in 60 mL distilled water Biweekly treatment for 5 treatments. If no tumor was present at the 3-month assessment the treatment interval was lengthened to every 4 weeks for 6 months. If there still was no recurrence, there was no further treatment. If tumor recurred during the primary treatment, patients were given the opposite drug.	Duration, mean: 16.1 months Method: Cystoscopy and cytology every 3 months for 1 year, then every 6 months for 1 year, and yearly thereafter	Age (mean): 64 Male: 71/83 Race/ethnicity: not reported Tumor grade: G1: 16/29 vs. 13/29 G2: 23/47 vs. 24/47 G3, G4: 3/7 vs. 4/7

CIS = carcinoma in situ; G1 = Grade 1; G2 = Grade 2; G3 = Grade 3; MMC = Mitomycin C; pT1 = Tumor stage 1 determined by pathology; pTa = Tumor stage a determined by pathology; T1 = Tumor stage 1; Ta = Tumor stage a; Tis = carcinoma in situ; TURBT = transurethral resection of bladder tumor; WHO = World Health Organization

Table 8. Summary of MMC study results

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Addeo, 2010[194]	A: MMC, 40 mg (in 50 mL normal saline). Total 5 instillations: First within 2 days after TURBT, then 4 weekly treatments. (n=55) B: Gemcitabine, 2,000 mg (in 50 mL normal saline). "6-week induction course of infusion", dosing not otherwise specified. (n=54) A and B: Maintenance therapy of 10 monthly treatments for initial responders who remained free of recurrence.	Recurrence rate/100 patient-months: 1.72 vs.1.26; p=0.31 Median time to recurrence: 15.0 months vs. "not reached" Relative risk of recurrence: 0.94 vs. 0.72; p=0.291 Disease-free survival: B>A; log-rank test, p=0.0021	Patients with tumor progression by stage: 18.2% (10/55) vs. 11.1% (6/54); p=0.14	
Akaza, 1987[112] Study One (followup of Niijima, 1983[116])	A: Doxorubicin, 30 mg (in 30 mL saline). Total 8 instillations. B: Doxorubicin, 20 mg (in 40 mL saline). Total 8 instillations. C: MMC: 20 mg (in 40 mL saline). Total 8 instillations. D: No adjuvant treatment. TURBT alone. For A, B, and C: First instillation within 1 week of TURBT. Twice weekly X 4 weeks	Recurrence-free survival at 1800 days, generalized Wilcoxon test: B>D, p<0.05 C>D, p<0.05		

Table 8. Summary of MMC study results (continued)

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Akaza, 1987[112] Study Two	A: Doxorubicin, 30 mg (in 30 mL saline). Total 21 instillations over 2 years. B: Doxorubicin, 20 mg (in 40 mL saline). Total 21 instillations over 2 years. C: MMC: 20 mg (in 40 mL saline). Total 21 instillations over 2 years. D: No adjuvant treatment. TURBT alone. For A, B, and C: First instillation within 1 week of TURBT. Once weekly X 2 weeks, then once every 2 weeks X 14 weeks, then once monthly X 8 months, then once every 3 month X 1 year	Recurrence-free survival rate at 1 year: 74.8% vs. 75.0 vs. 76.3% vs. 66.7%. Recurrence-free survival rate at 2 years: 62.3% vs. 59.1 vs. 62.3% vs. 51.8%. Recurrence-free survival at 1260 days, generalized Wilcoxon test: A>D, $p<0.05$ B>D, $p<0.05$ C>D, $p<0.05$		

Table 8. Summary of MMC study results (continued)

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Akaza, 1992[113] Study Two (followup of sub-group of Akaza, 1987[112])	A: Doxorubicin, 30 mg (in 30 mL saline). Total 21 instillations over 2 years. B: Doxorubicin, 20 mg (in 40 mL saline). Total 21 instillations over 2 years. C: MMC: 20 mg (in 40 mL saline). Total 21 instillations over 2 years. D: No adjuvant treatment. TURBT alone. For A, B, and C: First instillation within 1 week of TURBT. Once weekly X 2 weeks, then once every 2 weeks X 14 weeks, then once monthly X 8 months, then once every 3 month X 1 year	Recurrence/year (number of recurrences/total observation period): 0.473 vs. 0.512 vs. 0.472 vs. 0.510	Progression (in stage, grade, or both): 43.2% (19/44) vs. 31.0% (13/42) vs. 26.8% (11/41) vs. 38.7% (12/31) "Statistics: no difference"	
Boccardo, 1994[193]	A: MMC, 40 mg (in 50 mL saline). Total 8 instillations: weekly dose X 8 weeks. (n=141) B: Interferon alfa-2b, 50 million units (in 50 mL normal saline). Total 8 instillations: weekly dose X 8 weeks. (n=146)	Recurrence: 36.9% (52/141) vs. 47.9% (70/146) Relative recurrence rate: 0.82 vs. 1.2; p=0.04 Median time to recurrence, months: 36.0 vs. 21.0; p=0.048 Recurrence rate/100 patient/month: 2.4 vs. 3.4; p=0.04	Patients developing muscle-invasive cancer or second tumor: 5.7% (8/141) vs. 4.1% (6/146)	

Table 8. Summary of MMC study results (continued)

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
De Nunzio, 2011[114]	A: MMC, 40 mg (in 50 mL saline). Single instillation within 24 hours of TURBT. (n=97) B: TURBT only. No adjuvant therapy. (n=105)	Recurrence: 10.3% (10/97) vs. 43.8% (46/105), p=0.001; HR (95% CI): 0.20 (0.10-0.395) Early recurrence (≤1 year): 40.0% (4/10) vs. 34.8% (16/46), p=0.008 Early recurrence tumor size, median: 0.8 cm vs. 0.8, p=0.34 Early recurrence grade: G1: 75% (3/4) vs. 87.5% (14/16), p=0.53; G2: 25% (1/4) vs. 12.5% (2/16), p=0.53; G3: 0.0% vs. 0.0%, p=0.53 Late recurrence (>1 year): 60.0% (6/10) vs. 60.9% (28/46), p=0.0001 Late recurrence tumor size, median: 1.2 cm vs. 1.5, p=0.001 Late recurrence grade: G1: 66.7% (4/6) vs. 71.4% (20/28), p=0.60; G2: 33.3% (2/6) vs. 21.4% (6/28), p=0.60; G3: 0.0% (0/6) vs. 7.1% (2/28), p=0.60 All recurrences in treatment arm were Ta; 30.4% (14/46) of recurrences in control arm were T1 Absolute risk reduction (A vs. B): Overall=31%, Early recurrence=11%, Late recurrence=20% NNT to prevent one recurrence: Overall=3.26, Early=8.99; Late=5.12	Progression (≥T2): 0.0% (0/97) vs. 0.95% (1/105), p=0.33	
Flanigan, 1986[143]	A: MMC 40 mg in 40 cc sterile water, 8 weekly instillations, then monthly for 2 years (n=25) B: Thiotepa 60 mg in 60 cc sterile water, 8 weekly instillations, then monthly for 2 years (n=22, includes 7 cross-overs due to MMC toxicity)	Recurrence: 16% vs. 9.1%, RR 1.76 (95% CI 0.36 to 8.70) Recurrence, by tumor stage: Ta, G1 or G2: 0 vs. 0 T1, G1: 0 vs. 0 T1, G2: 3/13 vs. 1/11 T1, G3: 1/3 vs. 1/2	Progression: 12% vs. 4.5%, RR 2.64 (95% CI 0.30 to 23.6)	

Table 8. Summary of MMC study results (continued)

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Giannopoulos, 2003[141]	A: Interferon-gamma 1b, 15 million units (in 50 mL normal saline). Total 20 instillations: First instillation 2 weeks after TURBT; then once a week X 7, then once biweekly X 4, then once monthly X 8. (n=60) B: MMC, 40 mg (in 50 mL normal saline). Total 20 instillations: First instillation 2 weeks after TURBT; then once a week X 7, then once biweekly X 4, then once monthly X 8. (n=63)	Recurrence-free at 1 year: 90.0% (54/60) vs. 76.2% (48/63) Recurrence-free survival at 1 year, log-rank test, p=0.04 Recurrence-free for total study period: 73.3% (44/60) vs. 57.1% (36/63) Recurrence-free survival for total study period, log-rank test, p=0.051		
Gustafson, 1991[115]	A: MMC. Dosages "varied according to individual patient's bladder capacity". Range: "5 mg in 20 mL" to "40 mg in 250 mL". Total 15 instillations: First instillation approximately 2 weeks after TURBT; instillations weekly X 4 weeks, then monthly X 11 months. (n=19) B: Doxorubicin. Dosages "varied according to individual patient's bladder capacity". Range: "10 mg in 20 mL" to "80 mg in 250 mL". Total 15 instillations: Same protocol as A. (n=20) C: TURBT only. No adjuvant therapy. (n=21)	Recurrence-free survival during treatment year: 52.6% (10/19) vs. 15.0% (3/20) vs. 14.3% (3/21) Recurrence-free survival for duration of followup: 26.3% (5/19) vs. 10.0% (2/20) vs. 4.8% (1/21) Recurrence rate/100 patient-months: 7.7 vs. 18.3 vs. 18.6, p=0.02 Mean disease-free interval, months (A vs. B): 14 vs. 6, p=0.02	Progression: Increased stage only: 0.0% (0/19) vs. 5.0% (1/20) vs. 4.8% (1/21) Increased grade only: 0.0% (0/19) vs. 15.0% (3/20) vs. 9.5% (2/21) Increased stage and grade: 10.5% (2/19) vs. 10.0% (2/20) vs. 0.0% (0/21)	

Table 8. Summary of MMC study results (continued)

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Huland, 1990[191]	A: MMC (20 mg/20 mL). Total 42 instillations: Every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year. (n=209) B: MMC (20 mg/20 mL). Total 42 instillations: Every week X 8 weeks, then every 4 weeks for rest of 1st year and 2 additional years. (n=96) C: MMC (20 mg/20 mL). Total 20 instillations: Every week X 20 weeks. (n=75) D: Doxorubicin (50 mg/50 mL). Total 42 instillations: Every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year. (n=39) For all groups: Instillations started 4 to 6 weeks after discharge from hospital.	Recurrence: 15.3% (32/209) vs. 9.4% (9/96) vs. 17.3% (13/75) vs. 23.1% (9/39); differences reported as not statistically significant, p-values not reported. Recurrence per 100 patient-months: 0.68 vs. 0.49 vs. 0.65 vs. 0.76	Progression of stage: 2.9% (6/209) vs. 1.0% (1/96) vs. 5.3% (4/75) vs. 7.7% (3/39) Progression of grade: 1.9% (4/209) vs. 1.0% (1/96) vs. 4.0% (3/75) vs. 10.3% (4/39)	
Jauhiainen, 1987[144]	A: MMC, range 20 mg to 40 mg. Dosages varied according to patient's bladder capacity. (n=26) B: Doxorubicin, range: 50 mg to 100 mg. Dosages varied according to patient's bladder capacity. (n=15) For A and B: First instillation not less than 14 days after TURBT; then 5 times weekly, then monthly.	Recurrence: 11.5% (3/26) vs. 40.0% (6/15) Disease-free interval: A>B, Mantel-Cox statistic p=0.0079.	Progression of stage, multifocality, or grade: 7.7% (2/26) vs. 0.0% (0/15)	

Table 8. Summary of MMC study results (continued)

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Kim, 1989[97]	A: MMC, 40 mg (in 50 mL saline). Weekly for 8 weeks. (n=21) B: TURBT alone. (n=22)	Recurrence rate: 42.9% vs. 40.9% (3 months); 81.0% vs. 77.3% (24 months); 81.0% vs. 81.0% (3 years; log-rank test p>0.05). Mean tumor free interval: 7.24 months vs. 7.24 months. Recurrence per 100 patient-months: 8.7 vs. 8.9	Progression to muscle invasive or metastases: 9.5% (2/21) vs. 18.2% (4/22). Stage: T1: 100% (2/2) vs. 100% (4/4) Grade: G2: 50% (1/2) vs. 50% (2/4); G3: 50% (1/2) vs. 50% (2/4) Recurrent: 50% (1/2) vs. 75% (3/4) Size: <3 cm: 50% (1/2) vs. 25% (1/4); ≥3 cm: 50% (1/2) vs. 75% (3/4) Number of tumors: <3: 0.0% (0/2) vs. 25% (1/4); >3: 100% (2/2) vs. 75% (3/4)	
Krege, 1996[111]	A. MMC 20 mg (in 50 mL saline). Total 38 instillations: First approximately 7 days after TURBT, then every 2 weeks during year 1 and monthly during year 2 (n=113) B. TURBT only. No adjuvant therapy. (n=122)	Recurrence: 27% (30/113) vs. 46% (56/122)		
Liu, 2006[192]	A: Epirubicin, 80 mg (in 40 mL normal saline). Single instillation within 6 hours of TURBT. (n=14) B: Epirubicin, 40 mg. Total 16 - 18 instillations: Every week for 6 ~ 8 weeks, then every month for 10 months. (n=15) C: MMC, 40 mg. Total 16 - 18 instillations: Every week for 6 ~ 8 weeks, then every month for 10 months. (n=15)	Recurrence: 35.7% (5/14) vs. 33.3% (5/15) vs. 40% (6/15), p>0.05 Recurrence-free at 1 year: 100% (14/14) vs. 86.7% (13/15) vs.93.3% (14/15) Recurrence-free at 2 years: 85.7% (12/14) vs. 80.0% (12/15) vs.66.7% (13/15) Recurrence-free at 3 years: 71.4% (10/14) vs. 73.3% (11/15) vs. 80.0% (12/15) Recurrence-free at 5 years: 64.3% (9/14) vs. 66.7% (10/15) vs.60.0% (9/15) Mean interval to recurrence, months: 8 vs. 4 vs. 5		

Table 8. Summary of MMC study results (continued)

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Niijima, 1983[116]	A: Doxorubicin, 30 mg (in 30 mL saline). Total 8 instillations. B: Doxorubicin, 20 mg (in 40 mL saline). Total 8 instillations. C: MMC: 20 mg (in 40 mL saline). Total 8 instillations. D: No adjuvant treatment. TURBT alone. For A, B, and C: First instillation within 1 week of TURBT. Twice weekly X 4 weeks	Recurrence-free survival rate at 540 days: 56.6% vs. 52.0% vs. 42.4% vs. 38.5%, generalized Wilcoxon test: A vs. D, p<0.05 B vs. D, p<0.05 C vs. D, p<0.10		
Solsona, 1999[117]	A: MMC, 30 mg (in 50 mL saline). Single intravesical dose, usually within 6 hours of TURBT. (n=57) B: TURBT only. No adjuvant therapy. (n=64)	Recurrence: 40.4% (23/57) vs. 54.7% (35/64), p=0.115 Early recurrence (≤2 years): 15.8% (9/57) vs. 34.4% (22/64), p=0.019 Late recurrence (>2 years): 22.8% (13/57) vs. 21.9% (14/64), p=0.575 Early + Late: 10.5% (6/57) vs. 12.5% (8/64), p=0.734 Recurrence free at 24 months: 84.2% vs. 65.6%; log-rank test, p=0.013 Recurrence free at 108 months: 57.0% vs. 42.2%; log-rank test, p=0.057	Progression: 1.8% (1/57) vs. 1.6% (1/64)	

Table 8. Summary of MMC study results (continued)

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Tolley, 1996[118] (followup Tolley, 1988[261])	A: MMC, 40 mg (in 40 mL water). Single instillation within 24 hours of TURBT. (n=149) B: MMC, 40 mg (in 40 mL water). Total 5 instillations: First within 24 hours of TURBT, then every 3 months x 1 year. (n=146) C: TURBT only. No adjuvant therapy. (n=157)	Recurrence at 24 months: 42% vs. 31% vs. 82%; A vs. C, p=0.001; B vs. C, p<0.001; A vs. B, p=0.14 Recurrence, relative risk, HR (95% CI): A vs. C (ref): 0.66 (0.48 to 0.91), log-rank test, p=0.01; B vs. C (ref): 0.50 (0.36 to 0.70), log-rank test, p=0.0001; A vs. B (ref): 0.74 (0.51 to 1.06), log-rank test, p=0.10	Progression, relative risk, HR (95% CI): A vs. C: 0.84 (0.42 to 1.52), log-rank test, p=0.64; B vs. C: 0.82 (0.40 to 1.68), log-rank test, p=0.59; A vs. B: 0.97 (0.46 to 2.06), log-rank test, p=0.94	All-cause mortality: 33.6% (50/149) vs. 42.5% (62/146) vs. 32.5% (51/157); A+B vs. C (ref): HR 1.1 (95% CI 0.80 to 1.53) Bladder cancer mortality: 5.4% (8/149) vs. 5.5% (8/146) vs. 7.6% (12/157)
Zincke, 1985[146]	A. MMC 40 mg in 40 mL distilled water (n=42) B. Thiotepa 60 mg in 60 mL distilled water (n=41) Biweekly treatment for 5 treatments. If no tumor was present at the 3-month assessment the treatment interval was lengthened to every 4 weeks for 6 months. If there still was no recurrence, there was no further treatment. If tumor recurred during the primary treatment, patients were given the opposite drug.	Recurrence: 14/42 (33%) vs. 12/41 (29%), RR 1.14 (95% CI 0.60 to 2.16) Percent free of recurrence at 1 year: 67% vs. 78% Recurrence, months from diagnosis to treatment: <1 month: 3/18 vs. 1/20, p=0.3 ≥1 month: 11/24 vs. 11/21, p=0.8 Recurrence, age: <65 years: 7/20 vs. 2/21, p=0.04 ≥65 years: 7/22 vs. 10/20, 0.2		

CI = confidence interval; G1 = Grade 1; G2 = Grade 2; G3 = Grade 3; HR = hazard ratio; MMC = Mitomycin C; NNT = number needed to treat; T1 = Tumor stage 1; T2 = tumor stage 2; Ta = Tumor stage a; TURBT = transurethral resection of bladder tumor

Table 9. Summary of doxorubicin study characteristics

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Abrams, 1981[95]	United Kingdom Single center Study years not reported	A: Doxorubicin, 50 mg (in 50 mL saline). Single instillation, within 24 hours of TURBT. B: No adjuvant treatment. TURBT alone.	Duration: 6 months for all patients. Method: Cystoscopy	All characteristics reported for 60 randomized patients (30 per group), not the groups analyzed: Age (mean), years: 72 vs. 68 Male: 70% vs. 79% Race/ethnicity: Not reported Recurrent bladder cancer: 100% vs. 100% Stage: Ta: 73.3% vs. 76.7%; T1: 26.7% vs. 23.3%; Functional Status: Not reported
Akaza, 1987[112] [Study One] (followup of Niijima, 1983[116])	Japan Multicenter 1980 - 1985	A: Doxorubicin, 30 mg (in 30 mL saline). Total 8 instillations: First within 1 week of TURBT, twice weekly X 4 weeks. (n=149) B: Doxorubicin, 20 mg (in 40 mL saline). Total 8 instillations: First within 1 week of TURBT, twice weekly X 4 weeks. (n=148) C: MMC: 20 mg (in 40 mL saline). Total 8 instillations: First within 1 week of TURBT, twice weekly X 4 weeks. (n=139) D: No adjuvant treatment. TURBT alone. (n=139)	Duration: 5 years, maximum; Not reported as median/mean, nor for each group. Method: Cystoscopy and urinary cytology.	Age (average), years: 62.3 vs. 62.9 vs. 62.9 vs. 62.9 Male: 82.6% vs. 75.7% vs. 74.8% vs. 74.1% Race/ethnicity: Not reported Recurrent bladder cancer: 29.5% vs. 31.1% vs. 33.8% vs. 35.3% Stage: Not reported ("no differences") Functional Status: Not reported Number of tumors: 1: 64.4% vs. 63.5% vs. 48.2% vs. 60.4%; 2-4: 26.2% vs. 25.7% vs. 39.6% vs. 30.2%; 5+: 80.5% vs. 10.8% vs. 11.5% vs. 9.4%

Table 9. Summary of doxorubicin study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Akaza, 1987[112] [Study Two]	Japan Multicenter 1982 - 1985	A: Doxorubicin, 30 mg (in 30 mL saline). Total 21 instillations. (n=151) B: Doxorubicin, 20 mg (in 40 mL saline). Total 21 instillations. (n=158) C: MMC: 20 mg (in 40 mL saline). Total 21 instillations. (n=150) D: No adjuvant treatment. TURBT alone. (n=148) For A, B, and C: First instillation within 1 week of TURBT; once weekly X 2 weeks, then once every 2 weeks X 14 weeks, then once monthly X 8 months, then once every 3 month X 1 year.	Duration: 3.5 years, maximum; Not reported as median/mean, nor for each group. Method: Cystoscopy and urinary cytology	Age (average), years: 63.1 vs. 62.1 vs. 62.3 vs. 62.0 Male: 80.1% vs. 82.3% vs. 82.0% vs. 81.1% Race/ethnicity: Not reported Recurrent bladder cancer: None (primary only) Stage: Not reported ("no differences") Functional Status: Not reported

Table 9. Summary of doxorubicin study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Akaza, 1992[113] [Study Two] (followup of Akaza, 1987[112])	Japan Multicenter 1982 - 1990	A: Doxorubicin, 30 mg (in 30 mL saline). Total 21 instillations. (n=44) B: Doxorubicin, 20 mg (in 40 mL saline). Total 21 instillations. (n=42) C: MMC: 20 mg (in 40 mL saline). Total 21 instillations. (n=41) D: No adjuvant treatment. TURBT alone. (n=31) For A, B, and C: First instillation within 1 week of TURBT; once weekly X 2 weeks, then once every 2 weeks X 14 weeks, then once monthly X 8 months, then once every 3 month X 1 year.	Duration: median 2,366 days (6.5 years); range: 480-2,817 days. Method: Cystoscopy and urinary cytology.	Not reported by treatment group Age: ≤50 years: 13.3%; ≤60 years: 17.7%; <70 years: 35.4%; ≥70 years: 33.5% Male: 84.8% Race/ethnicity: Not reported Recurrent bladder cancer: None (primary only) Stage: Tis: 1.3%; Ta: 44.3%; T1: 40.5%; Ta or T1: 13.9% Functional Status: Not reported

Table 9. Summary of doxorubicin study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Ali-El-Dein, 1997[119] (Journal of Urology)	Egypt Single center 1991 - 1995	A: Epirubicin, 50 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10. (n=64) B: Epirubicin, 80 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10. (n=68) C: Doxorubicin, 50 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10. (n=60) D: TURBT only. No adjuvant therapy. (n=61)	Duration: 30.1 months (mean) for all groups. Method: Cysto-urethroscopy, urine cytology, and flow cytometry	Age: Not reported Male: 81.4%,overall; not reported by group Race/ethnicity: Not reported Recurrent bladder cancer: 37.5% vs. 41.2% vs. 43.3% vs.45.9% Stage: pTa: 10.9% vs. 17.6% vs. 6.7% vs.9.8%; pT1: 89.1% vs. 82.4% vs. 93.3% vs.90.2%; Tis associated: 6.3% vs. 11.8% vs. 0.0% vs.0.0% Functional Status: Not reported
Cheng, 2005[120]	Hong Kong Single center 1986 - 1991	A: Doxorubicin, 50 mg (in 50 mL saline). Total 12 instillations: First at 2 weeks after TURBT, then weekly X 4 weeks, then monthly X 5 months, then every 3 months X 6 months. (n=46) B: TURBT only. No adjuvant therapy. (n=36)	Duration, median: Recurrence: 45 months Progression: 128 months Mortality: 131.5 months Method: Cystoscopy and urine cytology.	Age (mean), years: 65.5 vs. 62.1 Male: 71.7% vs. 86.1% Race/ethnicity: Not reported Recurrent bladder cancer: Not reported Stage: Ta: 67.4% vs. 63.9%; T1: 21.7% vs. 13.9%; Not reported: 10.9% vs. 22.2% Functional Status: Not reported

Table 9. Summary of doxorubicin study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Eto, 1994[195]	Japan Multicenter 1990 - 1992	A: Epirubicin, 30 mg (in 30 mL physiological saline). Total 19 instillations: 2 times/week for 4 weeks, then 1 time/month for 11 months. (n=60) B: Doxorubicin, 30 mg (in 30 mL physiological saline). Total 19 instillations: 2 times/week for 4 weeks, then 1 time/month for 11 months. (n=54)	Duration: 674 days vs. 606 days (mean). Method: Cystoscopy and urine cytology.	Age (median), years: 65 vs. 67 Male: 85.0% vs. 87.0% Race/ethnicity: Not reported Recurrent bladder cancer: 14.8% vs. 16.3%; Unknown: 10% vs. 9.3% Stage: Ta: 35.0% vs. 31.5%; T1: 48.3% vs. 57.4%; Unknown: 16.7% vs. 11.1% Functional Status: Not reported
Gustafson, 1991[115]	Sweden Number centers not reported Study years not reported	A: MMC. Dosages "varied according to individual patient's bladder capacity". Range: "5 mg in 20 mL" to "40 mg in 250 mL". Total 15 instillations: First instillation approximately 2 weeks after TURBT; instillations weekly X 4 weeks, then monthly X 11 months. (n=19) B: Doxorubicin. Dosages "varied according to individual patient's bladder capacity". Range: "10 mg in 20 mL" to "80 mg in 250 mL". Total 15 instillations: Same protocol as A. (n=20) C: TURBT only. No adjuvant therapy. (n=21)	Duration: 47 months vs. 45 months vs. 35 months (mean). Method: Followup with cystoscopy.	Age (mean), years: 67 (overall) Male: "Four to one", male/female (overall) Race/ethnicity: Not reported Recurrent bladder cancer: Not reported Stage: Ta: 89.5% vs. 90.0% vs. 95.2%; T1: 10.5% vs. 10.0% vs. 4.8% Functional Status: Not reported

Table 9. Summary of doxorubicin study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Huland, 1990[191]	Germany Multicenter 1983 - 1985	A: MMC (20 mg/20 mL). Total 42 instillations: First at 4-6 weeks after hospital discharge, then every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year. (n=209)B: MMC (20 mg/20 mL). Total 42 instillations: First at 4-6 weeks after hospital discharge, then every week X 8 weeks, then every 4 weeks for rest of 1st year and 2 additional years. (n=96)C: MMC (20 mg/20 mL). Total 20 instillations: First at 4-6 weeks after hospital discharge, then every week X 20 weeks. (n=75)D: Doxorubicin (50 mg/50 mL). Total 42 instillations: First at 4-6 weeks after hospital discharge, then every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year. (n=39)	Duration: 26.7 months vs. 27.4 months vs. 26.7 months vs. 30.2 months (mean). Method: Cystoscopy	Age (mean), men/women, years: 61.1/67.5 vs. 66.3/68.1 vs. 65.1/64.6 vs. .68.0/58.3 Male: 82.3% vs. 77.1% vs. 77.3% vs. 74.4% Race/ethnicity: Not reported Recurrent bladder cancer: 32.1% vs. 25.0% vs. 25.3% vs. 43.6% Stage: Ta: 73.7% vs. 78.1% vs. 76.0% vs. 59.0%; T1: 23.0% vs. 19.8% vs. 21.3% vs. 33.3%; Tis: 3.3% vs. 2.1% vs. 2.7% vs. 7.7% Functional Status: Not reported

Table 9. Summary of doxorubicin study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Kurth, 1997[121]	Europe Multicenter 1979 - 1983	A: Doxorubicin, 50 mg (in 50 mL normal saline). Total 15 instillations: First at 3 to 14 days after TURBT, then weekly for 1 month, then monthly for 11 months. Nitrofurantoin, 100 mg, was given after each instillation 3 times/day X 3 days. (n=166) B: TURBT only. No adjuvant therapy. (n=70)	Duration: Median followup: Recurrence: 3.4 years Progression: 5 years Mortality from malignancy: 7.2 years Mortality overall: 10.7 years. Method: Cystoscopy.	Age: <50 years: 8% vs. 7%; 50-59 years: 21% vs. 28%; 60-69 years: 28% vs. 35%; 70-79 years: 39% vs. 24%; ≥80 years: 4% vs. 7%; Unknown: 1% vs. 0% Male: 80% vs. 90% Race/ethnicity: Not reported Recurrent bladder cancer: 30.2% vs. 34.7% Stage: T0: 0% vs. 0%; Ta: 50% vs. 58%; T1: 45% vs. 40%; Tis: 4% vs. 1%; Unknown: 1% vs. 0% Functional Status: Not reported
Martinez-Pineiro, 1990[172]	Spain Single center 1980-1988	A. Thiotepa 50 mg (in 50 mL saline). (n=56) B. Doxorubicin 50 mg (in 50 mL saline). Total 16 instillations. (n=53) A and B: First treatment within 14 days of TURBT, then weekly X 4 weeks, then monthly X 11 months.	Duration: 34 months vs. 40 months Range (months): (6-78) vs. (5-97) Method: Cystoscopy and urinary cytology.	Age (Median), years: 64 vs. 62 Male: 84% vs. 89% Race/ethnicity: Not reported Stage: Ta: 41% vs. 40%; T1: 59% vs. 60% Associated Tis: 9% vs. 11%

Table 9. Summary of doxorubicin study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Matsumura, 1992[123]	Japan Multicenter 1987 - 1989	A: Doxorubicin, 20 mg (in 40 mL physiological saline). Total 21 instillations over 2 years after TURBT: Timing of first dose not specified; instillations once a week X 2, then every 2 weeks X 7, then once a month X 8, then once every 3 months X 4. (n=126) B: Doxorubicin, 20 mg (in 40 mL physiological saline). Total 6 instillations over 2 weeks before TURBT: specific schedule not reported. (n=75) C: No adjuvant treatment. TURBT alone. (n=83)	Duration: 240 days, (n=284) 720 days (maximum), (n=156) Method: not reported.	Age: ≤49 years: 7.1% vs. 4.0% vs.12.1%; 50-59 years: 15.1% vs. 20.0% vs. 13.3%; 60-69 years: 34.1% vs. 32.0% vs. 31.3%; ≥70 years: 42.9% vs. 44.0% vs. 42.2% Male: 81.7% vs. 78.7% vs. 84.3% Race/ethnicity: Not reported Recurrent bladder cancer: 59.5% vs. 61.3% vs. 50.6% Stage: Ta: 32.5% vs. 20.6% vs. 32.5%; T1: 42.9% vs. 20.6% vs. 36.1%; Tis: 0.8% vs. 2.7% vs. 3.6%; Unknown: 23.8% vs. 28.0% vs. 26.5% Functional Status: Not reported
Niijima, 1983[116] (see Akaza, 1987[112])	Japan Multicenter 1980 - 1985	A: Doxorubicin, 30 mg (in 30 mL saline). Total 8 instillations. (n=149) B: Doxorubicin, 20 mg (in 40 mL saline). Total 8 instillations. (n=148) C: MMC: 20 mg (in 40 mL saline). Total 8 instillations. (n=139) D: No adjuvant treatment. TURBT alone. (n=139) For A, B, and C: First instillation within 1 week of TURBT. Twice weekly X 4 weeks	Duration: 5 years (maximum) Method: Cystoscopy and urinary cytology.	Age (average), years: 62.3 vs. 62.9 vs. 62.9 vs. 62.9 Male: 82.6% vs. 75.7% vs. 74.8% vs. 74.1% Race/ethnicity: Not reported Recurrent bladder cancer: 29.5% vs. 31.1% vs. 33.8% vs. 35.3% Stage: Not reported Grade: Not reported Functional Status: Not reported

Table 9. Summary of doxorubicin study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Obata, 1994[124]	Japan Multicenter 1985 - 1987	A: Doxorubicin, 20 mg (in 40 mL physiological saline). Total 19 instillations over 1 year, after TURBT: Timing of first dose not specified; instillations twice a week X 4 weeks, then once a month X 11 months. (n=90) B: No adjuvant treatment. TURBT alone. (n=76)	Duration: Until January, 1991. Not reported as mean/median nor by group. Method: not reported.	Age: ≤49 years: 11.1% vs. 8.0%; 50-59 years: 15.6% vs. 25.0%; 60-69 years: 40.0% vs. 32.9%; ≥70 years: 33.3% vs. 34.2% Male: 77.8% vs. 81.6% Race/ethnicity: Not reported Recurrent bladder cancer: 54.4% vs. 48.7% Stage: Ta: 33.3% vs. 43.4%; T1: 52.2% vs. 42.1%; Tx: 12.2% vs. 11.8% Functional Status: Not reported
Okamura, 2002[125]	Japan Multicenter 1994 - 1998	A: Doxorubicin, 30 mg (in 30 mL normal saline). Single intravesical instillation within 6 hours of TURBT. (n=81) B: TURBT only. No adjuvant therapy. (n=79)	Duration: 40.8 months (median) all patients. Method: Cystoscopy and urine cytology.	Age (mean), years: 59.7 vs. 61.9 Male: Not reported Race/ethnicity: Not reported Recurrent bladder cancer: 7.4% vs. 2.5% Stage: pTa: 95.1% vs. 93.7%; pT1: 4.9% vs. 6.3% Functional Status: All patients had Eastern Cooperative Oncology Group performance status ≤2

Table 9. Summary of doxorubicin study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Shuin, 1994[196]	Japan Multicenter 1990 - 1993	A: Epirubicin, 30 mg (in 40 mL saline). Total 17 instillations: Timing of first not specified; every 2 weeks X 3 months, then every 4 weeks for remainder of 1 year. B: Doxorubicin, 30 mg (in 40 mL saline). Total 17 instillations: Timing of first not specified; every 2 weeks X 3 months, then every 4 weeks for remainder of 1 year.	Duration: Overall 43 months. Mean/median followup duration not reported. Method: not described.	Age: <40 years: 6% vs. 3%; 40-49 years: 3% vs. 9% 50-59 years: 9% vs. 24% 60-69 years: 25% vs. 21% ≥70: 56% vs. 42% Male: 81% vs. 82% Race/ethnicity: Not reported Recurrent bladder cancer: All (recurrent only) Stage Ta: 69% vs. 64% Stage T1: 25% vs. 27% Stage unknown: 6% vs. 9% Functional status: Not reported

G0 = lowest grade bladder cancer; G1 = Grade 1 ; G2 = Grade 2; G3 = Grade 3; Gx = Grade unknown; MMC = Mytomycin C; pTa = Tumor stage a determined by pathology; pT1 = Tumor stage 1 determined by pathology; T0 = no evidence of a primary tumor in the bladder; T1 = Tumor stage 1; Ta = Tumor stage a; Tis = Carcinoma in situ; TURBT = transurethral resection of bladder tumor; Tx = tumor stage unknown

Table 10. Summary of doxorubicin study results

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Abrams, 1981[95]	A: Doxorubicin, 50 mg (in 50 mL saline). Single instillation, within 24 hours of TURBT. B: No adjuvant treatment. TURBT alone.	Recurrence at 6 months: 79.3% (23/29) vs. 89.3% (25/28)		
Akaza, 1987[112] [Study One] (followup of Niijima, 1983[116])	A: Doxorubicin, 30 mg (in 30 mL saline). Total 8 instillations: First within 1 week of TURBT, twice weekly X 4 weeks. (n=149) B: Doxorubicin, 20 mg (in 40 mL saline). Total 8 instillations: First within 1 week of TURBT, twice weekly X 4 weeks. (n=148) C: MMC: 20 mg (in 40 mL saline). Total 8 instillations: First within 1 week of TURBT, twice weekly X 4 weeks. (n=139) D: No adjuvant treatment. TURBT alone. (n=139)	Recurrence-free survival rate at 540 days*: 56.6% vs. 52.0% vs. 42.4% vs. 38.5%, generalized Wilcoxon test: A vs. D, $p<0.05$ B vs. D, $p<0.05$ C vs. D, $p<0.10$ Recurrence-free survival at 1800 days, generalized Wilcoxon test: B>D, $p<0.05$ C>D, $p<0.05$ * from Niijima, 1983		

Table 10. Summary of doxorubicin study results (continued)

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Akaza, 1987[112] [Study Two]	A: Doxorubicin, 30 mg (in 30 mL saline). Total 21 instillations. (n=151) B: Doxorubicin, 20 mg (in 40 mL saline). Total 21 instillations. (n=158) C: MMC: 20 mg (in 40 mL saline). Total 21 instillations. (n=150) D: No adjuvant treatment. TURBT alone. (n=148) For A, B, and C: First instillation within 1 week of TURBT; once weekly X 2 weeks, then once every 2 weeks X 14 weeks, then once monthly X 8 months, then once every 3 month X 1 year.	Recurrence-free survival rate at 1 year: 74.8% vs. 75.0% vs. 76.3% vs. 66.7% Recurrence-free survival rate at 2 years: 62.3% vs. 59.1% vs. 62.3% vs. 51.8% Recurrence-free survival at 1260 days, generalized Wilcoxon test: A>D, p<0.05 B>D, p<0.05 C>D, p<0.05		
Akaza, 1992[113] [Study Two] (followup of Akaza, 1987[112])	A: Doxorubicin, 30 mg (in 30 mL saline). Total 21 instillations. (n=44) B: Doxorubicin, 20 mg (in 40 mL saline). Total 21 instillations. (n=42) C: MMC: 20 mg (in 40 mL saline). Total 21 instillations. (n=41) D: No adjuvant treatment. TURBT alone. (n=31) For A, B, and C: First instillation within 1 week of TURBT; once weekly X 2 weeks, then once every 2 weeks X 14 weeks, then once monthly X 8 months, then once every 3 month X 1 year.	Recurrence: Recurrence/year (number of recurrences/total observation period: 0.473 vs. 0.512 vs. 0.472 vs. 0.510	Progression (in stage, grade, or both): 43.2% (19/44) vs. 31.0% (13/42) vs. 26.8% (11/41) vs. 38.7% (12/31), "Statistics: no difference"	

Table 10. Summary of doxorubicin study results (continued)

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Ali-El-Dein, 1997[119] (Journal of Urology)	A: Epirubicin, 50 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10. (n=64) B: Epirubicin, 80 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10. (n=68) C: Doxorubicin, 50 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10. (n=60) D: TURBT only. No adjuvant therapy. (n=61)	Recurrence: 25.0% (16/64) vs. 17.6% (12/68) vs. 36.7% (22/60) vs.65.6% (40/61); A, B, and C vs. D, p=0.0002; A and B vs. C, p=0.02; A vs. B, p>0.05. Mean time to first recurrence, months (95% CI): 16 (12.2-19.8) vs. 15.4 (11.4-19.4) vs. 18.9 (14.4-23.4) vs. 6.3 (5.2-7.4), A, B, and C vs. D, p<0.001; A and B vs. C, p=0.05; A vs. B, p=0.05 (all log-rank test) Recurrence rate/100 patient/months: 0.83 vs. 0.60 vs. 1.18 vs. 2.73, A, B, and C vs. D, p<0.001; A and B vs. C, p<0.05; A vs. B, p<0.05.	Progression: 10.9% (7/64) vs. 4.4% (3/68) vs. 10.0% (6/60) vs.8.2% (5/61). Mean interval to progression, months (95% CI): 31 (22-40) vs. 31 (18-44) vs. 33 (26-40) vs. 37 (30-44), log-rank test, p=0.6 (all log-rank test).	
Cheng, 2005[120]	A: Doxorubicin, 50 mg (in 50 mL saline). Total 12 instillations: First at 2 weeks after TURBT, then weekly X 4 weeks, then monthly X 5 months, then every 3 months X 6 months. (n=46) B: TURBT only. No adjuvant therapy. (n=36)	Recurrence: 37.0% (17/46) vs. 52.8% (19/36) Recurrence-free survival (median), months: 190 vs. 89 Recurrence-free survival at 10 years (Kaplan-Meier estimate): 67% vs. 50% Recurrence-free survival, log rank test, p=0.12 Time to recurrence (median), months: 13 vs. 8	Progression: 13.0% (6/46) vs. 5.6% (2/36) Progression-free survival at 10 years (Kaplan-Meier estimate): 84% vs. 89% Progression-free survival, log rank test, p=0.44 Time to progression (median), months: 34 vs. 61	Mortality (disease-specific): 6.5% vs. 2.8% Disease-specific survival at 10 years (Kaplan-Meier estimate): 95% vs. 97% Median time to death (disease-specific), months: 73 vs. 55 Mortality (other causes): 30.4% vs. 16.7% Overall survival at 10 years (Kaplan-Meier estimate): 68% vs. 83%

Table 10. Summary of doxorubicin study results (continued)

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Eto, 1994[195]	A: Epirubicin, 30 mg (in 30 mL physiological saline). Total 19 instillations: 2 times/week for 4 weeks, then 1 time/month for 11 months. (n=60) B: Doxorubicin, 30 mg (in 30 mL physiological saline). Total 19 instillations: 2 times/week for 4 weeks, then 1 time/month for 11 months. (n=54)	Recurrence free at 1 year: 92.8% vs. 86.4%, generalized Wilcoxon test, p=nonsignificant. Recurrence free at 2 years: 88.6% vs. 81.8%, generalized Wilcoxon test, p=nonsignificant.		
Gustafson, 1991[115]	A: MMC. Dosages "varied according to individual patient's bladder capacity". Range: "5 mg in 20 mL" to "40 mg in 250 mL". Total 15 instillations: First instillation approximately 2 weeks after TURBT; instillations weekly X 4 weeks, then monthly X 11 months. (n=19) B: Doxorubicin. Dosages "varied according to individual patient's bladder capacity". Range: "10 mg in 20 mL" to "80 mg in 250 mL". Total 15 instillations: Same protocol as A. (n=20) C: TURBT only. No adjuvant therapy. (n=21)	Recurrence-free survival during treatment year: 52.6% (10/19) vs. 15.0% (3/20) vs. 14.3% (3/21) Recurrence-free survival for duration of followup: 26.3% (5/19) vs. 10.0% (2/20) vs. 4.8% (1/21) Recurrence rate/100 patient-months: 7.7 vs. 18.3 vs. 18.6, p=0.02 Mean disease-free interval, months (A vs. B): 14 vs. 6, p=0.02	Progression: Increased stage only: 0.0% (0/19) vs. 5.0% (1/20) vs. 4.8% (1/21) Increased grade only: 0.0% (0/19) vs. 15.0% (3/20) vs. 9.5% (2/21) Increased stage and grade: 10.5% (2/19) vs. 10.0% (2/20) vs. 0.0% (0/21)	

Table 10. Summary of doxorubicin study results (continued)

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Huland, 1990[191]	A: MMC (20 mg/20 mL). Total 42 instillations: First at 4-6 weeks after hospital discharge, then every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year. (n=209) B: MMC (20 mg/20 mL). Total 42 instillations: First at 4-6 weeks after hospital discharge, then every week X 8 weeks, then every 4 weeks for rest of 1st year and 2 additional years. (n=96) C: MMC (20 mg/20 mL). Total 20 instillations: First at 4-6 weeks after hospital discharge, then every week X 20 weeks. (n=75) D: Doxorubicin (50 mg/50 mL). Total 42 instillations: First at 4-6 weeks after hospital discharge, then every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year. (n=39)	Recurrence: 15.3% (32/209) vs. 9.4% (9/96) vs. 17.3% (13/75) vs. 23.1% (9/39); differences reported as not statistically significant, p-values not reported. Recurrence per 100 patient-months: 0.68 vs. 0.49 vs. 0.65 vs. 0.76	Progression of stage: 2.9% (6/209) vs. 1.0% (1/96) vs. 5.3% (4/75) vs. 7.7% (3/39) Progression of grade: 1.9% (4/209) vs. 1.0% (1/96) vs. 4.0% (3/75) vs. 10.3% (4/39)	

Table 10. Summary of doxorubicin study results (continued)

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Kurth, 1997[121]	A: Doxorubicin, 50 mg (in 50 mL normal saline). Total 15 instillations: First at 3 to 14 days after TURBT, then weekly for 1 month, then monthly for 11 months. Nitrofurantoin, 100 mg, was given after each instillation 3 times/day X 3 days. (n=166) B: TURBT only. No adjuvant therapy. (n=70)	Recurrence: 50% (83/166) vs. 67% (47/70) Recurrence-free at 3 years: 48% (95% CI 40-56) vs. 29% (95% CI 17-41) Recurrence rate per year: 0.30 vs. 0.68; p-value significant. Time to first recurrence: A>B, log-rank test, p<0.001.	Progression: 13.8% (25/181) vs. 18.1% (13/72) Progression-free at 5 years: 86% (95% CI 80-92) vs. 87% (95% CI 77-96) Free of distant metastases at 5 years: 97% (95% CI 94-100) vs. 98% (95% CI 95-100)	Survival (death from malignancy) at 5 years: 92% (95% CI 88-96) vs. 97% (95% CI 92-100) Survival (death from malignancy) at 10 years: 82% (95% CI 75-89) vs. 82% (95% CI 70-95) Survival (all cause) at 5 years: 74% (95% CI 67-81) vs. 73% (95% CI 61-84) Survival (all cause) at 10 years: 46% (95% CI 37-54) vs. 42% (95% CI 29-56)
Martinez-Pineiro, 1990[172]	A. Doxorubicin 50 mg (in 50 mL saline). Total 16 instillations. (n=53) B. Thiotepa 50 mg (in 50 mL saline). (n=56) A and B: First treatment within 14 days of TURBT, then weekly X 4 weeks, then monthly X 11 months.	Recurrence: 43% (23/53) vs. 36% (20/56), p>0.05; Mantel-Haenszel test, p=NS Months to recurrence (mean): 31 vs. 29	Progression: 8% (4/53) vs. 4% (2/56)	Death due to metastatic disease: 1 vs. 0 Noncancer death: 0 vs. 1

Table 10. Summary of doxorubicin study results (continued)

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Matsumura, 1992[123]	A: Doxorubicin, 20 mg (in 40 mL physiological saline). Total 21 instillations over 2 years after TURBT: Timing of first dose not specified; instillations once a week X 2, then every 2 weeks X 7, then once a month X 8, then once every 3 months X 4. (n=126) B: Doxorubicin, 20 mg (in 40 mL physiological saline). Total 6 instillations over 2 weeks before TURBT: specific schedule not reported. (n=75) C: No adjuvant treatment. TURBT alone. (n=83)	Recurrence-free survival rate at 240 days: 73.8% vs. 57.8% vs. 61.2%; A vs. B, p<0.05; other comparisons, p=NS Recurrence-free survival rate at 480 days: 52.0% vs. 37.0% vs. 32.0%; A vs. C, p<0.01; other comparisons, p=NS Recurrence-free survival rate at 720 days: 38.2% vs. 18.8% vs. 17.8%; A vs. B, p<0.05; A vs. C, p<0.01; other comparisons, p=NS		
Niijima, 1983[116]	A: Doxorubicin, 30 mg (in 30 mL saline). Total 8 instillations. B: Doxorubicin, 20 mg (in 40 mL saline). Total 8 instillations. C: MMC: 20 mg (in 40 mL saline). Total 8 instillations. D: No adjuvant treatment. TURBT alone. For A, B, and C: First instillation within 1 week of TURBT. Twice weekly X 4 weeks	Recurrence-free survival rate at 540 days: 56.6% vs. 52.0% vs. 42.4% vs. 38.5%, generalized Wilcoxon test: A vs. D, p<0.05 B vs. D, p<0.05 C vs. D, p<0.10		

Table 10. Summary of doxorubicin study results (continued)

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Obata, 1994[124]	A: Doxorubicin, 20 mg (in 40 mL physiological saline). Total 19 instillations over 1 year, after TURBT: Timing of first dose not specified; instillations twice a week X 4 weeks, then once a month X 11 months. (n=90) B: No adjuvant treatment. TURBT alone. (n=76)	Recurrence-free survival rate at 3 years: 44% vs. 30% (p-value not reported).		
Okamura, 2002[125]	A: Doxorubicin, 30 mg (in 30 mL normal saline). Single intravesical instillation within 6 hours of TURBT. (n=81) B: TURBT only. No adjuvant therapy. (n=79)	Recurrence-free survival: A>B, log-rank test, p=0.0026. Time to initial recurrence (mean), months: 41.9 vs. 18.0 Recurrence rate per year: 0.11 ± 0.22 vs. 0.24 ± 0.36, p=0.007 Adjusted HR for recurrence (B as reference): 0.31 (95% CI 0.17-0.56, p=0.0001); adjusted covariates not specified.		
Shuin, 1994[196]	A: Epirubicin, 30 mg (in 40 mL saline). Total 17 instillations: Timing of first not specified; every 2 weeks X 3 months, then every 4 weeks for remainder of 1 year. B: Doxorubicin, 30 mg (in 40 mL saline). Total 17 instillations: Timing of first not specified; every 2 weeks X 3 months, then every 4 weeks for remainder of 1 year.	Recurrence: 25% (8/32) vs. 27% (9/33), chi-square test, p=NS. Recurrence-free period, mean (range): 9.7 months (4 to 17) vs. 8.5 months (3 to 16), "no significant difference" (type of statistical testing and p-value not specified).	Progression: "There has been no case of grade G3 or invasive cancer in either group."	

CI = confidence interval; G3 = Grade 3; HR = hazard ratio; MMC = Mytomycin C; NS = not significant; TURBT = transurethral resection of bladder tumor

Table 11. Summary of epirubicin study characteristics

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Ali-El-Dein, 1997[119] (Journal of Urology)	Egypt Single center 1991 - 1995	A: Epirubicin, 50 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10. (n=64) B: Epirubicin, 80 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10. (n=68) C: Doxorubicin, 50 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10. (n=60) D: TURBT only. No adjuvant therapy. (n=61)	Duration, mean: 30.1 months for all groups. Method: Cysto-urethroscopy, urine cytology, and flow cytometry.	Age: Not reported Male: 81.4%,overall; not reported by group Race/ethnicity: Not reported Recurrent bladder cancer: 37.5% vs. 41.2% vs. 43.3% vs.45.9% Stage: pTa: 10.9% vs. 17.6% vs. 6.7% vs.9.8%; pT1: 89.1% vs. 82.4% vs. 93.3% vs.90.2%; Tis associated: 6.3% vs. 11.8% vs. 0.0% vs.0.0% Functional Status: Not reported
Ali-El-Dein, 1997[126] (British Journal of Urology)	Egypt Single center 1992 - 1996	A: Epirubicin, 50 mg (in 50 mL normal saline). Single instillation immediately after TURBT. (n=55) B: Epirubicin, 50 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10. (n=59) C: TURBT only. No adjuvant therapy. (n=54)	Duration, mean: 32.2 months Method: Cystourethroscopy, urine cytology, and flow cytometry.	Age (mean), years: 52.1 vs. 55 vs. 53.4 Male: 67.3% vs. 74.6% vs. 70.4% Race/ethnicity: Not reported Recurrent bladder cancer: 47.2% vs. 52.5% vs. 44.4% Stage: pTa: 16.3% vs. 25.4% vs. 18.5%; pT1: 83.7% vs. 74.6% vs. 81.5% Functional Status: Not reported

Table 11. Summary of epirubicin study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Berrum-Svennung, 2008[127]	Sweden Multicenter 1998 - 2004	A: Epirubicin, 50 mg (in 50 mL saline). Single instillation within 6 hours after TURBT. (n=155) B: Placebo. Saline, 50 mL. Single instillation within 6 hours after TURBT. (n=152)	Duration: 2 years, not reported as median/mean, nor for each group. Method: Cystoscopy.	Age (median), years: 74 vs. 71 Age (mean), years: 71 vs. 69 Male: 69.7% vs. 77.6% Race/ethnicity: Not reported Recurrent bladder cancer: 49.7% vs. 50.7% Stage/Grade: Ta/G1-G2: 85.2% vs. 82.2%; T1/G1-G2: 5.7% vs. 8.0%; Unknown: 9.7% vs. 9.9% Functional Status: Not reported
Eto, 1994[195]	Japan Multicenter 1990 - 1992	A: Epirubicin, 30 mg (in 30 mL physiological saline). Total 19 instillations: 2 times/week for 4 weeks, then 1 time/month for 11 months. (n=60) B: Doxorubicin, 30 mg (in 30 mL physiological saline). Total 19 instillations: 2 times/week for 4 weeks, then 1 time/month for 11 months. (n=54)	Duration, mean: 674 days vs. 606 days Method: Cystoscopy and urine cytology.	Age (median), years: 65 vs. 67 Male: 85.0% vs. 87.0% Race/ethnicity: Not reported Recurrent bladder cancer: 14.8% vs. 16.3%; Unknown: 10% vs. 9.3% Stage: Ta: 35.0% vs. 31.5%; T1: 48.3% vs. 57.4%; Gx: 16.7% vs. 11.1% Functional Status: Not reported
Gudjónsson, 2009[128]	Sweden Multicenter 1997 - 2004	A: Epirubicin, 80 mg (in 30 mL saline). Single instillation within 24 hours of TURBT. (n=102) B: TURBT only. No adjuvant therapy. (n=117)	Duration, median: 3.9 years, for all patients. 3.6 years for patients without recurrence. Method: Cystoscopy and urine cytology.	Age (mean), years: 70 vs. 70 Male: 72.5% vs. 69.3% Race/ethnicity: Not reported Recurrent bladder cancer: 46.1% vs. 48.7% Stage: Ta: 81.4% vs. 86.3%; T1: 9.8% vs. 6.8%; Unknown: 7.8% vs. 6.0%; "Low malignant potential": 1.0% vs. 0.9% Functional Status: Not reported

Table 11. Summary of epirubicin study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Igawa, 1996[129]	JapanNumber centers not reported.Study years not reported.	A: Epirubicin, 20 mg (in 40 mL saline). Total 24 instillations: First instillation within 2 weeks of TURBT, once a month X 24 months. (n=43)B: TURBT only. No adjuvant therapy. (n=32)	Duration, median: 20 months, all patients Method: Cystoscopy.	Population characteristics not reported according to treatment status.
Liu, 2006[192]	China Number centers not reported 1997 - 1998	A: Epirubicin, 80 mg (in 40 mL normal saline). Single instillation within 6 hours of TURBT. (n=14) B: Epirubicin, 40 mg. Total 16 - 18 instillations: Every week for 6 ~ 8 weeks, then every month for 10 months. (n=15) C: MMC, 40 mg. Total 16 - 18 instillations: Every week for 6 ~ 8 weeks, then every month for 10 months. (n=15)	Duration: 5 years (all patients). Method: Cystoscopy and urine cytology.	Age (mean), years: 62.2 Male: Not reported Race/ethnicity: Not reported Recurrent bladder cancer: 23.4% (overall) Stage and Grade: TaG1: 6.3% vs. 0.0% vs. 0.0%; TaG2: 6.3% vs. 6.6% vs. 6.3%; T1G1: 12.5% vs. 26.7% vs. 12.5%; T1G2: 75.0% vs. 66.7% vs. 81.3% Functional Status: Not reported
Melekos, 1992[130]	Greece Number centers not reported. Study years not reported.	A: Epirubicin, 50 mg (in 5 mL sterile saline). Total minimum 6 instillations for all patients: First instillation within 2 weeks after TURBT, one dose weekly X 6 weeks. Then, single dose given at each followup exam for patients who were recurrence-free during following 2 years. (n=43) B: TURBT only. No adjuvant therapy. (n=22)	Duration: not reported. Method: Cystoscopy and urine cytology.	Age (mean), years: 66.2 vs. 67.4 Male: 83.7% vs. 86.4% Race/ethnicity: Not reported Recurrent bladder cancer: 32.6% vs. 31.8% Stage: Ta: 60.5% vs. 59.1%; T1: 39.5% vs. 40.1%; Associated Tis: 4.7% vs. 4.5% Functional Status: Not reported

Table 11. Summary of epirubicin study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Melekos, 1993[103]	Greece Number of centers not reported. Study years not reported.	A. Epirubicin, 50 mg (in 50 mL saline). Total instillations variable: All patients received initial 6-week course, then maintenance therapy every 3 months for first 2 years then every 6 months if at high risk for recurrence and initially responsive to treatment then received a separate 4-week course at month 6 of followup. (n=67) B. TURBT only. No adjuvant therapy. (n=32)	Duration: 50 months, overall. Method: Cystoscopy and urine cytology.	Age (mean), years: 66 vs. 68 Male: 84% vs. 84% Race/ethnicity: Not reported Stage: Ta: 63% vs. 66%; T1: 37% vs. 34% Tis: 4% vs. 6% Functional Status: Not reported
Oosterlinck, 1993[131]	Europe Multicenter 1986 - 1989	A: Epirubicin, 80 mg (in 50 mL physiological solution). Single instillation minimum for each patient, within 6 hours after TURBT. For recurrence, repeat TURBT and repeat instillation for each recurrence until maximum of 3 additional instillations. (n=194) B: Placebo. Sterile water, 50 mL. Single instillation minimum for each patient, within 6 hours after TURBT. For recurrence, repeat TURBT and repeat instillation for each recurrence until maximum of 3 additional instillations. (n=205)	Duration, average: 2 years, 4.5 years maximum Method: Cystoscopy and urine cytology.	Reported for randomized groups (205 vs. 215) Age: Not reported % Male: Not reported Race/ethnicity: Not reported Recurrent bladder cancer: 21.0% vs. 23.0% Stage: pTa: 70.7% vs. 76.7%; pT1: 29.3% vs. 23.0%; Unknown: 0.0% vs. 0.5% Functional Status: Not reported

Table 11. Summary of epirubicin study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Rajala, 1999[133]	Finland Multicenter 1991 - 1994	A: Interferon-α-2b, 50 million units (in 100 mL physiological saline). Single intravesical instillation immediately after TURBT. (n=66) B: Epirubicin, 100 mg (in 100 mL physiological saline). Single intravesical instillation immediately after TURBT. (n=68)C: TURBT only. No adjuvant therapy. (n=66)	Duration: 2 years Method: Cystoscopy and urine cytology.	Age: Not reported Male: 81.8% vs. 70.6% vs. 65.2 Race/ethnicity: Not reported Recurrent bladder cancer: None (primary only) Stage: pTa: 80.3% vs. 79.4% vs. 83.3%; pT1: 19.7% vs. 20.6% vs. 16.7% Functional Status: Not reported
Rajala, 2002[132]	Finland Multicenter 1991 - 1994	A: Interferon-α-2b, 50 million units (in 100 mL physiological saline). Single intravesical instillation immediately after TURBT. (n=66) B: Epirubicin, 100 mg (in 100 mL physiological saline). Single intravesical instillation immediately after TURBT. (n=68) C: TURBT only. No adjuvant therapy. (n=66)	Duration, median: 72 months Method: Cystoscopy and urine cytology.	Age (mean), years: 66.3 vs. 65.1 vs. 64.6 Male: 81.8% vs. 70.6% vs. 65.2 Race/ethnicity: Not reported Recurrent bladder cancer: None (primary only) Stage: pTa: 80.3% vs. 79.4% vs. 83.3%; pT1: 19.7% vs. 20.6% vs. 16.7% Functional Status: Not reported

Table 11. Summary of epirubicin study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Saika, 2010[134]	Japan Multicenter 1995 - 2001	A. Epirubicin, 20 mg (in 40 mL physiological saline). Total 2 instillations: First immediately after (<1 hour) TURBT, second in the early morning of the following day. (n=79) B. Epirubicin, 50 mg (in 100 mL physiological saline). Total 2 instillations: First immediately after (<1 hour) TURBT, second in the early morning of the following day. (n=84) C. TURBT only. No adjuvant therapy. (n=77)	Duration, median: 44 months vs. 46 months vs. 42 months Method: Cystoscopy.	Based on eligible patents (n=257): Age (median), years: 69 vs. 69 vs. 71 Male: 81% vs. 89% vs. 88% Race/ethnicity: Not reported Recurrent bladder cancer: 40% vs. 43% vs. 40% Stage Ta: 54% vs. 60% vs. 64% Stage T1: 46% vs. 40% vs. 36% Functional status: Not reported
Shuin, 1994[196]	Japan Multicenter 1990 - 1993	A: Epirubicin, 30 mg (in 40 mL saline). Total 17 instillations: Timing of first not specified; every 2 weeks X 3 months, then every 4 weeks for remainder of 1 year. B: Doxorubicin, 30 mg (in 40 mL saline). Total 17 instillations: Timing of first not specified; every 2 weeks X 3 months, then every 4 weeks for remainder of 1 year.	Duration: not reported Method: not described	Age: <40 years: 6% vs. 3% 40-49 years: 3% vs. 9% 50-59 years: 9% vs. 24% 60-69 years: 25% vs. 21% ≥70: 56% vs. 42% Male: 81% vs. 82% Race/ethnicity: Not reported Recurrent bladder cancer: All (recurrent only) Stage Ta: 69% vs. 64% Stage T1: 25% vs. 27% Stage unknown: 6% vs. 9% Functional status: Not reported

G1 = Grade 1; G2 = Grade 2; G3 = Grade 3; Gx = Grade unknown; MMC = Mytomycin C; pT1 = Tumor stage 1 determined by pathology; pTa = Tumor stage a determined by pathology; T1 = Tumor stage 1; Ta = Tumor stage a; Tis = carcinoma in situ; TURBT = transurethral resection of bladder tumor

Table 12. Summary of epirubicin study results

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Ali-El-Dein, 1997[119] (Journal of Urology)	A: Epirubicin, 50 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10. (n=64) B: Epirubicin, 80 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10. (n=68) C: Doxorubicin, 50 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10. (n=60) D: TURBT only. No adjuvant therapy. (n=61)	Recurrence: 25.0% (16/64) vs. 17.6% (12/68) vs. 36.7% (22/60) vs.65.6% (40/61); A, B, and C vs. D, p=0.0002; A and B vs. C, p=0.02; A vs. B, p>0.05. Mean time to first recurrence, months (95% CI): 16 (12.2-19.8) vs. 15.4 (11.4-19.4) vs. 18.9 (14.4-23.4) vs. 6.3 (5.2-7.4), A, B, and C vs. D, p<0.001; A and B vs. C, p=0.05; A vs. B, p=0.05 (all log-rank test) Recurrence rate/100 patient/months: 0.83 vs. 0.60 vs. 1.18 vs. 2.73, A, B, and C vs. D, p<0.001; A and B vs. C, p<0.05; A vs. B, p<0.05.	Progression: 10.9% (7/64) vs. 4.4% (3/68) vs. 10.0% (6/60) vs.8.2% (5/61). Mean interval to progression, months (95% CI): 31 (22-40) vs. 31 (18-44) vs. 33 (26-40) vs. 37 (30-44), log-rank test, p=0.6 (all log-rank test).	
Ali-El-Dein, 1997[126] (British Journal of Urology)	A: Epirubicin, 50 mg (in 50 mL normal saline). Single instillation immediately after TURBT. (n=55) B: Epirubicin, 50 mg (in 50 mL normal saline). Total 18 instillations: First at 7 to 14 days after TURBT, then once a week X 7, then once monthly X 10. (n=59) C: TURBT only. No adjuvant therapy. (n=54)	Recurrence: 23.6% (13/55) vs. 25.4% (15/59) vs. 51.8% (28/54); A vs. B vs. C, p=0.002; A and B vs. C, p<0.001; A vs. B, p=0.8. Mean interval to first recurrence, months: 16 vs. 18 vs. 6.9; A and B vs. C, p<0.05; A vs. B, p>0.05. Recurrence rate/100 patient/months: 0.79 vs. 0.84 vs. 2.01	Progression: 5.5% (3/55) vs. 3.4% (2/59) vs. 9.3% (5/54), p=0.4	

Table 12. Summary of epirubicin study results (continued)

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Berrum-Svennung, 2008[127]	A: Epirubicin, 50 mg (in 50 mL saline). Single instillation within 6 hours after TURBT. (n=155) B: Placebo. Saline, 50 mL. Single instillation within 6 hours after TURBT. (n=152)	Recurrence, during 2 years: 51.0% (79/155) vs. 62.5% (95/152); Mann-Whitney U test, p=0.04, log-rank test, p=0.022	Progression (stage to muscle invasion): 2.6% (4/155) vs. 1.3% (2/152), (difference "not significant").	
Eto, 1994[195]	A: Epirubicin, 30 mg (in 30 mL physiological saline). Total 19 instillations: 2 times/week for 4 weeks, then 1 time/month for 11 months. (n=60) B: Doxorubicin, 30 mg (in 30 mL physiological saline). Total 19 instillations: 2 times/week for 4 weeks, then 1 time/month for 11 months. (n=54)	Recurrence (at 1 year): 6.7% (4/60) vs. 13.0% (7/54) Recurrence free at 1 year, generalized Wilcoxon test, p=nonsignificant. Recurrence (at 2 years): 11.6% (7/60) vs. 18.5% (10/54) Recurrence free at 2 years, generalized Wilcoxon test, p=nonsignificant.		
Gudjónsson, 2009[128]	A: Epirubicin, 80 mg (in 30 mL saline). Single instillation within 24 hours of TURBT. (n=102) B: TURBT only. No adjuvant therapy. (n=117)	Recurrence: 62% (63/102) vs. 77% (90/117) Difference in Recurrence-free survival, log-rank test, p=0.016. Univariate HR (95% CI): 0.67 (0.49-0.93), p=0.017 Multivariate HR (95% CI): 0.56 (0.39-0.80), p=0.002 (adjusted for tumor multiplicity, number of recurrences per year, sex, age, and tumor grade).		
Igawa, 1996[129]	A: Epirubicin, 20 mg (in 40 mL saline). Total 24 instillations: First instillation within 2 weeks of TURBT, once a month X 24 months. (n=43) B: TURBT only. No adjuvant therapy. (n=32)	Recurrence: 60.5% (26/43) vs. 68.8% (22/32), p-value not reported.	Progression: 20.9% (9/43) vs. 3.1% (1/32), p=0.024	

Table 12. Summary of epirubicin study results (continued)

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Liu, 2006[192]	A: Epirubicin, 80 mg (in 40 mL normal saline). Single instillation within 6 hours of TURBT. (n=14) B: Epirubicin, 40 mg. Total 16 - 18 instillations: Every week for 6 ~ 8 weeks, then every month for 10 months. (n=15) C: MMC, 40 mg. Total 16 - 18 instillations: Every week for 6 ~ 8 weeks, then every month for 10 months. (n=15)	Recurrence: 35.7% (5/14) vs. 33.3% (5/15) vs. 40% (6/15), p>0.05 Recurrence-free at 1 year: 100% (14/14) vs. 86.7% (13/15) vs.93.3% (14/15) Recurrence-free at 2 years: 85.7% (12/14) vs. 80.0% (12/15) vs.66.7% (13/15) Recurrence-free at 3 years: 71.4% (10/14) vs. 73.3% (11/15) vs.80.0% (12/15) Recurrence-free at 5 years: 64.3% (9/14) vs. 66.7% (10/15) vs.60.0% (9/15) Mean interval to recurrence, months: 8 vs. 4 vs. 5		
Melekos, 1992[130]	A: Epirubicin, 50 mg (in 5 mL sterile saline). Total minimum 6 instillations for all patients: First instillation within 2 weeks after TURBT, one dose weekly X 6 weeks. Then, single dose given at each followup exam for patients who were recurrence-free during following 2 years (maximum 7 additional instillations). (n=43) B: TURBT only. No adjuvant therapy. (n=22)	Recurrence: 37.2% (16/43) vs. 54,5% (12/22), p>0.50 Recurrence-free survival (40 months), A>B, Mantel-Haenszel test, p=0.11 Relative recurrence rate: 0.81 vs. 1.46, p>0.05 Recurrence rate/100 patient-months: 1.4 vs. 2.6, p>0.10 Mean time to recurrence: 18.7 month vs. 12.2 months, p<0.02	Progression (stage and/or grade): 9.3% (4/43) vs. 22.7% (5/22), p>0.30	

Table 12. Summary of epirubicin study results (continued)

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Melekos, 1993[103]	A. Epirubicin, 50 mg (in 50 mL saline). Total instillations variable: All patients received initial 6-week course, then maintenance therapy every 3 months for first 2 years then every 6 months if at high risk for recurrence and initially responsive to treatment then received a separate 4-week course at month 6 of followup. (n=67) B. TURBT only. No adjuvant therapy. (n=32)	Recurrence: 40% (27/67) vs. 59% (19/32) Interval before recurrence: 16 months vs. 11 months Progression: 9% vs. 22% Muscle invasion: 4% vs. 13%	Progression (stage or muscle invasion): 13% (9/67) vs. 34% (11/32)	
Oosterlinck, 1993[131]	A: Epirubicin, 80 mg (in 50 mL physiological solution). Single instillation minimum for each patient, within 6 hours after TURBT. For recurrence, repeat TURBT and repeat instillation for each recurrence until maximum of 3 additional instillations. (n=194) B: Placebo. Sterile water, 50 mL. Single instillation minimum for each patient, within 6 hours after TURBT. For recurrence, repeat TURBT and repeat instillation for each recurrence until maximum of 3 additional instillations. (n=205)	Recurrence: 29% (56/194) vs. 41% (84/205), log-rank test, p=0.02Recurrence rate/year: 0.17 vs. 0.32, p<0.0001	Progression: 8.8% (17/194) vs. 7.3% (15/205), "no evidence of difference", p-value not reported.	

Table 12. Summary of epirubicin study results (continued)

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Rajala, 1999[133]	A: Interferon-α-2b, 50 million units (in 100 mL physiological saline). Single intravesical instillation immediately after TURBT. (n=66) B: Epirubicin, 100 mg (in 100 mL physiological saline). Single intravesical instillation immediately after TURBT. (n=68) C: TURBT only. No adjuvant therapy. (n=66)	Recurrence: 63.7% (42/66) vs. 33.8% (23/68) vs. 60.6 (40/66)		
Rajala, 2002[132]	A: Interferon-α-2b, 50 million units (in 100 mL physiological saline). Single intravesical instillation immediately after TURBT. (n=66) B: Epirubicin, 100 mg (in 100 mL physiological saline). Single intravesical instillation immediately after TURBT. (n=68) C: TURBT only. No adjuvant therapy. (n=66)	Recurrence: 68.2% (45/66) vs. 45.6% (31/68) vs. 72.7 (48/66), p=0.002. Recurrence-free at 72 months: 31.4% vs. 50.8% vs. 23.7% Recurrence-free survival: B>A or C, log-rank test, p=0.002. Median time to first recurrence, months (95% CI): 12 (9-15) vs. [not attained] vs. 9 (5-13)		
Saika, 2010[134]	A. Epirubicin, 20 mg (in 40 mL physiological saline). Total 2 instillations: First immediately after (<1 hour) TURBT, second in the early morning of the following day. (n=79) B. Epirubicin, 50 mg (in 100 mL physiological saline). Total 2 instillations: First immediately after (<1 hour) TURBT, second in the early morning of the following day. (n=84) C. TURBT only. No adjuvant therapy. (n=77)	Median recurrence-free survival, months: 24 vs. 38 vs. 13; A vs. B, p=0.48; A vs. C, p=0.25; B vs. C, p=0.05 (all log-rank test).	Progression: 0.0% (0/83) vs. 1.1% (1/90) vs. 0.0% (0/84).	

Table 12. Summary of epirubicin study results (continued)

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Shuin, 1994[196]	A: Epirubicin, 30 mg (in 40 mL saline). Total 17 instillations: Timing of first not specified; every 2 weeks X 3 months, then every 4 weeks for remainder of 1 year. B: Doxorubicin, 30 mg (in 40 mL saline). Total 17 instillations: Timing of first not specified; every 2 weeks X 3 months, then every 4 weeks for remainder of 1 year.	Recurrence: 25% (8/32) vs. 27% (9/33), chi-square test, p=NS.Recurrence-free period, mean (range): 9.7 months (4 to 17) vs. 8.5 months (3 to 16), "no significant difference" (type of statistical testing and p-value not specified).	Progression: "There has been no case of grade G3 or invasive cancer in either group."	

CI = confidence interval; G3 = Grade 3; HR = hazard ratio; MMC = Mytomycin C; NS = not significant; TURBT = transurethral resection of bladder tumor

Table 13. Summary of gemcitabine, interferon, or thiotepa study characteristics

Intervention	Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Gemcitabine vs. no intravesical therapy	Bohle, 2009[135]	Germany and Turkey Multicenter Study years: January 2004 - June 2005	A: Gemcitabine (GEM), 2000 mg (in 100 mL saline (0.9% NaCl)), instilled over 30 - 40 minutes immediately after TUR, followed by continuous irrigation with saline for ≥20 hours. (n=124) B: Placebo (PBO), 100 mL saline (0.9% NaCl), instilled over 30 - 40 minutes immediately after TUR, followed by continuous irrigation with saline for ≥20 hours. (n=124)	Duration (median): 23.6 months (range: 0 - 46). Method: Cystoscopy at least at month 3 and month 6, and every 6 months thereafter.	Age, median (range): 65 years (24 - 89) vs. 67 years (39 - 87) Race/ethnicity: not reported Sex (male): 76.6% vs. 83.1% Recurrent bladder cancer: 24.2% vs. 21.0% Stage: pTa: 75.0% vs. 71.0%; pT1: 25.0% vs. 29.0% Functional Status (Karnofski score): score 90-100: 91.9% vs. 94.4%; score 80-85: 7.3% vs. 4.0%; score <80: 0.8% vs. 0.8%
Interferon vs. no intravesical therapy	Portillo, 1997[137]	Spain Number of sites unclear 1990-1994	A: Interferon-α-2b, 60 million units. (n=39) B: Placebo (double distilled water).(n=39) A and B: First instillation 2-3 weeks after TURBT; Once weekly X 12 weeks, then once monthly X 9 months	Duration: mean 43months. Method: Cystoscopy, cytology, laboratory blood tests, urinalysis every 3 months X 1 year, then every 4 months X 1 year, then every 6 months thereafter.	Age, mean: 64.9 years Race/ethnicity: not reported Sex (male): 87.2% (68/78) Recurrent bladder cancer: 19.1%, overall (not reported by group, p=NS) Stage and Grade: T1G1: 2.6% (1/39) vs. 12.8% (5/39); T1G2: 82.1% (32/39) vs. 61.5% (24/39); T1G3: 15.4% (6/39) vs. 25.6% (10/39) Functional Status: not reported

Table 13. Summary of gemcitabine, interferon, or thiotepa study characteristics (continued)

Intervention	Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
	Stavropoulos, 2002[138]	Greece Number of sites unclear Study years not reported	A. Interferon-γ, 21 MU in 50 mL saline weekly for 8 weeks. (n=26) B. No adjuvant treatment. TURBT alone.(n=28)	Duration: Mean: 12.1 months Method: Cystoscopy every 3 months for 15 months and every 6 months thereafter.	Mean age: 66 vs. 64 years Male: 88% (23/26) vs. 71% (20/28) Race/ethnicity: not reported Recurrent bladder cancer: 27% (7/26) vs. 29% (8/28) Stage Ta: 42% (11/26) vs. 64% (18/28) Stage T1: 58% (15/26) vs. 36% (10/28) Functional status: not reported
Thiotepa vs. no intravesical therapy	Burnand, 1976[96]	UK Single center Study years not reported	A: Thiotepa, 90 mg (in 100 mL sterile water) immediately after TURBT (n=19) B: No adjuvant treatment. TURBT alone (n=32)	Duration: 2 to 5 years Method: Cystoscopy, interval not reported	Age, mean (years): 60 vs. 62 Sex (male): 84% vs. 84% Race/ethnicity: not reported Recurrent bladder cancer: Not reported Stage: Not reported
	Hirao, 1992[139]	Japan Single center 1986-1990	A: Thiotepa, 30 mg (in 30 mL physiological saline), for a total of 32 instillations over a 2-year period. (n=45) B: No adjuvant therapy. TURBT only. (n=48)	Duration (mean): 19.6 ± 10.8 vs. 14.9 ± 10.7 months Method: Cystoscopy and urinary cytology every 3 months for 3 years, every 6 months thereafter "until at least 5 years".	Age, mean years: 59.1 vs. 64.2 Race/ethnicity: not reported Sex (male): 73.1% vs. 76.5% Recurrent bladder cancer: not reported Stage: Ta: 31.1% vs. 41.7%; T1: 68.9% vs. 58.3% Functional Status: not reported

Table 13. Summary of gemcitabine, interferon, or thiotepa study characteristics (continued)

Intervention	Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
	Medical Research Council Working Party on Urological Cancer, 1994[98] Medical Research Council Working Party on Urological Cancer, 1985[99]	UK Multicenter 1981 - 1984	A: Thiotepa, 30 mg in 50 mL saline immediately following TURBT, then every 3 months for 1 year (n=122) B: Thiotepa , 30 mg in 50 mL saline immediately following TURBT (n=126) C: No adjuvant treatment. TURBT alone.(n=131)	Duration: median 8 years, 9 months Method: Cystoscopy every 3 months for one year, at least every 6 months for 2 years, then annually	Age: 51-59 years: 24% vs. 17% vs. 26%; 60-69 years: 37% vs. 43% vs. 31%; 70-79 years: 23% vs. 25% vs. 24% Sex: not reported Race/ethnicity: not reported Recurrent bladder cancer: All primary Ta: 76% vs. 72% vs. 78% T1: 15% vs. 18% vs. 14%
	Schulman, 1978[100]	Europe Multicenter 1975-1978	A. Thiotepa 30 mg in 30 mL sterile water. First instillation 1 month after TURBT, then weekly for 4 weeks, then every 4 weeks for 11 months. (n=75) B. No adjuvant therapy. TURBT alone. (n=69)	Duration: average 10 months; some patients with followup as long as 2 years. Method: Followup with cystoscopy every 12 weeks for first and second year,	Age: not reported Sex: not reported Race/ethnicity: not reported Recurrent bladder cancer: 38.7% vs. 43.5% Stage: T1: 100%

BCG = bacillus Calmette-Guérin; CI = confidence interval; HR = hazard ratio; MMC = mytomycin C; RR = risk ratio

Table 14. Summary of gemcitabine, interferon, or thiotepa study results

Intervention	Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Gemcitabine vs. no intravesical therapy	Bohle, 2009[135]	A: Gemcitabine (GEM), 2000 mg (in 100 mL saline (0.9% NaCl)), instilled over 30 - 40 minutes immediately after TUR, followed by continuous irrigation with saline for ≥20 hours. (n=124) B: Placebo (PBO), 100 mL saline (0.9% NaCl), instilled over 30 - 40 minutes immediately after TUR, followed by continuous irrigation with saline for ≥20 hours. (n=124)	Recurrence: 35.5% vs. 36.3% 12-month recurrence-free survival, HR (95% CI): G1/G2: 1.05 (0.69-1.59) G3: 0.48 (0.15-1.51) 12-month recurrence-free survival, according to receipt of concomitant BCG: With BCG: HR=1.44 (0.49-4.17) Without BCG: HR=0.88 (0.58-1.34)	Progression to muscle-invasive: 2.4% vs. 0.8%	Mortality, disease-specific: 0.8% vs. 0.8% Mortality, overall: 2.4% vs. 4.8%
Interferon vs. no intravesical therapy	Portillo, 1997[137]	A: Interferon-α-2b, 60 million units. (n=39) B: Placebo (double distilled water).(n=39) A and B: First instillation 2-3 weeks after TURBT; Once weekly X 12 weeks, then once monthly X 9 months	Recurrence at 12 months: 28.2% (11/39) vs. 35.9% (14/39) Recurrence at mean followup of 43 months: 53.8% (21/39) vs. 51.3% (20/39), p=NS. Recurrence-free interval: 17 months vs. 9.6 months, p=NS	Progression (stage, grade, diffuse CIS, and/or metastasis): 7.7% (3/39) vs. 17.9% (7/39), p=NS	Mortality due to bladder cancer: 5.1% (2/39) vs. 5.1% (2/39), p=NS
	Stavropoulos, 2002[138]	A. Interferon-γ, 21 MU in 50 mL saline weekly for 8 weeks. (n=26) B. No adjuvant treatment. TURBT alone.(n=28)	Recurrence: 61.5% (16/26) vs. 85.7% (24/28); p=0.043 Median time to first recurrence:12.0 months vs. 7.5 months Disease-free survival, median months (95% CI): 12.0 (8.3-15.7) vs. 7.0 (4.4-9.6); log-rank test, p=0.024.	Progression to muscle-invasive disease: 3.8% (1/26) vs. 3.6% (1/28).	

Table 14. Summary of gemcitabine, interferon, or thiotepa study results (continued)

Intervention	Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Thiotepa vs. no intravesical therapy	Burnand, 1976[96]	A: Thiotepa, 90 mg (in 100 mL sterile water) immediately after TURBT (n=19) B: No adjuvant treatment. TURBT alone (n=32)	Recurrence: 58% vs. 97% at 2 to 5 years, RR 0.60 (95% CI 0.41 to 0.88) Time to recurrence (months): 2.20 vs. 2.66		
	Hirao, 1992[139]	A: Thiotepa, 30 mg (in 30 mL physiological saline), for a total of 32 instillations over a 2-year period. (n=45) B: No adjuvant therapy. TURBT only. (n=48)	Recurrence at 3 years: 15% vs. 46%, p<0.05 Cumulative recurrence rate (CRR)*, all cases: 0.70 vs. 3.07 Cumulative recurrence rate (CRR): Ta: 0.97 vs. 2.03 T1: 0.55 vs. 3.80 G1: 1.33 vs. 1.92 G2: 0.64 vs. 3.99 Solitary: 0.77 vs. 2.44 Multiple: 0.48 vs. 4.86		
	Medical Research Council Working Party on Urological Cancer, 1994[98] Medical Research Council Working Party on Urological Cancer, 1985[99]	A: Thiotepa, 30 mg in 50 mL saline immediately following TURBT, then every 3 months for 1 year (n=122) B: Thiotepa , 30 mg in 50 mL saline immediately following TURBT (n=126) C: No adjuvant treatment. TURBT alone.(n=131)	Recurrence-free time at median 8.75 years: HR 1.09 (95% CI 0.96 to 1.56) for A vs. C, HR 1.11 (95% CI 0.78 to 1.5) for B vs. C Recurrence at 1 year: 51% (62/122) vs. 46% (58/126) vs. 40% (50/124), HR 1.15 (95% CI 0.76 to 1.79) for A vs. C, HR 1.27 (95% CI 0.81 to 1.89) for B vs. C	Failure-free (no progression or death from bladder cancer) at median 8.75 years: HR 1.75 (95% CI 0.79 to 3.85) for A vs. C, HR 1.59 (95% CI 0.68 to 3.70) for B vs. C	Mortality: 31% (38/122) vs. 29% (36/1216) vs. 31% (40/131) at median 8.75 years, HR 0.99 (95% CI 0.56 to 1.82) for A or B vs. C Bladder cancer mortality: 7.4% (9/122) vs. 7.9% (10/126) vs. 4.6% (6/131)

Table 14. Summary of gemcitabine, interferon, or thiotepa study results (continued)

Intervention	Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
	Schulman, 1978[100]	A. Thiotepa 30 mg in 30 mL sterile water. First instillation 1 month after TURBT, then weekly for 4 weeks, then every 4 weeks for 11 months. (n=75) B. No adjuvant therapy. TURBT alone. (n=69)	Recurrence: 49.3% (37/75) vs. 52.2% (36/69) Recurrence rate/100 patient months: 6.93 vs. 9.97; p=0.04 Recurrence: Primary: 37.0% (17/46) vs. 41.0% (16/39) Recurrent: 69.0% (20/29) vs. 66.7% (20/30) Recurrence rate/100 patient months: Primary: 4.98 vs. 6.74 Recurrent: 9.33 vs. 14.19	Progression of stage: 4.0% (3/75) vs. 5.8% (4/69) Progression of grade: 6.7% (5/75) vs. 7.2% (5/69) Progression of stage and grade: 2.7% (2/75) vs. 2.9% (2/69) Progression of stage: Primary: 0.0% (0/46) vs. 0.0% (0/39) Recurrent: 10.3% (3/29) vs. 13.3% (4/30) Progression of grade: Primary: 4.4% (2/46) vs. 0.0% (0/39) Recurrent: 10.3% (3/29) vs. 16.7% (5/30) Progression of stage and grade: Primary: 0.0% (0/46) vs. 0.0% (0/39) Recurrent: 6.9% (2/29) vs. 6.7% (2/30)	

BCG = bacillus Calmette-Guérin; CI = confidence interval; MMC = Mitomycin C; RR = risk ratio

Table 15. Summary of results for intravesical therapy versus no intravesical therapy

Intravesical Therapy	All-Cause Mortality	Bladder Cancer-Specific Mortality	Bladder Cancer Recurrence	Bladder Cancer Progression
BCG	No trials	1 trial, RR 0.62, 95% CI 0.32 to 1.19	3 trials, RR 0.56, 95% CI 0.43 to 0.71, I^2=0%	4 trials, RR 0.39, 95% CI 0.24 to 0.64, I^2=40%
MMC	1 trial, HR 1.17, 95% CI 0.89 to 1.53	1 trial, HR 0.71, 95% CI 0.34 to 1.46	8 trials, RR 0.71, 95% CI 0.57 to 0.89, I^2=72%	5 trials, RR 0.68, 95% CI 0.39 to 1.20, I^2=0%
Doxorubicin	2 trials, RR 1.83, 95% CI 0.78 to 4.28 and RR 0.93, 95% CI 73 to 1.18	2 trials, RR 2.35, 95% CI 0.25 to 21.6 and RR 0.97, 95% CI 0.54 to 1.76	10 trials, RR 0.80, 95% CI 0.72 to 0.88, I^2=46%	5 trials, RR 1.03, 95% CI 0.72 to 1.46, I^2=0.0%
Epirubicin	No trials	No trials	9 trials, RR 0.63, 95% CI 0.53 to 0.75, I^2=64%	8 trials, RR 0.79, 95% CI 0.48 to 1.30, I^2=27%
Gemcitabine	1 trial, RR 0.50, 95% CI 0.13 to 2.00	1 trial, RR 1.00, 95% CI 0.06 to 15.8	1 trial, RR 0.98, 95% CI 0.70 to 1.36	1 trial, RR 3.00, 95% CI 0.32 to 28.4
Interferon-alpha	1 trial, RR 1.00, 95% CI 0.15 to 6.75	1 trial, RR 1.00, 95% CI 0.15 to 6.75	3 trials, RR 0.75, 95% CI 0.53 to 1.06, I^2=50%	2 trials, RR 0.33, 95% CI 0.14 to 0.76, I^2=0%
Thiotepa	1 trial, HR 0.99, 95% CI 0.56 to 1.82	1 trial HR 1.61, 95% CI 0.59 to 4.30 (multi-instillation regimen) and HR 1.73, 95% CI 0.65 to 4.63 (single dose)	5 trials, RR 0.78, 95% CI 0.58 to 1.06, I^2=69%	1 trial, RR 0.92, 95% CI 0.13 to 6.36

BCG = bacillus Calmette Guérin; CI = confidence interval; HR = hazard ratio; RR = relative risk

Table 16. Summary of results for intravesical therapy head-to-head trials

Comparison	All-Cause Mortality	Bladder Cancer-Specific Mortality	Bladder Cancer Recurrence	Bladder Cancer Progression
BCG vs. MMC	7 trials, RR 0.94, 95% CI 0.83 to 1.06, I^2=0%	5 trials, RR 0.77, 95% CI 0.54 to 1.10, I^2=0%	10 trials, RR 0.95, 95% CI 0.81 to 1.11, I^2=67%	7 trials, RR 0.88, 95% CI 0.66 to 1.17, I^2=18%
BCG vs. BCG plus MMC given sequentially	1 trial, RR 1.57, 95% CI 0.67 to 3.71	2 trials, RR 1.10, 95% CI 0.50 to 2.38, I^2=17%	4 trials, RR 1.03, 95% CI 0.70 to 1.52, I^2=75%	3 trials, RR 0.87, 95% CI 0.40 to 1.91, I^2=22%
BCG plus MMC given sequentially vs. MMC	2 trials, RR 1.53, 95% CI 0.72 to 1.74 and RR 0.95, 95% CI 0.71 to 1.30	2 trials, RR 0.64, 95% CI 0.22 to 1.88 and RR 0.95, 95% CI 0.45 to 1.56	2 trials, RR 0.88, 95% CI 0.75 to 1.03, I^2=0%	2 trials, RR 0.82, 95% CI 0.40 to 1.68 and RR 1.28, 95% CI 0.35 to 4.61
BCG vs. doxorubicin	2 trials, RR 0.40, 95% CI 0.01 to 12 and RR 1.00, 95% CI 0.71 to 1.37	No evidence	2 trials, RR 0.31, 95% CI 0.16 to 0.6 and RR 0.75, 95% CI 0.64 to 0.88	1 trial, RR 0.20, 95% CI 0.02 to 1.72
BCG vs. epirubicin	3 trials, RR 0.72, 95% CI 0.44 to 1.19, I^2=87%	3 trials, RR 0.72, 95% CI 0.25 to 2.08, I^2=80%	5 trials, RR 0.54, 95% CI 0.40 to 0.74, I^2=76%	5 trials, RR 0.60, 95% CI 0.36 to 1.01, I^2=47%
BCG vs. BCG plus epirubicin given sequentially	No evidence	No evidence	3 trials, RR 1.25, 95% CI 0.92 to 1.69, I^2=0%	3 trials, RR 1.92, 95% CI 0.73 to 5.07, I^2=0%
BCG vs. gemcitabine	1 trial, RR 1.20, 95% CI 0.04 to 34	No evidence	3 trials, RR 1.67, 95% CI 1.21 to 2.29; RR 0.53, 95% CI 0.28 to 1.01 and RR 0.76, 95% CI 0.44 to 1.90	2 trials, RR 1.11, 95% CI 0.53 to 2.34 and RR 0.52, 95% CI 0.13 to 2.06
BCG vs. BCG plus gemcitabine given sequentially	No evidence	No evidence	1 trial, RR 0.86, 95% CI 0.49 to 1.51	1 trial, RR 1.18, 95% CI 0.30 to 4.61
BCG vs. Interferon alpha-2a	No evidence	No evidence	1 trial, RR 0.57, 95% CI 0.39 to 0.82	1 trial, RR 0.69, 95% CI 0.25 to 1.92
BCG vs. alternating BCG and interferon alpha-2a	No evidence	No evidence	1 trial, RR 0.42, 95% CI 0.30 to 0.59	No evidence
BCG vs. coadministration of BCG and interferon alpha-2a	No evidence	No evidence	1 trial, RR 0.88, 95% CI .71 to 1.08	1 trial, RR 0.76, 95% CI 0.17 to 3.30
BCG vs. thiotepa	No evidence	No evidence	1 trial, RR 0.38, 95% CI 0.19 to 0.76	1 trial, RR 0.42, 95 5CI 0.19 to 0.76
MMC vs. doxorubicin	No evidence	No evidence	4 trials, RR 1.02, 95% CI 0.86 to 1.21, I^2=30%	3 trials, RR 0.48, 95% CI 0.26 to 0.90, I^2=53%
MMC vs. epirubicin	No evidence	No evidence	1 trial, RR 1.16, 95% CI 0.52 to 2.58	No evidence
MMC vs. gemcitabine	No evidence	No evidence	1 trial, no difference (p=0.29)	1 trial, RR 1.64, 95% CI 0.64 to 4.19
MMC vs. interferon alpha	No evidence	No evidence	1 trial, RR 0.77, 95% CI 0.58 to 1.01	1 trial, RR 1.38, 95% CI 0.49 to 3.88
Doxorubicin vs. epirubicin	No evidence	No evidence	3 trials, RR 1.56, 95% CI 1.08 to 2.22, I^2=0%	1 trial, RR 1.32, 95% CI 0.50 to 3.47
Doxorubicin vs. thiotepa	Not reported	1 trial, RR 3.17, 95% CI 0.13 to 76.1	1 trial, RR 1.22, 95% CI 0.76 to 1.94	1 trial, RR 2.11, 95% CI 0.40 to 11.06
Epirubicin vs. interferon alpha	No evidence	No evidence	1 trial, RR 0.67, 95% CI 0.49 to 0.91	No evidence

BCG = bacillus Calmette Guérin; CI = confidence interval; MMC = Mitomycin C; RR = risk ratio

Table 17. Study characteristics for trials comparing doses, duration, and timing of administration

Trial Type	Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration and Method of Followup
BCG Trials	Badalament, 1987[200] USA Single center 1981-1984	Recurrent Ta, T1, or Tis bladder cancer without immediate indication for cystectomy who underwent BCG induction therapy	A: BCG Pasteur strain 120 mg (in 50 mL sterile saline) weekly for 6 weeks starting at 2-3 weeks after TURBT, then monthly B: BCG Pasteur strain 120 mg (in 50 mL sterile saline) weekly for 6 weeks	93/unclear	Duration, median 22 months (range 3 to 44 months) Method: Cystoscopy 3-5 weeks after induction, then every 3 months, with cytology
	Fellows, 1994[201] UK Multicenter 1988-1991	Histologically proven recurrent multiple pTa/pT1 bladder tumors difficult to control endoscopically	A: BCG Evans strain (1-5 x 109 CFU) B: BCG Pasteur strain (1-3 x 109 CFU) 6 weekly instillations	99/97	Duration: 3 months Method: Cystoscopy 3 months after start of BCG
	Gruenwald, 1997[215] Israel Single center 1992-1994	Multifocal (≥3) tumors of any stage or grade, ≥3 recurrences within 12 months (regardless of stage), concomitant Tis, stage T1, or grade G3	A: Pasteur strain BCG 120 mg/50 mL saline (begun within 1 month after TURBT, once weekly for 6 weeks) B: Pasteur strain BCG 120 mg/50 mL saline (begun within 1 month after TURBT, once weekly for 12 weeks)	89/89	Duration, median: 29 months Method: Cystoscopy and cytology every 3 months during year 1, every 6 months during year 2
	Hinotsu, 2011[176] Japan Multicenter 2004-2006	Recurrent or multiple tumors with confirmed Ta or T1 transitional cell carcinoma; must have 1 of the following: (a) at least 3 tumors (b) recurrence is at least the third such event or with recurrence diagnosed within 12 months from previous TURBT for NMIBC	Within 1 month of TURBT: A. BCG 81 mg (Connaught strain) in 40 mL saline weekly for 6 weeks then once weekly for 3 weeks at 3, 6, 12,and 18 months from start of induction therapy B. BCG 81 mg (Connaught strain) in 40 mL saline weekly for 6 weeks C. Epirubicin 40 mg in 40 mL saline twice at 1-week interval and then 7 times at 2-week intervals	116/110	Duration, median: 2 years Method: Cystoscopy and cytology every 3 months for 3 years then every 6 months
	Inamoto, 2013[204] Japan Single center 2008-2009	Histologically proven, single or multiple, primary or recurrent, stage Ta, T1, grades 1-3 urothelial carcinoma of the bladder, or carcinoma in situ.	A: Tokyo 172 strain BCG 40mg in 40 mL of saline B: Connaaught strain BCG 81 mg in 40 mL of saline Given for six consecutive weeks starting 14 days after TURBT	38/38	Duration: Median followup: 16.4 months vs. 16.5 months Method: Cystoscopy and urine cytology every 3 months

Table 17. Study characteristics for trials comparing doses, duration, and timing of administration (continued)

Trial Type	Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration and Method of Followup
	Irie, 2003[218] Japan Single center 1996-2001	Superficial papillary bladder cancer, no prior BCG or chemotherapeutic agents, stage Ta or T1	A. BCG (Tokyo 172 strain) 40 mg/40 mL saline, 6 instillations weekly starting 7-50 days after TURBT B: BCG (Tokyo 172 strain) 80 mg/40 mL saline, 6 instillations weekly starting 7-50 days after TURBT	Not Reported/ 80	Duration, mean: 27.5 months in 40 mg group and 20 months in 80 mg group Method: Cystoscopy and cytology every 3 months for 2 years, then every 6 months
	Koga, 2010[205] Japan Multicenter 2002-2005	Histologically-confirmed Ta, T1 transitional cell carcinoma or CIS of bladder, responded to induction therapy	BCG 80 mg (Tokyo strain) within 4 weeks of biopsy or TURBT and repeated weekly for 8 weeks; patients with complete response were randomized to: A. BCG 80 mg (Tokyo strain) within 3 months of randomization followed by instillations at 3, 6, and 9 months B. No BCG	53/51	Duration: Median followup: 27 vs. 29 months Method: Cytology and cystoscopy 2 months after randomization and then every 3 months for 3 years and thereafter every 6 months
	Lamm, 2000[206] USA Multicenter 1986-1989 Lerner, 2007[207]	Histologically confirmed transitional cell carcinoma of the bladder within 6 months before enrollment; papillary tumors Ta or T1; 2 tumors (primary and recurrent or 2 recurrences) within 1 year, 3 or more within the most recent 6 months and/or CIS, responded to induction therapy with BCG	At least 1 week following TURBT patients received BCG 81 mg (Connaught strain) in 50.5 mL saline and simultaneous percutaneous BCG 0.5 cc (10^7 CFU) to inner thigh weekly for 6 weeks, responders randomized to: A. BCG intravesically and percutaneously 3 successive weekly treatments at 3 months, 6 months and every 6 months to 3 years B. No BCG	550/384	Duration: Median followup: 120 months Method: Cytology and cystoscopy every 3 months for 2 years then every 6 months for 2 years then yearly
	Martinez-Pineiro, 2002[222] Spain Multicenter 1991-1992	Primary or r4ecurrent TaG2/3 or T1G1-3 bladder cancer with or without CIS; primary Tis; recurrent TaG1 cancers	A: BCG Connaught strain 81 mg, 12 instillations (starting 7 to 14 days after TURBT, once weekly for 6 weeks, then once every 2 weeks for 12 weeks) B: BCG Connaught strain 27 mg, 12 instillation (starting 7 to 14 days after TURBT, once weekly for 6 weeks, then once every 2 weeks for 12 weeks)	500/499	Duration, median: 69 months Method: Not reported

Table 17. Study characteristics for trials comparing doses, duration, and timing of administration (continued)

Trial Type	Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration and Method of Followup
	Martinez-Pineiro, 2005[223] Spain Multicenter 1995-1999	T1G3 and Tis bladder cancer	A: BCG Connaught strain 81 mg, 12 instillations (starting 7 to 14 days after TURBT, once weekly for 6 weeks, then once every 2 weeks for 12 weeks) B: BCG Connaught strain 27 mg, 12 instillation (starting 7 to 14 days after TURBT, once weekly for 6 weeks, then once every 2 weeks for 12 weeks)	155/ 155	Duration, median: 61 months Method: Not reported
	Morales, 1992[226] Canada Single center 1979-1988	Tis or T1 transitional cell carcinoma of the bladder with residual neoplasm; in patients with recurrences must have had a least 2 histologically documented but completely ablated tumors on 2 separate cystoscopic studies in the last 12 months	A: Armand Frappier BCG 60 mg weekly for 6 weeks B: Armand Frappier BCG 120 mg weekly for 6 weeks	97/97	Duration, mean: 21 months Method: Cystoscopy at 4, 12, and 24 weeks, then at 6 to 12 months
	Mukherjee, 1992[208] UK Single center 1984- unclear end date	Multiple recurrent superficial bladder tumors that were increasingly difficult to keep under endoscopic control	A: BCG Glaxo strain (1.2 x 109 CFU) B: BCG Pasteur strain (1.2 x 109 CFU) 6 weekly instillations, followed by either monthly instillations if there was a complete response or 6-weeks if there was a partial or no response.	21/21	Duration: mean 60 months Method: Cystoscopy 3 months after final instillation, and then according to clinical criteria

Table 17. Study characteristics for trials comparing doses, duration, and timing of administration (continued)

Trial Type	Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration and Method of Followup
	Oddens, 2013[228] Europe Multicenter 1997-2005	Solitary T1G3 or multiple Ta-T1, G1-3 urothelial carcinoma of the bladder	A: BCG (OncoTICE strain) 5 x 10^8 CFU at 1/3 dose, 15 instillations (started within 14 days after TURBT, one weekly for 6 weeks, then 3 weekly instillations at months 3 ,6, and 12) B: BCG full dose, 15 instillations (started within 14 days after TURBT, one weekly for 6 weeks, then 3 weekly instillations at months 3 ,6, and 12) C: BCG at 1/3 dose, 27 instillations (started within 14 days after TURBT, one weekly for 6 weeks, then 3 weekly instillations at months 3 ,6,12, 18, 24, 30, and 36) D: BCG full dose, 27 instillations (started within 14 days after TURBT, one weekly for 6 weeks, then 3 weekly instillations at months 3 ,6,12, 18, 24, 30, and 36)	1805/ 1355	Duration, median: 7.1 years Method: Cystoscopy and cytology every 3 months for 3 years, then every 6 months
	Ojea, 2007[151] Spain Multicenter 1995-1998	Intermediate risk with stages TaG2 and T1G1-2 superficial bladder tumors without carcinoma in situ	14-21 days after transurethral resection with histological confirmation of bladder cancer, patients received 6 weekly instillations then another 6 instillations one every 2 weeks; if a recurrence was diagnosed a further TURBT was performed and the treatment continued A. BCG 27 mg (Connaught strain) B. BCG 13.5 mg (Connaught strain) C. MMC: 30 mg	430/397	Duration, median: 57 months vs. 61 months vs. 53 months Method: Cystoscopy every 3 months during first year and then every 4 months for the next 4 years
	Pagano, 1995[230] Bassi, 1992[262] (Abstract of interim results) Italy Single center 1990	Multiple papillary tumors (Ta-T1) and CIS	6-week course of intravesical therapy: A. Pasteur strain BCG 75 mg B. Pasteur strain BCG 150 mg	Not Reported/ 138	Duration: Not reported Method: Not reported

Table 17. Study characteristics for trials comparing doses, duration, and timing of administration (continued)

Trial Type	Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration and Method of Followup
	Palou, 2001[209] Spain, England Multicenter 1989-1995	Primary or relapsing stage Ta or T1 grade 3 superficial bladder tumors with or without associated CIS or isolated CIS or associated with grade 2 superficial bladder tumors, responded to induction therapy with BCG	Initial treatment with 6 weekly instillations of BCG 81 mg (Connaught strain); if relapse then 6 additional weekly instillations; if disease free then randomized to: A. BCG 81 mg (Connaught) 6 weekly instillations every 6 months for 2 years B. No further treatment	131/126	Duration: Median followup 78 months Method: Alternating cytology and cystoscopy every 3 months for 2 years and then cytology and cystoscopy every 6 months
	Rentsch, 2014[210] Switzerland Single center 1998-2010	High risk NMIBC (any high-grade tumor, any low-grade tumor with more than two recurrences within 2 years, or carcinoma in situ)	A: BCG Connaught (6.6-19.2 x 108 CFU) B: BCG Tice (2-8 x 108 CFU) 6 weekly intravesical instillations	142/131	Duration: Median 47.6 vs. 51.4 months Method: Cystoscopy and cytology at 3-month intervals for the first 3 years, then at 6-month intervals for the following 2 years. Urography or CT scan at 1 and 3 years after BCG.
	Sengiku, 2013[233] Japan Single center 2004-2012	Stage Ta/T1 or Tis, multiple tumors and recurrence-free period of 3 months or less	At least 2 weeks after removing as much of visible lesion as possible by TURBT, patients received weekly up to 8 times: A. BCG 80 mg (Tokyo strain) in 40 mL saline B. BCG 81 mg (Connaught strain) in 40 mL saline	178/129	Method: Cystoscopy and urine cytology every 3 months for first 2 years and every 3-6 months thereafter

Table 17. Study characteristics for trials comparing doses, duration, and timing of administration (continued)

Trial Type	Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration and Method of Followup
	Witjes, 1993[148] Witjes, 1996[156] Vegt, 1995[211] The Netherlands Multicenter 1987-1990	Histologically proven papillary pTa-pT1 transitional cell transitional cell carcinoma of the bladder with or without CIS	A. MMC 30 mg in 50 mL saline once a week for 4 weeks and thereafter once a month for 5 months. If a superficial recurrence or persistent CIS after 6 months, 3 additional monthly instillations given B. BCG-Tice C. BCG RIVM BCG 5X108 bacilli in 50 mL saline, administered once a week for 6 weeks. At the time of first superficial recurrence or persistent CIS at 3 or 6 months, a second 6 week course with BCG instillations was given after complete TURBT or biopsy.	469/437	Duration, median: 32 months Method: Cystoscopy every 3 months for 2 years, every 4 months in years 3 and 4 and every 6 months thereafter
MMC Trials	Au, 2001[197] USA, Europe, and Canada Multicenter 1992-2000	Transitional cell carcinoma of bladder at high risk for recurrence based on 1) two or more episodes of Ta, Tis, or T1 cancers, 2) multifocal (≥3 papillary tumors or Tis involving ≥25% of bladder surface and/or in two or more biopsy sites), 3) tumors >5 cm, G3, or DNA aneuploidy	A: MMC 40 mg/20 mL sterile water, 6 instillations (once weekly for 6 weeks), optimized by instruction to refrain from fluids for 8 hour prior to and during instillations, oral doses of 1.3 g sodium bicarbonate the night before, Foley to empty bladder prior to instillation for post void residual <10 mL B: MMC 20 mg/20 mL sterile water, 6 instillations (once weekly for 6 weeks), without additional optimization measures	230/201	Duration: 5 years Method: Cystoscopy and cytology every 3 months for 2 years, every 6 months for years 3-5, and once yearly thereafter
	Colombo, 2012[213] Italy Single center 2010-2011	Recurrent, single, small (<1.5 cm) bladder cancers following TURBT of low-grade NMIBC	A: Mitomycin C (MMC), 40 mg (in 40 mL saline) three instillations per week for 2 weeks, prior to TURBT B: Mitomycin C (MMC), 40 mg (in 40 mL saline) one instillation per week for 6 weeks, prior to TURBT	54/54	Duration, 9 to 11 days following end of instillations Method: Cystoscopy with 14 days of completion of therapy

Table 17. Study characteristics for trials comparing doses, duration, and timing of administration (continued)

Trial Type	Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration and Method of Followup
	Ersoy, 2013[198] Turkey Single center 2006- 2010	Primary low-risk NMIBC. Stage Ta, Grade G1. Solitary tumor; Size <3 cm.	A: MMC, 40 mg (in 40 mL sterile saline) intravesical; infusion within 6 hours of TURBT; MMC retained in bladder for 2 hours. B: Urinary alkalinization prior to MMC instillation: Sodium bicarbonate, 1.3 g, orally X 3 doses (night before TURBT, morning of TURBT, 30 minutes prior to MMC). MMC, 40 mg (in 40 mL sterile saline) intravesical; infusion within 6 hours of TURBT; MMC retained in bladder for 2 hours. C: No drugs given in the first 6 hours after TURBT.	53/49	Duration, median: A vs. B vs. C: 51 vs. 50 vs. 54 months, p=0.815 Method: Cystoscopy: month 3, month 12, then annually for 5 years.
	Friedrich, 2007[154] Germany Multicenter 1995-2002	Patients with primary transitional cell carcinoma of the bladder or patients with tumor recurrence after TURBT without prior adjuvant; histopathologic evaluation of their completely resected tumor revealed an intermediate risk pTaG1 tumor (size >3 cm, recurrent or multifocal tumor) or pTaG2 up to pT1 tumor (G1-3). Patients with T1G3 tumor were eligible in case of a unifocal small tumor (≤2.5 cm).	A. MMC 20 mg, 6 weekly instillations B. BCG RIVM 2 x 10^8 CFU, 6 weekly instillations C. MMC 20 md, 6 weekly instillations followed by monthly instillations of MMC 20 mg for 3 years	495/ 495	Duration, median: 2.9 years Method: Cytology and cystoscopy every 3 months in the first 2 years and every 6 months thereafter
	Fukui, 1992[202] Japan Single center 1986-1989	Ta, T1, or Tis transitional cell carcinoma of the bladder who had complete response to 5 weeks induction therapy with sequential MMC and adriamycin	A: MMC 20 mg (in 20 mL saline) on day 1 and adriamycin 40 mg (in 20 mL saline) on day 2 for 5 weeks, followed by maintenance therapy once monthly for 12 months B: MMC 20 mg (in 20 mL saline) on day 1 and adriamycin 40 mg (in 20 mL saline) on day 2 for 5 weeks, No maintenance therapy	51/51	Duration: Unclear Method: Cystoscopy and urine cytology every 3 months

Table 17. Study characteristics for trials comparing doses, duration, and timing of administration (continued)

Trial Type	Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration and Method of Followup
	Huland, 1990[191] Germany Multicenter 1983 - 1985	Superficial bladder carcinoma (primary or recurrent). Stages Ta, T1 or Tis; Grade G1, G2 or G3. CIS. Single or multiple tumors.	A: MMC, 20 mg/20 mL. Total 42 instillations. Every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year. B: MMC, 20 mg/20 mL. Total 42 instillations. Every week X 8 weeks, then every 4 weeks for rest of 1st year and 2 additional years. C: MMC, 20 mg/20 mL. Total 20 instillations. Every week X 20 weeks. D: Doxorubicin, 50 mg/50 mL. Total 42 instillations. Every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year. For all groups: Instillations started 4 to 6 weeks after discharge from hospital.	477/419	Duration, mean: A vs. B vs. C vs. D: 26.7 vs. 27.4 vs. 26.7 vs. 30.2 months Method: Cystoscopy every 3 months.
	Schwaibold, 1997[232] Germany Single center 1983-1987	Ta, T1, or Tis transitional cell carcinoma of the bladder	A: MMC 20 mg/20 mL saline, 42 instillations (every 2 weeks for 1 year, every 4 weeks for 1 year, every 3 months for 1 year) B: MMC 20 mg/20 mL saline, 42 instillation (every week for 8 weeks, every 4 weeks for 44 weeks and 2 additional years) C: MMC 20 mg/20 mL saline, 20 instillations (every week for 20 weeks) D: Doxorubicin 50 mg/50 mL saline, 42 instillations (same schedule as A)	477/ 419	Duration, median: 57 months Method: Cystoscopy every 3 months
	Tolley, 1996[118] United Kingdom Multicenter 1984 - 1986	Patients with newly diagnosed stage Ta or T1 transitional cell carcinoma of the bladder; Grades 1 -3.	A: MMC 20 mg/20 mL saline, 42 instillations (every 2 weeks for 1 year, every 4 weeks for 1 year, every 3 months for 1 year) B: MMC 2 mg/20 mL saline, 42 instillation (every week for 8 weeks, every 4 weeks for 44 weeks and 2 additional years) C: MMC 20 mg/20 mL saline, 20 instillations (every week for 20 weeks) D: Doxorubicin 50 mg/50 mL saline, 42 instillations (same schedule as A)	452/452	Duration, median: 57 months Method: Cystoscopy every 3 months

Table 17. Study characteristics for trials comparing doses, duration, and timing of administration (continued)

Trial Type	Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration and Method of Followup
Doxorubicin Trials	Akaza, 1987[112] Japan Unclear if single or multicenter 1982-1985	Histologically proven superficial bladder cancer (primary only). Stages Ta or T1; Grade G1 or G2. Absence of tumor after TURBT.	A: Doxorubicin, 30 mg (in 30 mL saline). B: Doxorubicin, 20 mg (in 40 mL saline). C: MMC: 20 mg (in 40 mL saline). D: No adjuvant treatment. TURBT alone. For A, B, and C: First instillation within 1 week of TURBT. Once weekly X 2 weeks, then once every 2 weeks X 14 week, then once monthly X 8 months, then once every 3 month X 1 year (Total: 21 doses over 2 years)	665/607	Duration: 3.5 years, maximum; Mean, median not reported Method: Cystoscopy and urinary cytology studies at 12-week intervals throughout study period
	Flamm, 1990[214] Austria Single center 1979-1981	Primary or recurrent transitional cell carcinoma of the bladder, otherwise not specified	A: Doxorubicin 50 mg/50 mL saline weekly for 6 weeks, then monthly for 2 years B: Doxorubicin 50 mg/50 mL saline weekly for 6 weeks	160/146	Duration: 5 years Method: Cystoscopy every 3 months for 2 years, then every 6 months
	Matsumura, 1992[123] Japan Multicenter 1987-1989	Ta, T1, or Tis transitional cell carcinoma of the bladder; primary with multiple lesions or recurrent with one or more lesions	A: Doxorubicin 20 mg/40 mL saline, 21 instillations (following TURBT, once weekly for 2 weeks, then every 2 weeks for 14 weeks, once monthly for 8 months, and once every three months for 1 year) B: Doxorubicin 20 mg/40 mL saline, 6 instillations (over 2 weeks prior to TURBT) C: No doxorubicin	443/284	Duration, median: 240 days Method: Not reported
	Niijima, 1983[116] Japan Multicenter 1980 – 1985	Histologically proven superficial bladder cancer (primary or recurrent). Stages Ta or T1; Grade not specified. Absence of tumor after TURBT.	A: Doxorubicin, 30 mg (in 30 mL saline). B: Doxorubicin, 20 mg (in 40 mL saline). C: MMC: 20 mg (in 40 mL saline). D: No adjuvant treatment. TURBT alone. For A, B, and C: First instillation within 1 week of TURBT. Twice weekly X 4 weeks (Total: 8 doses)	707/575	Duration: 5 years, maximum; Mean/Median not reported Method: Cystoscopy and urinary cytology studies at 12-week intervals during the observation period.

Table 17. Study characteristics for trials comparing doses, duration, and timing of administration (continued)

Trial Type	Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration and Method of Followup
	Rubben, 1988[231] Germany Single center 1979-1981	Primary or recurrent NMIBC, any grade	A: Doxorubicin 50 mg/50 mL saline, 13 instillations (2 hours prior to TURBT, then twice weekly for 6 weeks) B: Doxorubicin 50 mg/50 mL saline, 28 instillations (2 hours prior to TURBT, then twice weekly for 6 weeks, twice monthly for 4.5 months, once monthly for 6 months) C: No intravesical therapy	965/834	Duration: Mean, median not reported Method: Cystoscopy and cytology every 3 months for 2 years, then every 6 months
	Ueda, 1992[236] Japan Multicenter 1984-1986	Ta and T1 transitional cell carcinoma of bladder	A: Doxorubicin 30 mg/30 mL saline, 19 instillations (immediately and 2 days after TURBT, then weekly for 2 weeks, every 2 weeks for 14 weeks, monthly for 8 months) B: Doxorubicin 30 mg/30 mL saline, 19 instillations (immediately and 2 days after TURBT, then weekly for 2 weeks, every 2 weeks for 14 weeks, monthly for 8 months) plus 5-fluorouracil 200 mg/day starting at 1 week C: Doxorubicin 30 mg/30 mL saline, 17 instillations (starting 7 days after TURBT weekly for 2 weeks, every 2 weeks for 14 weeks, monthly for 8 months)	275/187	Duration, mean: 31 months Method: Cystoscopy at 4 weeks then every 3 months

Table 17. Study characteristics for trials comparing doses, duration, and timing of administration (continued)

Trial Type	Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration and Method of Followup
Epirubicin Trials	Ali-El-Dein, 1997[119] (J Urol) Egypt Single center 1991 – 1995	TCC of the bladder (primary or recurrent). Stages Ta or T1; Associated CIS or other dysplastic mucosal changes; Grade G1 - G3. Rapid recurrence within 6 months of initial resection; Multicentricity; Positive posterior urethral biopsy and/or positive postoperative urinary cytology (only 2 patients with positive posterior urethral biopsy, who underwent resection of multiple tumors to provide bladder neck incompetence and sufficient contact of drug with prostatic urethra).	A: Epirubicin, 50 mg (in 50 mL normal saline). B: Epirubicin, 80 mg (in 50 mL normal saline). C: Doxorubicin, 50 mg (in 50 mL normal saline). D: No adjuvant treatment. TURBT alone. For Groups A - C: First instillation 7 to 14 days after TURBT. Retained intravesically for 2 hours; Instillations once a week X 8 weeks, then once monthly to complete 1 year of treatment.	253/ 253	Duration, mean: 30.1 months Method: Cystourethroscopy, urine cytology, and flow cytometry every 3 months during first 2 years, and every 6 months thereafter.
	Ali-El-Dein, 1997[126] (British J Urol) Egypt Single center 1992 – 1996	TCC of the bladder (primary or recurrent). G2 or G3, multiple recurrent, pT1, aneuploidy, or ≥3 cm; pTa if multiple, large (≥3 cm), recurrent and/or grade 2-3 tumors.	A: Epirubicin, 50 mg (in 50 mL normal saline); Single instillation immediately after TURBT. Retained intravesically for 2 hours. B: Epirubicin, 50 mg (in 50 mL normal saline); Initial instillation 1 - 2 weeks after TURBT. Retained intravesically for 2 hours; Then, instillations once a week X 7, then once monthly X 10 to complete 1 year of treatment. C: No adjuvant treatment. TURBT alone.	179/168	Duration, mean: 32.2 months Method: Cysto-urethroscopy, cytology, and DNA flow cytometry 8 weeks after resection, then every 3 months during first 2 years, and every 6 months thereafter during the next 2 years.

Table 17. Study characteristics for trials comparing doses, duration, and timing of administration (continued)

Trial Type	Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration and Method of Followup
	Hendricksen, 2008[216] the Netherlands Multicenter 1998-2004	≤85 years of age, solitary T1 tumor, or multiple primary or recurrent T1 or Ta G1-G3 urothelial cell carcinoma of the bladder in whom complete TURBT was possible	A. Epirubicin 50 mg/50 mL saline, 9 instillations over 6 months (once weekly for 4 weeks started within 2 weeks of TURBT, then once monthly for 5 months) B. Epirubicin 50 mg/50 mL saline, 10 instillations over 6 months (within 48 hours of TURBT, once weekly for 4 weeks starting within 2 weeks of TURBT, once monthly for 5 months) C: Epirubicin 50 mg/50 mL saline, 11 instillations over 12 months (once weekly for 4 weeks starting within 2 weeks of TURBT, once monthly for 5 months, once every three months for 6 months)	1000/731	Duration, median (A and B, not reported for C): 7 years Method: Cystoscopy every 3 months for a year, then every 6 months for a year, annually thereafter.
	Koga, 2004[219] Japan Multicenter 1993-1995	New, untreated transitional cell carcinoma of the bladder, Ta or T1 disease, no residual tumor based on cystoscopy and cytology	A: Epirubicin 30 mg/30 mL saline 19 times (within 24 hours of TURBT, then 2-3 days, 1 week, and 2 weeks after TURBT, then once every 2 weeks for 12 weeks, then once a month for 9 months) B: Epirubicin 30 mg/30 mL saline 9 times (within 24 hours of TURBT, then 2-3 days, 1 week, and 2 weeks after TURBT, then once every 2 weeks for 10 weeks)	171/150	Duration, median: 30.6 months Method: Cytology every month, cystoscopy every 3 months for 2 years, then every 6 months
	Kuroda, 2004[220] Japan Multicenter 1994-1996	Primary or recurrent superficial transitional cell carcinoma of the bladder (Ta or T1, G1 or G2)	A. Epirubicin 20 mg/40 mL saline, 17 instillations over 12 months (starting about 7 days after TURBT, once weekly for 2 weeks, once every other week for 14 weeks, once a month for 8 months) B: Epirubicin 30 mg/40 mL saline, 12 instillations over 12 months (starting about 7 days after TURBT, once weekly for 2 weeks, once every other week for 14 weeks, once a month for 3 months) C: Epirubicin 40 mg/40 mL saline, 9 instillations over 4 months (starting about 7 days after TURBT, once weekly for 2 weeks, once every other week for 14 weeks)	622/614	Duration, median: 3.5 years Method: Cystoscopy every 3 months

Table 17. Study characteristics for trials comparing doses, duration, and timing of administration (continued)

Trial Type	Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration and Method of Followup
	Liu, 2006[192] China Unclear if single or multicenter 1997 – 1998	Superficial bladder carcinoma (primary or recurrent). Stages Ta or T1; Grade G1 or G2	A: Epirubicin, 80 mg (in 40 mL normal saline). Single intravesical instillation within 6 hours of TURBT. B: Epirubicin, 40 mg, intravesical instillation every week for 6 ~ 8 weeks, then every month for 10 months. C: MMC, 40 mg, intravesical instillation every week for 6 ~ 8 weeks, then every month for 10 months.	47/44	Duration: All patients followed-up for 5 years until June 2003. Method: Cystoscopy and urinary cytology every 3 months X 2 years, then every 6 months X 3 years.
	Masters, 1999[224] UK Multicenter 1991-1993	Primary or recurrent Ta or T1 bladder cancer	A: Epirubicin 50 mg/50 mL saline, 5 instillations (starting 10-14 days after TURBT, every 3 months for 12 months) B: Epirubicin 100 mg/50 mL saline, 5 instillations (starting 10-14 days after TURBT, every 3 months for 12 months) First 102 patients had a marker tumor left after initial TURBT (0.5 cm)	126/122	Duration: 834 vs. 774 days Method: Cystoscopy every 3 months
	Mitsumori, 2004[225] Japan Multicenter 1998-2001	Recurrent or primary Ta or T1 bladder cancer	A: Epirubicin 30 mg/40 mL saline, 6 instillations (starting 1 week after TURBT once every 2 weeks for 12 weeks, total 180 mg) B: Epirubicin 30 mg/40 mL saline, 6 instillations (3 instillations within first 5-7 days after TURBT, then once every 2 weeks for 6 weeks, total 180 mg) C: Epirubicin 30 mg/40 mL saline, 12 instillations (starting 1 week after TURBT, once weekly for 12 weeks, total 360 mg) D: Epirubicin 30 mg/40 mL saline, 12 instillations (3 instillations within first 5-7 days after TURBT, then once weekly for 9 weeks, total 360 mg)	91/69	Duration, median: 13.3 months Method: Cystoscopy and urine cytology every 3 months for 3 years, then every 6 months

Table 17. Study characteristics for trials comparing doses, duration, and timing of administration (continued)

Trial Type	Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration and Method of Followup
	Nomata, 2002[227] Japan Multicenter 1995-1998	Ta or T1/G1 or G2 transitional cell carcinoma of the bladder, ECOG performance status 0 or 1, age 20 to 80 years, post TURBT with no evidence of residual cancer based on cytological evaluation of voided urine	A. Epirubicin 30 mg/30 mL saline 19 times over 1 year (once weekly for 4 weeks, then every 2 weeks for 4 months) B. Epirubicin 30 mg/30 mL saline 12 times over 5 months (once weekly for 4 weeks, then every 2 weeks for 4 months, then once per month for 7 months)	138/125	Duration, median: 18.1 months Method: Cystoscopy every 3 months
	Okamura, 1998[229] Japan Multicenter 1991-1993	Ta-T1 papillary bladder cancer resectable by TURBT, ECOG performance status 0 or 1, age <85 years; primary or recurrent bladder cancer if recurrence-free interval >1 year	A: Epirubicin 40 mg/40 mL saline 17 times (within 24 hours of TURBT, during first week, once weekly for 4 weeks, then once monthly for 11 months) B: Epirubicin 40 mg/40 mL saline 6 times (within 24 hours of TURBT, during first week, then once weekly for 4 weeks)	148/138	Duration, median: 29.6 months Cystoscopy and cytology at 4 weeks, then every 3 months
	Saika, 2010[134] Japan Multicenter 1995 – 2001	Transitional cell carcinoma of the bladder (primary or recurrent). Stages Ta or T1; Grade G1, G2, or G3. Age ≥20 years.	A. Epirubicin, 20 mg (in 40 mL physiological saline). Two intravesical infusions, one immediately after (<1 hour) TURBT and one in the early morning of the following day, retained in bladder for 1 hour. B. Epirubicin, 50 mg (in 100 mL physiological saline). Same procedure as A. C. No adjuvant therapy. TURBT only.	303/240	Duration, median: Overall: 44 months; A vs. B vs. C: 44 vs. 46 vs. 42 Method: Cystoscopy every 3 months for 2 years and every 6 months thereafter.
	Serretta, 2010[234] Italy Multicenter 2002-2003	Multiple and recurrent Ta tumors; recurrent, single or multiple T1 tumors	A: Epirubicin 80 mg/50 mL saline, 16 instillations (within 6 hours of TURBT, then once weekly for 5 weeks, once weekly for 10 months) B: Epirubicin 80 mg/50 mL saline, 6 instillations (within 6 hours of TURBT, then once weekly for 5 weeks)	482/395	Duration, median: 48 months Method: Cystoscopy and cytology every 3 months for 2 years, then 6 months from years 3 to 5

Table 17. Study characteristics for trials comparing doses, duration, and timing of administration (continued)

Trial Type	Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration and Method of Followup
	Turkeri, 2010[235] Turkey Multicenter 2002-2004	Primary bladder tumor, ≤3 lesions, Ta (G2 or G3) or T1 (G1 or G2)	A: Epirubicin 100 mg within 6 hours after TURBT B: Epirubicin 100 mg within 6 hours and 12-hours after TURBT	299/143	Duration, mean: 16.9 months Method: Cystoscopy every 3 months for 1 year, then every 6 months during years 2 and 3, then once yearly
Gemcitabine Trials	Gardmark, 2007[157] Japan Single center 1986-1989	Recurrent multiple Ta G1/2 bladder cancer, with all lesions except one marker lesion resected	A: Gemcitabine 2000 mg (in 100 mL saline) once weekly for 6 weeks B: Gemcitabine 2000 mg (in 100 mL saline) twice weekly for 3 weeks C: Gemcitabine 2000 mg (in 100 mL saline) single instillation	32/30	Duration: 9 weeks after initial instillation Method: Cystoscopy
Thiotepa Trials	Koontz, 1981[140] (prophylaxis) USA Multicenter 1974-1977	Multifocal NMIBC or bladder cancer on ≥3 occasions in last 18 months; clinical assessment that prophylaxis warranted (2 tumors within 6 months); or complete response to thiotepa	A: Thiotepa 30 mg/30 mL distilled water (once every 4 weeks for maximum 2 years) B: Thiotepa 60 mg/60 mL distilled water (once every 4 weeks for maximum 2 years) C: No thiotepa	95/93 (30 responders from Koontz 1981 thiotepa treatment trial enrolled)	Duration, median: 15 months Method: Cystoscopy every 3 months
	Koontz, 1981[140] (treatment) USA Multicenter 1974-1977	Incompletely resected NMIBC (single or multiple) or Tis or carcinoma on random biopsy	A: Thiotepa 30 mg/30 mL distilled water (once weekly for 4 weeks, repeated after 4 weeks) B: Thiotepa 60 mg/60 mL distilled water (once weekly for 4 weeks, repeated after 4 weeks)	101/95	Duration: 4 weeks after 2 4-week treatment courses Method: Cystoscopy at 4 weeks after fourth instillation and 4 weeks after eight instillation

Table 17. Study characteristics for trials comparing doses, duration, and timing of administration (continued)

Trial Type	Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration and Method of Followup
Interferon alpha-2b Trials	Giannakopoulos, 1998[136] Greece Unclear if single or multicenter Study years not reported	Superficial transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Stages Ta or T1; Grade G2.	A: No adjuvant treatment. TURBT alone. B: Interferon-α-2b (interferon-α-2b), 40 MU (in 50 mL normal saline). C: Interferon-α-2b (interferon-α-2b), 60 MU (in 50 mL normal saline). D: Interferon-α-2b (interferon-α-2b), 80 MU (in 50 mL normal saline). For Groups B - D: First instillation after histological verification of stage and grade; 48 - 72 hours after TURBT. Retained intravesically for 1 hour; patient position changed every 15 minutes. Instillations once a week X 2 months, then once every 15 days X 4 months, then once monthly X 6 months.	89/89	Duration: 36 months Method: Cystoscopy and urine cytology, every 3 months for 18 months, and every 6 months thereafter.
	Glashan, 1990[203] USA, Europe, Australia, Canada Multicenter 1985-1988	Carcinoma in situ of the bladder and positive post-biopsy cytology	A: Interferon α-2b 100 million units (in 30 mL sterile water) B: Interferon α-2b 10 million units (in 30 mL sterile water) First instillation within 1 month of positive cytology, administered once weekly for 12 weeks, then monthly through one year	85/80	Duration: 36 months Method: Cystoscopy and cytology every 3 months
	Hoeltl, 1991[217] Austria Single center Study years not reported	Primary G1 or G2 papillary transitional cell carcinoma of bladder stages Ta, T1, or TIS or recurrent G1/Ta or T1 bladder cancer; Karnofsky performance status ≥50%	A: Interferon alfa-2b 100 x 10^6 IU (100 MU)/30 mL sterile water (once weekly for 10 weeks, then once monthly for 1 year total of therapy) B: Interferon alfa-2b 10 x 10^6 IU (10 MU)/30 mL sterile water (starting within 36 hours of TURBT, once weekly for 10 weeks, then once monthly for 1 year total of therapy) C: Ethoglucid 1.13 g/100 mL sterile water (once weekly for 10 weeks, then once monthly for 1 year total of therapy)	44/34	Duration, mean: 36.5 months Method: Cystoscopy and urine cytology every 3 months for 1 year, then every 6 months

Table 17. Study characteristics for trials comparing doses, duration, and timing of administration (continued)

Trial Type	Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration and Method of Followup
	Malmström, 2002[221] Europe Multicenter Study years: not reported	Histologically confirmed TCC of the bladder (primary or recurrent). Multiple tumors only. Stages Ta or T1; Grade G1 or G2. Karnofsky performance status >70%; No other malignancy within 5 years of the study, except nonmelanoma skin cancer; Age ≥18 years; Not pregnant and on appropriate birth control.	A: Interferon-α, 30 MU (in 30 mL sterile water). Retained in bladder X 2 hours; patient moved from side to side every 30 minutes. First instillation 1 to 2 weeks after TURBT or biopsy, then weekly X 12 weeks. B: Interferon-α, 50 MU (in 30 mL sterile water). Same procedure as A. C: Interferon-α, 80 MU (in 30 mL sterile water). Same procedure as A. D: MMC, 40 mg (in 40 mL sterile water). Retained in bladder X 2 hours; patient moved from side to side every 30 min. First instillation 1 to 2 weeks after TURBT or biopsy, then weekly X 8 weeks.	115/110	Method: followup at 9 weeks and 13 weeks for all treatment groups and at 9 weeks only for control group. Cystoscopy at week 9 for both groups.
Multiple Drugs	Bouffioux, 1995[212] Europe Multicenter 1983-1986	Completely resectable, Ta or T1 (0 or A), papillary transitional cell carcinoma of the bladder (single or multiple, primary or recurrent), previous intravesical treatment with cytotoxic drugs other than MMC allowed if >3 months prior	Initial randomization: A. MMC 30 mg/50 mL saline or doxorubicin 50 mg, 9 instillations starting on day of TURBT (once weekly for 4 weeks, then once monthly for 5 months) B. MMC 30 mg/50 mL saline or doxorubicin 50 mg, 9 instillations, starting between days 7 and 15 after TURBT (once weekly for 4 weeks, then once monthly for 5 months) Second randomization at 6 months: A: Continued instillations once a month for 6 months, total 15 B: No maintenance	965/834	Duration, average: 2.75 to 6.5 years (varied by outcome) Method: Cystoscopy every 3 months during year 1, every 4 months during year 2, every 6 months thereafter

BCG = bacillus Calmette-Guérin; BCG RIVM = RIVM strain of bacillus Calmette- Guérin; BCG-Tice = bacillus Calmette-Guérin Tice strain; CIS = carcinoma in situ; CFU = Colony Forming Unit; ECOG = Eastern Cooperative Oncology Group; G1 = Grade 1; G2 = Grade 2; G3 = Grade 3; MMC = Mitomycin C; MU = million units; NMIBC = non–muscle-invasive bladder cancer; pT1 = Tumor stage 1 determined by pathology; pTa = Tumor stage a determined by pathology; T1 = Tumor stage 1; Ta = Tumor stage a; TCC = transitional cell carcinoma; Tis = carcinoma in situ; TURBT = transurethral resection of the bladder tumor

Table 18. Results summary for trials comparing dosages, duration, and timing of administration

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
BCG Trials	Badalament, 1987[200] USA Single center 1981-1984	A: BCG Pasteur strain 120 mg (in 50 mL sterile saline) weekly for 6 weeks starting at 2-3 weeks after TURBT, then monthly B: BCG Pasteur strain 120 mg (in 50 mL sterile saline) weekly for 6 weeks	Progression: 26% (12/47) vs. 20% (9/46) at median 22 months, RR 1.31 (95% CI 0.61 to 2.80)		Mortality: 0% (0/47) vs. 0% (0/46) at median 22 months	Only reported for maintenance arm Discontinued due to adverse events: 45% (21/47) Dysuria: 89% (42/47) Frequency/urgency: 85% (40/47) Hematuria: 57% (27/47) Fever/chills: 43% (20/47) Flu-like symptoms: 13% (6/47) Suprapubic pain: 6% (3/47)
	Fellows, 1994[201] UK Multicenter 1988-1991	A: BCG Evans strain (1-5 x 109 CFU) B: BCG Pasteur strain (1-3 x 109 CFU) 6 weekly instillations	Responders at three months (marker tumor response and no new tumors): 12/51 vs. 18/43, p=0.064			Severe AEs: Frequency: 4/51 vs. 5/46 Dysuria: 2/51 vs. 2/46 Hematuria: 1/51 vs. 2/46 Fever/Malaise: 2/51 vs. 1/46 Joint pain: 1/51 vs. 0/46 Hepatic dysfunction: 0/51 vs. 0/46
	Gruenwald, 1997[215] Israel Single center 1992-1994	A: Pasteur strain BCG 120 mg/50 mL saline (begun within 1 month after TURBT, once weekly for 6 weeks) B: Pasteur strain BCG 120 mg/50 mL saline (begun within 1 month after TURBT, once weekly for 12 weeks)	Progression: 5.0% (2/40) vs. 10% (3/30), RR 0.50 (95% CI 0.09 to 2.81)	Percent recurrence-free: 55% (22/40) vs. 70% (21/30) (p>0.05); adjusted OR 2.17 for B vs. A (95% CI 0.9 to 5.22) (adjusted for stage and number of recurrences) Time to recurrence: 12.3 vs. 12.9 months Recurrence: 20% (8/40) vs. 13% (4/30) at 1 year, RR 1.5 (95% CI 0.50 to 4.5); 45% (18/40) vs. 30% (9/30) at 2 years, RR 1.5 (95% CI 0.79 to 2.86)	Bladder cancer and all-cause mortality: 5.0% (2/40) vs. 3.3% (1/30), RR 1.5 (95% CI 0.14 to 16)	Dysuria or frequency: 30% (12/40) vs. 40% (12/30) Hemorrhagic cystitis: 7.5% (3/40) vs. 13% (4/30) Fever (mild): 22% (9/40) vs. 30% (9/30) Severe side effects: 2.5% (1/40) vs. 6.7% (2/30)

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Hinotsu, 2011[176] Japan Multicenter 2004-2006	Within 1 month of TURBT: A. BCG 81 mg (Connaught strain) in 40 mL saline weekly for 6 weeks then once weekly for 3 weeks at 3, 6, 12,and 18 months from start of induction therapy B. BCG 81 mg (Connaught strain) in 40 mL saline weekly for 6 weeks C. Epirubicin 40 mg in 40 mL saline twice at 1-week interval and then 7 times at 2-week intervals	Progression at time of recurrence: 0% (0/41) vs. 7.1% (3/42), RR 0.15 (0.01 to 2.7)	Recurrence: 12% (5/41) vs. 33% (14/42), RR 0.37 (95% CI 0.14 to 0.92)	Recurrence-free survival: 85% vs. 65% (p=0.02)	Urinary frequency: 93% (39/42) vs. 71% (30/42), RR 1.3 (95% CI 1.1 to 1.6) Dysuria: 93% (39/42) vs. 69% (29/42), RR 1.3 (95% CI 1.1 to 1.7) Hematuria: 93% (39/42) vs. 71% (30/42), RR 1.3 (95 %CI 1.1 to 1.6) Fever: 43% (18/42) vs. 26% (11/42), RR 1.6 (95% CI 0.88 to 3.0)
	Inamoto, 2013[204] Japan Single center 2008-2009	A: Tokyo 172 strain BCG 40mg in 40 mL of saline B: Connaaught strain BCG 81 mg in 40 mL of saline Given for six consecutive weeks starting 14 days after TURBT		Recurrence-free survival: 72.2% vs. 83.5%, log rank p=0.698		All AEs: 14/18 (77%) vs. 14/20 (70%), p=0.7718 AEs in more than 10% of patients: Pollakisuria: 3/18 (16.7%) vs. 6/20 (31.6%), p=0.5637 Hematuria: 4/18 (22.2%) vs. 1/20 (5.3%), 0.0833 Miction pain: 4/18 (22.2%) vs. 1/20 (5.3%), p=0.0455 Fever: 2/18 (11.1%) vs. 7/20 (36.8%)

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Irie, 2003[218] Japan Single center 1996-2001	A. BCG (Tokyo 172 strain) 40 mg/40 mL saline, 6 instillations weekly starting 7-50 days after TURBT B: BCG (Tokyo 172 strain) 80 mg/40 mL saline, 6 instillations weekly starting 7-50 days after TURBT	Progression: 5.0% (2/40) vs. 6.4% (2/31), RR 0.78 (95% CI 0.12 to 5.20)	Recurrence: 28% (11/40) vs. 16% (5/31), RR 1.71 (95% CI 0.66 to 4.40)	Not reported	Discontinuation of treatment due to adverse effects: 2% (1/40) vs. 21% (8/39), RR 0.12 (95% CI 0.02 to 0.93) Fever: 6% (2/35) vs. 13% (5/39), RR 0.45 (95% CI 0.09 to 2.15) Bladder irritability: 27% (10/37) vs. 53% (20/38), RR 0.51 (95% CI 0.28 to 0.94) Macroscopic hematuria: 9% (3/34) vs. 23% (7/30), RR 0.38 (95% CI 0.11 to 1.33)
	Koga, 2010[205] Japan Multicenter 2002-2005	BCG 80 mg (Tokyo strain) within 4 weeks of biopsy or TURBT and repeated weekly for 8 weeks; patients with complete response were randomized to: A. BCG 80 mg (Tokyo strain) within 3 months of randomization followed by instillations at 3, 6, and 9 months B. No BCG	Progression: 0 vs. 1 (4%)	Recurrence: 1 (4%) vs. 7 (26%), p=0.078	Mortality: 2 (8%) vs. 2 (7%) Died due to bladder cancer: 0 vs. 1 (4%)	Dysuria: 17% vs. not reported

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Lamm, 2000[206] USA Multicenter 1986-1989 Lerner, 2007[207]	At least 1 week following TURBT patients received BCG 81 mg (Connaught strain) in 50.5 mL saline and simultaneous percutaneous BCG 0.5 cc (10^7 CFU) to inner thigh weekly for 6 weeks, responders randomized to: A. BCG intravesically and percutaneously 3 successive weekly treatments at 3 months, 6 months and every 6 months to 3 years B. No BCG			5 year survival: 83% vs. 78%	2 BCG related deaths
	Martinez-Pineiro, 2002[222] Spain Multicenter 1991-1992	A: BCG Connaught strain 81 mg, 12 instillations (starting 7 to 14 days after TURBT, once weekly for 6 weeks, then once every 2 weeks for 12 weeks) B: BCG Connaught strain 27 mg, 12 instillation (starting 7 to 14 days after TURBT, once weekly for 6 weeks, then once every 2 weeks for 12 weeks)	Progression: 12% (29/252) vs. 13% (33/247), RR 0.86 (95% CI 0.54 to 1.37) Progression-free survival (B vs. A): HR 1.17 (95% CI 0.71 to 1.93) Cystectomy: 4.8% (12/252) vs. 6.1% (15/247), RR 0.78 (95% CI 0.37 to 1.64)	Recurrence: 28% (71/252) vs. 31% (76/247), RR 0.92 (95% CI 0.70 to 1.20) Disease-free interval (B vs. A): HR 1.09 (95% CI 0.79 to 1.51)	All-cause mortality: 20% (51/252) vs. 22% (55/247), RR 0.93 (95% CI 0.66 to 1.31) Survival time (B vs. A): HR 1.08 (95% CI 0.74 to 1.58) Bladder cancer mortality: 7.9% (20/252) vs. 7.3% (18/247), RR 1.09 (95% CI 0.59 to 2.01) Cancer-free survival (B vs. A): HR 1.25 (95% CI 0.53 to 2.94)	Local side effects: 67% (168/252) vs. 55% (135/247), RR 1.22 (95% CI 1.06 to 1.41) Severe (grade 3 or 4) local side effects: 18% (44/252) vs. 6.5% (16/247), RR 2.70 (95% CI 1.56 to 4.65) Systemic side effects: 32% (80/252) vs. 15% (38/247), RR 2.06 (95% CI 1.46 to 2.91) Severe systemic side effects: 3.6% (9/252) vs. 4.4% (11/247), RR 0.80 (95% CI 0.34 to 1.90) Withdrawal due to side effects: 9.1% (23/252) vs. 4.0% (10/247), RR 2.25 (95% CI 1.10 to 4.64)

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Martinez-Pineiro, 2005[223] Spain Multicenter 1995-1999	A: BCG Connaught strain 81 mg, 12 instillations (starting 7 to 14 days after TURBT, once weekly for 6 weeks, then once every 2 weeks for 12 weeks) B: BCG Connaught strain 27 mg, 12 instillation (starting 7 to 14 days after TURBT, once weekly for 6 weeks, then once every 2 weeks for 12 weeks)	Progression: 24% (20/82) vs. 26% (19/73), RR 0.94 (95% CI 0.54 to 1.61) Progression-free survival (B vs. A): HR 1.08 (95% CI 0.58 to 2.03) Cystectomy: 8.4% (7/82) vs. 9.5% (7/73), RR 0.89 (95% CI 0.33 to 2.42)	Recurrence: 39% (32/82) vs. 45% (33/73), RR 0.86 (95% CI 0.60 to 1.25) Disease-free interval (B vs. A): HR 1.23 (95% CI 0.75 to 2.00) Cancer-free survival (B vs. A): HR 1.25 (95% CI 0.53 to 2.94)	All-cause mortality: 29% (24/82) vs. 29% (21/73), RR 1.01 (95% CI 0.62 to 1.67) Bladder cancer mortality: 12% (10/82) vs. 15% (11/73), RR 0.81 (95% CI 0.36 to 1.79)	Local side effects: 70% (57/82) vs. 48% (35/72), RR 1.43 (95% CI 1.08 to 1.89) Severe (grade 3 or 4) local side effects: 20% (16/82) vs. 11% (8/73), RR 1.78 (95% CI 0.81 to 3.92) Systemic side effects: 16% (13/82) vs. 5.5% (4/73), RR 2.89 (95% CI 0.99 to 8.48) Severe systemic side effects: 0% (0/82) vs. 1.4% (1/73), RR 0.30 (95% CI 0.01 to 7.18) Withdrawal due to side effects: 12.2% (10/83) vs. 9.6% (7/73), RR 1.26 (95% CI 0.50 to 3.13)
	Morales, 1992[226] Canada Single center 1979-1988	A: Armand Frappier BCG 60 mg weekly for 6 weeks B: Armand Frappier BCG 120 mg weekly for 6 weeks		Recurrence-free: 37% (18/49) vs. 67% (32/48), RR 0.55 (95% CI 0.36 to 0.84)		Side effects (not otherwise defined): 12% (6/49) vs. 33% (16/48), RR 0.37 (95% CI 0.16 to 0.86)
	Mukherjee, 1992[208] UK Single center 1984- unclear end date Kaisary, 1987[238]	A: BCG Glaxo strain (1.2 x 109 CFU) B: BCG Pasteur strain (1.2 x 109 CFU) 6 weekly instillations, followed by either monthly instillations if there was a complete response or 6-weeks if there was a partial or no response.	At 5 years: Complete response: 5/12 vs. 4/9 Failures: 7/12 vs. 5/9	At 5-year followup the Pasteur strain group was 1.12 times more likely to be free of disease than the Glaxo group, not statistically significant.		Most patients complained of hematuria and dysuria

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Oddens, 2013[228] Europe Multicenter 1997-2005	A: BCG (OncoTICE strain) 5 x 10^8 CFU at 1/3 dose, 15 instillations (started within 14 days after TURBT, one weekly for 6 weeks, then 3 weekly instillations at months 3 ,6, and 12) B: BCG full dose, 15 instillations (started within 14 days after TURBT, one weekly for 6 weeks, then 3 weekly instillations at months 3 ,6, and 12) C: BCG at 1/3 dose, 27 instillations (started within 14 days after TURBT, one weekly for 6 weeks, then 3 weekly instillations at months 3 ,6,12, 18, 24, 30, and 36) D: BCG full dose, 27 instillations (started within 14 days after TURBT, one weekly for 6 weeks, then 3 weekly instillations at months 3 ,6,12, 18, 24, 30, and 36)	Progression to ≥T2: 7.6% (26/341) vs. 9.1% (31/339) vs. 8.9% (30/337) vs. 6.5% (22/338) Distant metastasis: 4.4% (15/341) vs. 4.7% (16/339) vs. 5.3% (18/337) vs. 5.3% (18/338)	Recurrence: 49% (168/341) 43% (145/339) vs. 43% (145/337) vs. 39% (131/338) Percent recurrence-free at 5 years: 54% vs. 59% vs. 63% vs. 64% (unable to reject null hypothesis of inferiority of 1/3 dose or 1 year of treatment; >10% decrease was only observed for A vs. D, HR 0.75, 95% CI 0.59 to 0.94); 59% vs. 62% for A or C (1/3 dose) vs. B or D (full dose) (p=0.09); 57% for A or B (1 year maintenance) vs. 63% for C or D (3 years maintenance) (p=0.06)	Mortality: 24% (83/341) vs. 26% (88/339) vs. 30% (101/337) vs. 29% (97/338) Bladder cancer mortality: 3.8% (13/341) vs. 5.9% (20/339) vs. 5.0% (17/337) vs. 5.3% (18/338)	Systemic or local side effects within first year: 7.2% (24/334) vs. 7.0% (23/329) vs. 5.3% (7/323) vs. 5.5% (18/330) Systemic or local side effects after the first year: 0% (0/334) vs. 0% (0/329) vs. 2.8% (9/323) vs. 3.6% (12/330) No differences for A or C vs. B or D, or A or B vs. C or D

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Ojea, 2007[151] Spain Multicenter 1995-1998	14-21 days after transurethral resection with histological confirmation of bladder cancer, patients received 6 weekly instillations then another 6 instillations one every 2 weeks; if a recurrence was diagnosed a further TURBT was performed and the treatment continued A. BCG 27 mg (Connaught strain) B. BCG 13.5 mg (Connaught strain) C. MMC: 30 mg	Progression: 10% (14/142) vs. 13% (18/139), RR 0.76 (95% CI 0.39 to 1.47) Time to progression (B vs. A): HR 1.16 (95% CI 0.57 to 2.34)	Recurrence: 27% (38/142) vs. 36% (50/139), RR 0.74 (95% CI 0.52 to 1.06) Disease-free interval (B vs. A): HR 1.35, (95% CI 0.89 to 2.06), adjusted HR 1.49 (95% CI 0.97 to 2.28) Recurrence rate: 0.58 vs. 0.74 per 100 patient-months	A vs. B All-cause mortality: 9.2% (13/142) vs. 12% (17/139), RR 0.75 (95% CI 0.38 to 1.48) Bladder cancer death: 2.1% (3/142) vs. 3.6% (5/139), RR 0.59 (95% CI 0.14 to 2.41) Cancer-specific survival time (B vs. A): HR 1.60 (95% CI 0.38 to 6.72)	A vs. B Withdrawals due to AE: Not reported Local toxicity 65% vs. 64% Systemic toxicity: 11% vs. 11%
	Pagano, 1995[230] Bassi, 1992[262] (Abstract of interim results) Italy Single center 1990	6-week course of intravesical therapy: A. Pasteur strain BCG 75 mg B. Pasteur strain BCG 150 mg			Disease free survival Ta: no difference between doses (p=0.55) Disease free survival CIS: favors the low dose group (p<0.001) Disease free survival T1: number of patients enrolled to date does not allow a statistical conclusion (p=0.07)	Withdrawals due to AE: Not reported Fever: 18 vs. 33, p<0.05 Cystitis: 32 vs. 57, p<0.05 Macroscopic hematuria: 13 vs. 26, p<0.05

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Palou, 2001[209] Spain, England Multicenter 1989-1995	Initial treatment with 6 weekly instillations of BCG 81 mg (Connaught strain); if relapse then 6 additional weekly instillations; if disease free then randomized to: A. BCG 81 mg (Connaught) 6 weekly instillations every 6 months for 2 years B. No further treatment	Progression: 3 vs. 2	Tumor-free: 53 vs. 46 Superficial relapse: 10 (15%) vs. 16 (26%), p=0.07	Mortality: 11 vs. 8 Died of bladder cancer: 3 vs. 2	Discontinued instillations due to side effects: 32 in BCG maintenance group; number in control group not reported
	Rentsch, 2014[210] Switzerland Single center 1998-2010	A: BCG Connaught (6.6-19.2 x 108 CFU) B: BCG Tice (2-8 x 108 CFU) 6 weekly intravesical instillations	5- year progression-free survival: 94.1% (95% CI 87.8-100%) vs. 87.9 (95% CI 76.5-100), p=0.3442	5- year recurrence-free survival: 74% (95% CI 39.1-63.3 months) vs. 48% (95% CI 35.5-65.1 months), p=0.0108	Overall survival: 84.9% (95% CI 75.5-95.5) vs. 93.6 (95% CI 85.2-100), p=0.2652 Disease-specific survival: 93% (95% CI 86.5-100) vs. 100% (100-100), no p-value reported	Side effects caused by BCG: 20/71 vs. 25/60, p=0.09
	Sengiku, 2013[233] Japan Single center 2004-2012	At least 2 weeks after removing as much of visible lesion as possible by TURBT, patients received weekly up to 8 times: A. BCG 80 mg (Tokyo strain) in 40 mL saline B. BCG 81 mg (Connaught strain) in 40 mL saline		Percent recurrence-free: 73% vs. 69% at 2 years, 62% vs. 56% at 5 years (p=0.75)		Withdrawals due to AE: 7 (8%) vs. 9 (10%) Fever AE or complication events: 12 vs. 10 Cystitis AE or complication events: 33 vs. 28 Hematuria AE or complication events: 8 vs. 12

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Witjes, 1993[148] Witjes, 1996[156] Vegt, 1995[211] The Netherlands Multicenter 1987-1990	A. MMC 30 mg in 50 mL saline once a week for 4 weeks and thereafter once a month for 5 months. If a superficial recurrence or persistent CIS after 6 months, 3 additional monthly instillations given B. BCG-Tice C. BCG RIVM BCG 5X108 bacilli in 50 mL saline, administered once a week for 6 weeks. At the time of first superficial recurrence or persistent CIS at 3 or 6 months, a second 6 week course with BCG instillations was given after complete TURBT or biopsy.	Progression: 5% (7) vs. 6% (8)	B vs. C % Recurrence-free, all papillary tumors 1 year: 68% vs. 69% 2 year: 54% vs. 62% 5 year: 36% vs. 54% (log-rank, p=0.07) Recurrence: 64% (75/117) vs. 46% (62/134), RR 1.39 (95% CI 1.10 to 1.74)		B vs. C Drug-induced cystitis: 30% (42/140) vs. 32% (48/149) Drug-induced cystitis requiring treatment delay or discontinuation: 1.4% (2/140) vs. 2.0% (3/149) Systemic side-effects: 27% (38/140) vs. 18% (27/149) Systemic side-effects requiring treatment delay or discontinuation: 4.3% (6/140) vs. 2.0% (3/149) Withdrawals due to AE: 14 (total across 3 arms) Intercurrent death=10 (total across 3 arms)
MMC Trials	Au, 2001[197] USA, Europe, and Canada Multicenter 1992-2000	A: MMC 40 mg/20 mL sterile water, 6 instillations (once weekly for 6 weeks), optimized by instruction to refrain from fluids for 8 hour prior to and during instillations, oral doses of 1.3 g sodium bicarbonate the night before, Foley to empty bladder prior to instillation for post void residual <10 mL B: MMC 20 mg/20 mL sterile water, 6 instillations (once weekly for 6 weeks), without additional optimization measures		Percent recurrence-free at 5 years: 41% vs. 25% Recurrences: 51% (61/119) vs. 66% (73/111), RR 0.78 (95% CI 0.63 to 0.97) Time to recurrence (median, months): 29 vs. 12 (p=0.005)		Discontinuation of treatment due to adverse events: 1.8% vs. 1.9% Dysuria: 33% vs. 18%, RR 1.86 (95% CI 1.15 to 3.02) Cystitis: 23% vs. 16%, RR 1.46 (95% CI 0.84 to 2.53) Urinary frequency: 24% vs. 31% Urinary urgency: 22% vs. 26% Hematuria: 26% vs. 23% Fever: 3.6% vs. 4.7% Fatigue: 18% vs. 19% Nausea: 10% vs. 8.5%

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Colombo, 2012[213] Italy Single center 2010-2011	A: Mitomycin C (MMC), 40 mg (in 40 mL saline) three instillations per week for 2 weeks, prior to TURBT B: Mitomycin C (MMC), 40 mg (in 40 mL saline) one instillation per week for 6 weeks, prior to TURBT	Complete response (absence of residual tumor on histology): 70% (19/27) vs. 44% (12/27), RR 1.58 (95% CI 0.97 to 2.58) Progession: 0% (0/27) vs. 0% (0/27)			Grade 3 or 4 systemic toxicity or discontinuation due to systemic toxicity: No cases Urinary frequency: 69% vs. 67% Chemical cystitis: 42% vs. 47% Urinary incontinence: 15% vs. 27% Hematuria: 31% vs. 52% Lower urinary tract pain: 38% vs. 29%
	Ersoy, 2013[198] Turkey Single center 2006- 2010	A: MMC, 40 mg (in 40 mL sterile saline) intravesical; infusion within 6 hours of TURBT; MMC retained in bladder for 2 hours. B: Urinary alkalinization prior to MMC instillation: Sodium bicarbonate, 1.3 g, orally X 3 doses (night before TURBT, morning of TURBT, 30 minutes prior to MMC). MMC, 40 mg (in 40 mL sterile saline) intravesical; infusion within 6 hours of TURBT; MMC retained in bladder for 2 hours. C: No drugs given in the first 6 hours after TURBT.		A vs. B Recurrence free at 1 year: 100% vs. 86.7%, p=0.132 Recurrence free at 3 years: 100% vs. 79.4%, p=0.132 Recurrence free at 5 years: 100% vs. 79.4%, p=0.173 Mean time to recurrence, months (95% CI): not reported vs. 34.8 (28.5-41.1)		Not reported

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Friedrich, 2007[154] Germany Multicenter 1995-2002	A. MMC 20 mg, 6 weekly instillations B. BCG RIVM 2 x 10^8 CFU, 6 weekly instillations C. MMC 20 md, 6 weekly instillations followed by monthly instillations of MMC 20 mg for 3 years		A vs. C Recurrence: 26% (46/179) vs10% (16/153), RR 2.5 (95% CI 1.5 to 4.2) Percent recurrence-free at 2 years: 71% (126/179) vs. 88% (135/153) Percent recurrence-free at 3 years:69% (123/179) vs. 86% (132/153) (log-rank test, p=0.0006) Recurrence-free interval: Adjusted HR 0.38 (95% CI 0.21 to 0.69) for C vs. A after adjustment for facility, primary/recurrent, stage/grade		Withdrawals due to AE: 0 vs. 3 vs. 8 Dysuria: 12% vs. 20% Hematuria: 1% vs. 9% Fever: 2% vs. 2%
	Fukui, 1992[202] Japan Single center 1986-1989	A: MMC 20 mg (in 20 mL saline) on day 1 and adriamycin 40 mg (in 20 mL saline) on day 2 for 5 weeks, followed by maintenance therapy once monthly for 12 months B: MMC 20 mg (in 20 mL saline) on day 1 and adriamycin 40 mg (in 20 mL saline) on day 2 for 5 weeks, No maintenance therapy	Progression: 12% (3/25) vs. 3.8% (1/26), RR 3.12 (95% CI 0.35 to 28.0) Progression, according to stage: Ta or Ta: 0% (0/13) vs. 0% (0/15) Tis: 25% (3/12) vs. 9.1% (1/11)	Recurrence: 36% (9/25) vs. 65% (17/26), RR 0.55 (95% CI 0.30 to 1.0) Nonrecurrence, according to stage: Ta or T1: 59% vs. 38% (p>0.05) Tis: 73% vs. 24% (p<0.05) Recurrence, according to stage: Ta or T1: 38% (5/13) vs. 60% (9/15) Tis: 33% (4/12) vs. 73% (8/11)		

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Huland, 1990[191] Germany Multicenter 1983 - 1985	A: MMC, 20 mg/20 mL. Total 42 instillations. Every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year. B: MMC, 20 mg/20 mL. Total 42 instillations. Every week X 8 weeks, then every 4 weeks for rest of 1st year and 2 additional years. C: MMC, 20 mg/20 mL. Total 20 instillations. Every week X 20 weeks. D: Doxorubicin, 50 mg/50 mL. Total 42 instillations. Every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year. For all groups: Instillations started 4 to 6 weeks after discharge from hospital.	Progression of stage: 2.9% (6/209) vs. 1.0% (1/96) vs. 5.3% (4/75) Progression of grade: 1.9% (4/209) vs. 1.0% (1/96) vs. 4.0% (3/75)	A vs. B vs. C Recurrence: 15.3% (32/209) vs. 9.4% (9/96) vs. 17.3% (13/75) Recurrence per 100 patient-months: 0.68 vs. 0.49 vs. 0.65		A vs. B vs. C Chemical cystitis: 25% vs. 12% vs. 18% Allergy: 2% vs. 2% vs. 1% Other: 6% vs. 4% vs. 10% Total: 33% vs. 18% vs. 29%

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Schwaibold, 1997[232] Germany Single center 1983-1987	A: MMC 20 mg/20 mL saline, 42 instillations (every 2 weeks for 1 year, every 4 weeks for 1 year, every 3 months for 1 year) B: MMC 20 mg/20 mL saline, 42 instillation (every week for 8 weeks, every 4 weeks for 44 weeks and 2 additional years) C: MMC 20 mg/20 mL saline, 20 instillations (every week for 20 weeks) D: Doxorubicin 50 mg/50 mL saline, 42 instillations (same schedule as A)	Progression: 12% (24/209) vs. 5.2% (5/96) vs. 6.7% (5/75) vs. 18% (7/39) (p=0.01 for overall treatment effect in Cox proportional hazards model adjusted for number of prior recurrences, grade/Tis, recurrent cancer); RR for B vs. A 0.06, 95% CI 0.01 to 0.51	A vs. B vs. C vs. D Recurrence: 24% (51/209) vs. 18% (17/96) vs. 20% (15/75) vs. 31% (12/39) (p=0.21 for overall treatment effect in Cox proportional hazards model adjusted for number of prior recurrences, and grade/Tis); RR for B vs. A 0.53, 95% CI 0.29 to 0.96)		Not reported
	Tolley, 1996[118] United Kingdom Multicenter 1984 - 1986	A: MMC 20 mg/20 mL saline, 42 instillations (every 2 weeks for 1 year, every 4 weeks for 1 year, every 3 months for 1 year) B: MMC 2 mg/20 mL; saline, 42 instillation (every week for 8 weeks, every 4 weeks for 44 weeks and 2 additional years) C: MMC 20 mg/20 mL saline, 20 instillations (every week for 20 weeks) D: Doxorubicin 50 mg/50 mL saline, 42 instillations (same schedule as A)	Progression-free interval, group comparisons, HR 0.97 (95% CI 0.46 to 2.06)	A vs. B Recurrence at 24 months: 42% vs. 31% (p=0.14) Recurrence-free interval, group comparisons, HR 0.74 (95% CI 0.51 to 1.06)	All-cause mortality: 33.6% (50/149) vs. 42.5% (62/146), RR 0.79 (95% CI 0.59 to 1.1) Bladder cancer mortality: 5.4% (8/149) vs. 5.5% (8/146), RR 0.98 (95% CI 0.38 to 2.5)	A vs. B (none reported for C) Dysuria and frequency: 0% (0/149) vs. 6.2% (9/146), RR 0.05 (95% CI 0.003 to 0.88) Delayed healing of biopsy site: 0.7% (1/149) vs. 4.1% (6/146) Chemical cystitis was not reported as a side effect by any patient in either group.

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Doxorubicin Trials	Akaza, 1987[112] Japan Unclear if single or multicenter 1982-1985	A: Doxorubicin, 30 mg (in 30 mL saline). B: Doxorubicin, 20 mg (in 40 mL saline). C: MMC: 20 mg (in 40 mL saline). D: No adjuvant treatment. TURBT alone. For A, B, and C: First instillation within 1 week of TURBT. Once weekly X 2 weeks, then once every 2 weeks X 14 week, then once monthly X 8 months, then once every 3 month X 1 year (Total: 21 doses over 2 years)	Progression (in stage, grade, or both): 43.2% (19/44) vs. 31.0% (13/42) vs. 26.8% (11/41) vs. 38.7% (12/31); RR 1.40 (95% CI 0.79 to 2.45) for A vs. B	A vs. B vs. C vs. D Recurrence-free survival rate at 1 year: 74.8% vs. 75.0 vs. 76.3% vs. 66.7% Recurrence-free survival rate at 2 years: 62.3% vs. 59.1 vs. 62.3% vs. 51.8% Recurrence-free survival at 1260 days, generalized Wilcoxon test: A>D, p<0.05 B>D, p<0.05 C>D, p<0.05 Long-term (median, 6.6 years) followup in subgroup of 158 patients Recurrence/year (number of recurrences/total observation period: 0.473 vs. 0.512 vs. 0.472 vs. 0.510		A vs. B vs. C (not reported for group D) Pollakiuria: 16% vs. 18.7% vs. 23.8% Dysuria: 25.6% vs. 25.2% vs. 27.0% Hematuria: 13.6% vs. 7.3% vs. 11.1% Pyuria: 10.4% vs. 10.6% vs. 19.8% "No significant systemic side effects" A vs. B vs. C (not reported for group D) Pollakiuria: 16% vs. 18.7% vs. 23.8% Dysuria: 25.6% vs. 25.2% vs. 27.0% Hematuria: 13.6% vs. 7.3% vs. 11.1% Pyuria: 10.4% vs. 10.6% vs. 19.8% "No significant systemic side effects"
	Flamm, 1990[214] Austria Single center 1979-1981	A: Doxorubicin 50 mg/50 mL saline weekly for 6 weeks, then monthly for 2 years B: Doxorubicin 50 mg/50 mL saline weekly for 6 weeks	Progression: 19% (13/70) vs. 20% (15/76), RR 0.94 (95% CI 0.48 to 1.8)	Recurrence: 47% (33/70) vs. 42% (32/76), RR 1.1 (95% CI 0.78 to 1.6) Time to first recurrence (months): 16 vs. 13 (p=0.78) Recurrence rate: 1.7 vs. 1.4 per 100 patient-months (p>0.1)	All-cause mortality: 21% (15/70) vs. 24% (18/76), RR 0.90 (95% CI 0.49 to 1.7) Bladder cancer mortality: 13% (9/70) vs. 13% (10/76), RR 0.95 (95% CI 0.41 to 2.2)	Chemical cystitis: 12.8% vs. 11.8%

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Matsumura, 1992[123] Japan Multicenter 1987-1989	A: Doxorubicin 20 mg/40 mL saline, 21 instillations (following TURBT, once weekly for 2 weeks, then every 2 weeks for 14 weeks, once monthly for 8 months, and once every three months for 1 year) B: Doxorubicin 20 mg/40 mL saline, 6 instillations (over 2 weeks prior to TURBT) C: No doxorubicin		Percent recurrence-free at 1 year: 63.8% vs. 49.0% (p>0.05 for A vs. B) Percent recurrence-free at 2 years: 38.2% vs. 18.8% (p<0.05 for A vs. B)		A vs. B Urinary frequency: 10.3% (13/126) vs. 17.3% (13/75) Pain on urination: 10.3% (13/126) vs. 12.0% (9/75) Dysuria: 3.2% (4/126) vs. 4.0% (3/75) Hematuria: 4.0% (5/126) vs. 8.0% (6/75) Pyuria: 4.0% (5/126) vs. 9.3% (7/75)
	Niijima, 1983[116] Japan Multicenter 1980 – 1985	A: Doxorubicin, 30 mg (in 30 mL saline). B: Doxorubicin, 20 mg (in 40 mL saline). C: MMC: 20 mg (in 40 mL saline). D: No adjuvant treatment. TURBT alone. For A, B, and C: First instillation within 1 week of TURBT. Twice weekly X 4 weeks (Total: 8 doses)		Primary tumor: Recurrence-free survival rate at 1 year (A vs. B vs. C vs. D): 73.1% vs. 76.6% vs. 84.0% vs. 70% Recurrence-free survival at 1800 days, generalized Wilcoxon test: B>D, p<0.05 C>D, p<0.01 Comparisons not reported for other treatment group comparisons. Recurrent tumor: Recurrence-free survival at 1800 days, generalized Wilcoxon test: A>D; B>D; C>D; differences reported as nonsignificant, no p -values reported.		A vs. B vs. C (not reported for group D) Pollakiuria: 33.8% vs. 28.3% vs. 33.1% Dysuria: 36.9% vs. 27.5% vs. 27.4% Hematuria: 20.0% vs. 11.6% vs. 9.7% Pyuria: 23.8% vs. 19.6% vs. 8.9% "No significant systemic side effects"

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Rubben, 1988[231] Germany Single center 1979-1981	A: Doxorubicin 50 mg/50 mL saline, 13 instillations (2 hours prior to TURBT, then twice weekly for 6 weeks) B: Doxorubicin 50 mg/50 mL saline, 28 instillations (2 hours prior to TURBT, then twice weekly for 6 weeks, twice monthly for 4.5 months, once monthly for 6 months) C: No intravesical therapy		Recurrence rate (per 100 patient-months) (p>0.05 in all subgroups) Primary: 2.5 vs. 2.4 vs. 2.3 Recurrent: 2.6 vs. 2.8 vs. 3.9 Solitary: 1.8 vs. 3.0 vs. 2.0 Multiple: 3.6 vs. 3.6 vs. 4.6 <3 cm: 1.9 vs. 3.4 vs. 2.9 >3 cm: 2.7 vs. 2.9 vs. 2.6 Tis negative: 2.3 vs. 3.1 vs. 2.2 Tis positive: 3.2 vs. 3.2 vs. 4.4		Systemic side effects: None observed Local side effects resulting in incomplete treatment: 11% vs. 33% vs. 11%

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Ueda, 1992[236] Japan Multicenter 1984-1986	A: Doxorubicin 30 mg/30 mL saline, 19 instillations (immediately and 2 days after TURBT, then weekly for 2 weeks, every 2 weeks for 14 weeks, monthly for 8 months) B: Doxorubicin 30 mg/30 mL saline, 19 instillations (immediately and 2 days after TURBT, then weekly for 2 weeks, every 2 weeks for 14 weeks, monthly for 8 months) plus 5-fluorouracil 200 mg/day starting at 1 week C: Doxorubicin 30 mg/30 mL saline, 17 instillations (starting 7 days after TURBT weekly for 2 weeks, every 2 weeks for 14 weeks, monthly for 8 months)			Percent recurrence-free at 36 months: 79.4% vs. 73.7% vs. 67.6% vs. 63.1% (NS); 76.4% vs. 65.4% for A + B vs. C +D (p>0.05)	Bladder irritation: 48% (24/50) vs. 55% (30/55) vs. 26% (15/58) vs. 26% (16/61) Bladder irritation resulting in withdrawal: 8% (4/50) vs. 5% (3/55) vs. 2% (1/58) vs. 3% (2/61) Hematuria and bladder calculi: 0 vs. 0 vs. 0 vs. 2% (1/61)

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Epirubicin Trials	Ali-El-Dein, 1997[119] (J Urol) Egypt Single center 1991 - 1995	A: Epirubicin, 50 mg (in 50 mL normal saline). B: Epirubicin, 80 mg (in 50 mL normal saline). C: Doxorubicin, 50 mg (in 50 mL normal saline). D: No adjuvant treatment. TURBT alone. For Groups A - C: First instillation 7 to 14 days after TURBT. Retained intravesically for 2 hours; Instillations once a week X 8 weeks, then once monthly to complete 1 year of treatment.	Progression: 10.9% (7/64) vs. 4.4% (3/68), RR 2.5 (95% CI 0.67 to 9.2) Mean interval to progression, months (95% CI): 31 (22-40) vs. 31 (18-44)	A vs. B Recurrence: 25.0% (16/64) vs. 17.6% (12/68), RR 1.42 (95% CI 0.73 to 2.76) Mean time to first recurrence, months (95% CI): 16 (12.2-19.8) vs. 15.4 (11.4-19.4). Recurrence rate per 100 patient-months: 0.83 vs. 0.60, p<0.05.		A vs. B vs. C (No data for group D) Any adverse event: 15.6% (10/64) vs. 23.5% (16/68) Adverse events per Number of instillations: 7.3% (88/1199) vs. 8.7% (111/1280) Systemic toxicity: 0.0% (0/10) vs. 0.0% (0/16) Mild toxicity: 50.0% (5/10) vs. 68.8% (11/16) Severe toxicity (i.e., requiring permanent or temporary discontinuation of treatment): 20.0% (2/10) vs. 12.5% (2/16) Contracted bladder: 10.0% (1/10) vs. 6.3% (1/16) Hematuria: 10.0% (1/10) vs. 12.5% (2/16) UTI: 10.0% (1/10) vs. 0.0% (0/16)

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Ali-El-Dein, 1997[126] (British J Urol) Egypt Single center 1992 - 1996	A: Epirubicin, 50 mg (in 50 mL normal saline); Single instillation immediately after TURBT. Retained intravesically for 2 hours. B: Epirubicin, 50 mg (in 50 mL normal saline); Initial instillation 1 - 2 weeks after TURBT. Retained intravesically for 2 hours; Then, instillations once a week X 7, then once monthly X 10 to complete 1 year of treatment. C: No adjuvant treatment. TURBT alone.	Progression: 5.5% (3/55) vs. 3.4% (2/59)	A vs. B Recurrence: 23.6% (13/55) vs. 25.4% (15/59), p=0.8. Mean interval to first recurrence, months: 16 vs. 18 Recurrence rate per 100 patient-months: 0.79 vs. 0.84		A vs. B Any adverse event: 21.8% (12/55) vs. 25.4% (15/59), p=0.8. Mild toxicity: 75.0% (9/12) vs. 66.7% (10/15) , p=0.8. Severe toxicity (i.e., requiring permanent or temporary discontinuation of treatment): 25.0% (3/12) vs. 33.3% (5/15) , p=0.7. Contracted bladder: 0.0% (0/12) vs. 6.7% (1/15) Hematuria: 16.7% (2/12) vs. 20.0% (3/15) UTI: 8.3% (1/12) vs. 6.7% (1/15) No patients with systemic toxicity.

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Hendricksen, 2008[216] the Netherlands Multicenter 1998-2004	A. Epirubicin 50 mg/50 mL saline, 9 instillations over 6 months (once weekly for 4 weeks started within 2 weeks of TURBT, then once monthly for 5 months) B. Epirubicin 50 mg/50 mL saline, 10 instillations over 6 months (within 48 hours of TURBT, once weekly for 4 weeks starting within 2 weeks of TURBT, once monthly for 5 months) C: Epirubicin 50 mg/50 mL saline, 11 instillations over 12 months (once weekly for 4 weeks starting within 2 weeks of TURBT, once monthly for 5 months, once every three months for 6 months)	% progression-free at 5 years: 90.0% vs. 87.7% vs, 88.2% (p=0.593, log-rank)	Percent recurrence-free at 5 years: 44.4% vs. 42.7% vs. 45.0% (p=0.712, log-rank)		Therapy stopped or delayed due to side effects: 15% (39/266) vs. 22% (62/286) vs. 22% (61/277) Chemical cystitis: 32% (84/266) vs. 33% (95/286) vs. 24% (66/277) Hematuria: 13% (36/266) vs. 19% (54/286) vs. 11% (30/277) Systemic side effects: 13% (35/266) vs. 14% (40/286) vs. 14% (37/277)
	Koga, 2004[219] Japan Multicenter 1993-1995	A: Epirubicin 30 mg/30 mL saline 19 times (within 24 hours of TURBT, then 2-3 days, 1 week, and 2 weeks after TURBT, then once every 2 weeks for 12 weeks, then once a month for 9 months) B: Epirubicin 30 mg/30 mL saline 9 times (within 24 hours of TURBT, then 2-3 days, 1 week, and 2 weeks after TURBT, then once every 2 weeks for 10 weeks)		Percent recurrence-free at 3 years: 85.2% vs. 63.9% (p=0.005) Recurrence: 13.0% (10/77) vs. 31.5% (23/77); unadjusted HR 0.39 (0.18 to 0.82), adjusted HR 0.36 (0.17 to 0.78) (adjusted for multiplicity and tumor stage)		Severe local toxicity: 5.2% (4/77) vs. 8.2% (6/73), RR 0.63 (95% CI 0.19 to 2.15) Discontinuation due to pain: 1.3% (1/77) vs. 0% (0/73) Systemic toxicity (fatigue, low grade fever): 0% (0/77) vs. 2.7% (2/73) Macrohematuria (mild, moderate, severe): 30% (23/77) vs. 16% (12/73) Dysuria (mild, moderate, severe): 38% (29/77) vs. 37% (27/73) Frequency (mild, moderate, severe): 32% (25/77) vs. 30% (22/73)

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Kuroda, 2004[220] Japan Multicenter 1994-1996	A. Epirubicin 20 mg/40 mL saline, 17 instillations over 12 months (starting about 7 days after TURBT, once weekly for 2 weeks, once every other week for 14 weeks, once a month for 8 months) B: Epirubicin 30 mg/40 mL saline, 12 instillations over 12 months (starting about 7 days after TURBT, once weekly for 2 weeks, once every other week for 14 weeks, once a month for 3 months) C: Epirubicin 40 mg/40 mL saline, 9 instillations over 4 months (starting about 7 days after TURBT, once weekly for 2 weeks, once every other week for 14 weeks)		Percent recurrence-free at 1 year: 67% vs. 73% vs. 74% Percent recurrence-free at 2 years: 49% vs. 55% vs. 60% Percent recurrence-free at 4 years: 36% vs. 46% vs. 44% Time to recurrence (median, days): 688 vs. 1007 vs. 1186 (p=0.04 for dose-response)	Mortality: 5.4% (11/205) vs. 6.4% (13/204) vs. 8.8% (18/205); RR 0.84 (95% CI 0.39 to 1.8) for A vs. B, RR 0.61 (95% CI 0.30 to 1.3) for A vs. C, and RR 0.73 (95% CI 0.37 to 1.4) for B vs. C Bladder cancer mortality: 1.5% (3/205) vs. 1.5% (3/204) vs. 2.4% (5/205), RR 1.0 (95% CI 0.20 to 4.9) for A vs. B, 0.60 (95% CI 0.15 to 2.5) for A vs. C, and RR 0.60 (95% CI 0.15 to 2.5) for B vs. C	Frequency (mild, moderate, severe): 22% vs. 35% vs. 29% Pain on urination (mild, moderate, severe): 21% vs. 32% Vs. 30% Dysuria (mild, moderate, severe): 12% vs. 17% vs. 15% Hematuria (mild, moderate, severe): 19% vs. 25% vs. 20%

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Liu, 2006[192] China Unclear if single or multicenter 1997 - 1998	A: Epirubicin, 80 mg (in 40 mL normal saline). Single intravesical instillation within 6 hours of TURBT. B: Epirubicin, 40 mg, intravesical instillation every week for 6 ~ 8 weeks, then every month for 10 months. C: MMC, 40 mg, intravesical instillation every week for 6 ~ 8 weeks, then every month for 10 months.		A vs. B Tumor-free survival at 1 year: 100% (14/14) vs. 86.7% (13/15), RR 1.15 (95% CI 0.91 to 1.44) Tumor-free survival at 2 years: 85.7% (12/14) vs. 80.0% (12/15), RR 1.07 (95% CI 0.77 to 1.49) Tumor-free survival at 3 years: 71.4% (10/14) vs. 73.3% (11/15), RR 0.89 (95% CI 0.59 to 1.35) Tumor-free survival at 5 years: 64.3% (9/14) vs. 66.7% (10/15), RR 0.96 (95% CI 0.57 to 1.64) Mean interval to recurrence, months: 8 vs. 4 vs. 5 Recurrence rate: 35.7% (5/14) vs. 33.3% (5/15), RR 1.07 (95% CI 0.39 to 2.92)		A vs. B Any side effect: 13.6% vs. 53.3% Dysuria or urinary frequency/urgency: 6.3% (1/16) vs. 13.3% (2/15) Stricture of urethra: 0% (0/16) vs. 6.7% (1/15) No systemic adverse events

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Masters, 1999[224] UK Multicenter 1991-1993	A: Epirubicin 50 mg/50 mL saline, 5 instillations (starting 10-14 days after TURBT, every 3 months for 12 months) B: Epirubicin 100 mg/50 mL saline, 5 instillations (starting 10-14 days after TURBT, every 3 months for 12 months) First 102 patients had a marker tumor left after initial TURBT (0.5 cm)		Recurrence: 44% (27/61) vs. 56% (34/61), HR 0.68 (95% CI 0.41 to 1.13) Recurrence rate: 0.52 vs. 0.58 per patient-year, RR 0.90 (0.58 to 1.52)		UTI: 31% (19/61) vs. 21% (13/61), RR 1.46 (95% CI 0.79 to 2.69) Bladder spasm: 15% (9/61) vs. 44% (27/61), RR 0.33 (95% CI 0.17 to 0.65) Withdrawal or incomplete therapy due to adverse events: 11% (7/61) vs. 23% (14/61), RR 0.50 (95% CI 0.22 to 1.15)

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Mitsumori, 2004[225] Japan Multicenter 1998-2001	A: Epirubicin 30 mg/40 mL saline, 6 instillations (starting 1 week after TURBT once every 2 weeks for 12 weeks, total 180 mg) B: Epirubicin 30 mg/40 mL saline, 6 instillations (3 instillations within first 5-7 days after TURBT, then once every 2 weeks for 6 weeks, total 180 mg) C: Epirubicin 30 mg/40 mL saline, 12 instillations (starting 1 week after TURBT, once weekly for 12 weeks, total 360 mg) D: Epirubicin 30 mg/40 mL saline, 12 instillations (3 instillations within first 5-7 days after TURBT, then once weekly for 9 weeks, total 360 mg)		Recurrence rates A vs. B vs. C vs. D: 30% (6/20) vs. 25% (6/24) vs. 8.3% (1/12) vs. 0% (0/10) at 6 months, 50% (10/20) vs. 35% (8/23) vs. 45% (4/9) vs. 12% (1/8) at 12 months (p=0.04 for A vs. D with log-rank test, otherwise p>0.05) A or B (180 mg) vs. C or D (360 mg): 27% (12/44) vs. 5% (1/22) at 6 months; 42% (18/43) vs. 29% (5/17) at 12 months (p=0.01, log-rank test) A or C (starting 1 week after TURBT) vs. B or D (early instillations): 22% (7/32) vs. 18% (6/34) at 6 months; 48% (14/29) vs. 29% (9/31) at 12 months (p=0.36, log-rank test) In multivariate regression, total dose (180 vs. 360 mg, AOR 0.32, 95% CI 0.11 to 0.92) and urine cytology (I-II vs. III-IVAOR 3.11, 95% CI 1.08 to 8.94) independent predictors for local recurrence; delayed vs. early not significant (AOR 0.91, 95% CI 0.37 to 2.23)		Side effects (irritated bladder, UTI, or hematuria): 23% (5/22) vs. 24% (6/25) vs. 25% (3/12) vs. 40% (4/10) (P>0.05)

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Nomata, 2002[227] Japan Multicenter 1995-1998	A. Epirubicin 30 mg/30 mL saline 19 times over 1 year (once weekly for 4 weeks, then every 2 weeks for 4 months) B. Epirubicin 30 mg/30 mL saline 12 times over 5 months (once weekly for 4 weeks, then every 2 weeks for 4 months, then once per month for 7 months)		Percent recurrence-free at 3 years: 48.5% vs. 55.1% (p>0.05)		Urinary frequency (grade 1-3): 33% (18/55) vs. 20% (11/55) Dysuria (grade 1-3): 31% (17/55) vs. 21% (15/70) Macroscopic hematuria (grade 1-3): 42% (23/55) vs. 36% (25/70)
	Okamura, 1998[229] Japan Multicenter 1991-1993	A: Epirubicin 40 mg/40 mL saline 17 times (within 24 hours of TURBT, during first week, once weekly for 4 weeks, then once monthly for 11 months) B: Epirubicin 40 mg/40 mL saline 6 times (within 24 hours of TURBT, during first week, then once weekly for 4 weeks)	% disease progression at 3 years: 2.9% (2/69) vs. 1.4% (1/69)	Percent recurrence-free at 3 years: 75.1% vs. 77.2% (p=0.62) Time to first recurrence (mean, months): 36.0 vs. 36.9		Dysuria: 7.2% overall Macroscopic hematuria: 0.7% overall Withdrawal due to adverse events: 1.4% (2/138) Local toxicity: No difference between groups
	Saika, 2010[134] Japan Multicenter 1995 - 2001	A. Epirubicin, 20 mg (in 40 mL physiological saline). Two intravesical infusions, one immediately after (<1 hour) TURBT and one in the early morning of the following day, retained in bladder for 1 hour. B. Epirubicin, 50 mg (in 100 mL physiological saline). Same procedure as A. C. No adjuvant therapy. TURBT only.	Progression: 0.0% (0/83) vs. 1.1% (1/90), RR 0.36 (95% CI 0.01 to 8.74)	A vs. B Median recurrence-free survival, months: 24 vs. 38 (p>0.05)		A vs. B Bladder Grade 1 irritabilities (e.g., micturition pain and/or frequency): 22.9% vs. 35.6%; p=0.106 Grade 1 anemia: 2.4% (2/83) vs.2.2% (2/90) Grade 1 serum transaminases elevation: 1.2% (1/83) vs. 3.3% (3/90) Grade 1 leukopenia: 0.0% (0/83) vs.1.1% (1/90)

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Serretta, 2010[234] Italy Multicenter 2002-2003	A: Epirubicin 80 mg/50 mL saline, 16 instillations (within 6 hours of TURBT, then once weekly for 5 weeks, once weekly for 10 months) B: Epirubicin 80 mg/50 mL saline, 6 instillations (within 6 hours of TURBT, then once weekly for 5 weeks)	Progression to muscle-invasive: 2.9% (7/245) vs. 1.3% (3/237)	Percent recurrence-free at 3 months: 98.4% (182/185) vs. 94.8% (199/210) (p=0.06) Percent recurrence-free at 6 months: 95.1% (174/183) vs. 87.3% (157/180) (p=0.004) Percent recurrence-free at 12 months: 86.7% (143/165) vs. 79.1% (136/172) (p=0.03) Percent recurrence-free at 18 months: 77.8% (105/135) vs. 68.1% (98/144) (p=0.03) Percent recurrence-free at 24 months: 70.2% (87/124) vs. 63.0% (85/135) (p=0.11) Percent recurrence-free at 36 months: 62.1% (72/116) vs. 54.4% (69/127) (p=0.11) Percent recurrence-free at 48 months: 50.5% (48/95) vs. 45.9% (51/111) (p=0.26) Time to recurrence (median, months): 17 vs. 12 (p=0.10)		Serious adverse events: 0.2% overall Chemical cystitis with discontinuation of treatments: 0.4% overall Fever: 2.2% overall Dysuria and urgency resulting in treatment interruption: 7.1% overall Hematuria: 2.9% overall Treatment postponement: 15.7% overall

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Turkeri, 2010[235] Turkey Multicenter 2002-2004	A: Epirubicin 100 mg within 6 hours after TURBT B: Epirubicin 100 mg within 6 hours and 12-hours after TURBT	Progression: 1.5% (1/68) vs. 4.0% (3/75), RR 0.37 (95% CI 0.04 to 3.45)	Recurrence rates: 14.7% vs. 21.3%, adjusted HR 0.67 (95% CI 0.30 to 1.51) (adjusted for grade, stage, solitary vs. multiple, age <70 vs. ≥70 years)	Recurrence-free survival (months): 10.3 vs. 10.5 months (p=0.47, log-rank) Disease-free survival (months): 14.9 vs. 15.5 months	Not reported
Gemcitabine Trials	Gardmark, 2007[157] Japan Single center 1986-1989	A: Gemcitabine 2000 mg (in 100 mL saline) once weekly for 6 weeks B: Gemcitabine 2000 mg (in 100 mL saline) twice weekly for 3 weeks C: Gemcitabine 2000 mg (in 100 mL saline) single instillation	A vs. B vs. C Complete response (complete disappearance of marker lesion and no new tumor): 44% (4/9) vs. 40% (4/10) vs. 10% (1/10)			
Thiotepa Trials	Koontz, 1981[140] (prophylaxis) USA Multicenter 1974-1977	A: Thiotepa 30 mg/30 mL distilled water (once every 4 weeks for maximum 2 years) B: Thiotepa 60 mg/60 mL distilled water (once every 4 weeks for maximum 2 years) C: No thiotepa		Percent recurrence-free at 12 months: 63% vs. 69% vs. 40% (p=0.02 for A or B vs. C)		Leukopenia (WBC <3000): 0% (0/23) vs. 4.3% (1/23) vs. 0% (0/47) Thrombocytopenia (platelets <100,000): 0% (0/23) vs. 4.3% (1/23) vs. 0% (0/47) UTI: 0% (0/23) vs. 17% (4/23) vs. 0% (0/47)

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Koontz, 1981[140] (treatment) USA Multicenter 1974-1977	A: Thiotepa 30 mg/30 mL distilled water (once weekly for 4 weeks, repeated after 4 weeks) B: Thiotepa 60 mg/60 mL distilled water (once weekly for 4 weeks, repeated after 4 weeks)	Success (slight or moderate reduction of tumor, or complete remission): 70% (35/50) vs. 58% (26/45), RR 1.21, 95% CI 0.89 to 1.65 after first course; 48% (24/50) vs. 47% (21/45), RR 1.03, 95% CI 0.67 to 1.57) after second course			Leukopenia (WBC <3000): 2.0% (1/50) vs. 13% (6/45), RR 0.15 (95% CI 0.02 to 1.20) Thrombocytopenia (platelets <100,000): 6.0% (3/50) vs. 0% (0/45) UTI: 2.0% (1/50) vs. 2.2% (1/45)
Interferon alpha-2b Trials	Giannakopoulos, 1998[136] Greece Unclear if single or multicenter Study years not reported	A: No adjuvant treatment. TURBT alone. B: Interferon-α-2b (interferon-α-2b), 40 MU (in 50 mL normal saline). C: Interferon-α-2b (interferon-α-2b), 60 MU (in 50 mL normal saline). D: Interferon-α-2b (interferon-α-2b), 80 MU (in 50 mL normal saline). For Groups B - D: First instillation after histological verification of stage and grade; 48 - 72 hours after TURBT. Retained intravesically for 1 hour; patient position changed every 15 minutes. Instillations once a week X 2 months, then once every 15 days X 4 months, then once monthly X 6 months.	Progression: 13.6% (3/22) vs. 4.2% (1/24) vs. 4.3% (1/23); B vs. C, p=NS, B vs. D, p=NS; C vs. D, p=NS	B vs. C vs. D Recurrence: 36.4% (8/22) vs. 29.2% (7/24) vs. 21.7% (5/23); Differences between B, C, and D, p>0.10. Recurrence rate per 100 patient-months: 1.19 vs. 0.88 vs. 0.63; B vs. C, p="significant", B vs. D, p="significant"; C vs. D, p=0.026.	Recurrence-free survival time, months (mean): 21.4 vs. 26.1 vs. 30.0; B vs. C, p=0.02, B vs. D, p<0.01; C vs. D, p=NS.	No side effects of the drugs were noted. No adverse reactions noted. Five patients (groups not reported) developed fevers and were found to have urinary tract infections.

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Glashan, 1990[203] USA, Europe, Australia, Canada Multicenter 1985-1988	A: Interferon α-2b 100 million units (in 30 mL sterile water) B: Interferon α-2b 10 million units (in 30 mL sterile water) First instillation within 1 month of positive cytology, administered once weekly for 12 weeks, then monthly through one year				Flu-like symptoms: 14% (8/47) vs. 8% (3/38), RR 2.2 (95% CI 0.61 to 7.57) Withdrawal due to adverse events: None
	Hoeltl, 1991[217] Austria Single center Study years not reported	A: Interferon alfa-2b 100 x 10^6 IU (100 MU)/30 mL sterile water (once weekly for 10 weeks, then once monthly for 1 year total of therapy) B: Interferon alfa-2b 10 x 10^6 IU (10 MU)/30 mL sterile water (starting within 36 hours of TURBT, once weekly for 10 weeks, then once monthly for 1 year total of therapy) C: Ethoglucid 1.13 g/100 mL sterile water (once weekly for 10 weeks, then once monthly for 1 year total of therapy)	Progression (recurrence of G2 or G3 cancer, ≥T2, or metastatic): 36.4% (4/11) vs. 7.7% (1/13), RR 4.7 (95% CI 0.62 to 36)	A vs. B Recurrence rate: 2.76 vs. 4.4 per 100 months Percent recurrence-free: 54.5% (6/11) vs. 46.2% (6/13), RR 1.2 (95% CI 0.53 to 2.62) Time to recurrence (mean, months): 22.4 vs. 22.2		A vs. B Local toxicity (chemocystitis, dysuria): 0% (0/11) vs. 0% (0/13) Systemic side effects: None observed

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
	Malmström, 2002[221] Europe Multicenter Study years: not reported	A: Interferon-α, 30 MU (in 30 mL sterile water). Retained in bladder X 2 hours; patient moved from side to side every 30 min. First instillation 1 to 2 weeks after TURBT or biopsy, then weekly X 12 weeks. B: Interferon-α, 50 MU (in 30 mL sterile water). Same procedure as A. C: Interferon-α, 80 MU (in 30 mL sterile water). Same procedure as A. D: MMC, 40 mg (in 40 mL sterile water). Retained in bladder X 2 hours; patient moved from side to side every 30 min. First instillation 1 to 2 weeks after TURBT or biopsy, then weekly X 8 weeks.	A vs. B vs. C Complete response (macroscopic disappearance of marker lesion): 19% (5/27) vs. 30% (8/27) vs. 26% (7/27) at 9 weeks; 19% (5/27) vs. 33% (9/27) vs. 41% (11/27) at 13 weeks (p>0.05 for all comparisons)			A vs. B vs. C vs. D Adverse events reported: 37% (10/27) vs. 37% (10/27) vs. 48% (13/27) vs. 55% (16/29) Adverse events with frequency ≥10%, reported by treatment group: A: None B: Fever (11%); Pain (11%) C: Fever (11%); Pain (15%); Micturition frequency (11%) D: Pain (10%); Dysuria (10%); Hematuria (14%); Micturition disorder (14%); Micturition frequency (28%); UTI (10%)

Table 18. Results summary for trials comparing dosages, duration, and timing of administration (continued)

Intervention	Author, Year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Multiple Drugs	Bouffioux, 1995[212] Europe Multicenter 1983-1986	Initial randomization: A. MMC 30 mg/50 mL saline or doxorubicin 50 mg, 9 instillations starting on day of TURBT (once weekly for 4 weeks, then once monthly for 5 months) B. MMC 30 mg/50 mL saline or doxorubicin 50 mg, 9 instillations, starting between days 7 and 15 after TURBT (once weekly for 4 weeks, then once monthly for 5 months) Second randomization at 6 months: A: Continued instillations once a month for 6 months, total 15 B: No maintenance	Early vs. delayed treatment Progression to invasive bladder cancer: 11% (40/374) vs. 10% (38/378) after 6.5 years Distant metastasis: 6% (24/412) vs. 6% (17/412) Second primary: 7% (28/412) vs. 6% (25/412) Maintenance vs. no maintenance Progression to invasive bladder cancer: 9% (26/303) vs. 8% (25/314) Distant metastasis: 4% (12/304) vs. 4% (13/314) Second primary: 5% (15/304) vs. 7% (21/314) (p=0.41)	Early vs. delayed treatment Time to first recurrence: 43% (161/374) vs. 49% (187/378) after 2.75 years (p=0.18, log-rank test) Recurrence rate: 0.27 vs. 0.33 (p=0.08) Maintenance vs. no maintenance Time to first recurrence: 43% (130/303) vs. 50% (156/314) after 3 years (p=0.20, log-rank test) Recurrence rate: 0.23 vs. 0.28 (p=0.20)	Early vs. delayed treatment Mortality: 19% (78/412) vs. 21% (86/412) (p=0.60) Maintenance vs. no maintenance Mortality: 17% (53/304) vs. 20% (63/314)	Early vs. delayed Chemical cystitis requiring delay or discontinuation of therapy: 3% vs. 0% with MMC, 2.2% vs. 0.5% with doxorubicin Systemic toxicity requiring discontinuation of instillations: 1.8% with MMC, 0.8% with doxorubicin

AE = adverse event; AOR = adjusted odds ratio; BCG = bacillus Calmette-Guérin; BCG RIVM = RIVM strain of bacillus Calmette- Guérin; BCG-Tice = bacillus Calmette-Guérin Tice strain; CFU = colony forming unit; CI = confidence interval; CIS = carcinoma in situ; G2 = Grade 2 ; G3 = Grade 3; HR = hazard ratio; IU = international unit; MMC = Mitomycin C; MU = million units; NS = not significant; OR = odds ratio; RR = risk ratio; T1 = Tumor stage 1; T2 = tumor stage 2; Ta = Tumor stage a; Tis = carcinoma in situ; TURBT = transurethral resection of the bladder tumor; UTI = urinary tract infection; WBC = white blood cell count

Table 19. Fluorescent cystoscopy study characteristics

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Cystoscopic Followup Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Babjuk, 2005[241]	Czech Republic Single center 2001-2003	A: White light and 5-ALA fluorescent cystoscopy with TURBT (n=60) B: White light cystoscopy with TURBT (n=62) All patients with G1 or G2 tumors received adjuvant intravesical therapy; all patients with G3 tumors received intravesical BCG	Duration: 24 months Method: White light cystoscopy	Age (mean): 68 vs. 70 years Male: 72% vs. 63% Stage: 63% vs. 60% Ta, 37% vs. 40% T1 Grade: 50% vs. 53% G1, 40% vs. 35% G2, 10% vs. 11% G3
Dragoescu, 2011[245]	Romania Single center 2009	A: White light and HAL fluorescent cystoscopy with TURBT (n=22) B: White light cystoscopy with TURBT (n=22) All patients received postoperative intravesical epirubicin (Farmorubicin) and additional therapy based on risk group	Duration: 12 months Method: not reported	Age (mean): 59 vs. 62 years Male: 78% Stage: 22% vs. 18% Ta, 78% vs. 82% T1 Grade: 32% vs. 27% G1, 55% vs. 64% G2, 14% vs. 9.1% G3
Filbeck, 2002[246] (also Denzinger 2007a[243], Denzinger 2007b[244])	Germany Single center 1997-2000	A: White light and 5-ALA fluorescent cystoscopy with TURBT (n=88) B: White light cystoscopy with TURBT (n=103) All patients received intravesical prophylaxis based on AUA guidelines according to number of tumors, stage, and grade	Duration, mean: 21 months Method not reported	Age (median): 68 vs. 70 years Sex: Not reported Race/ethnicity: Not reported Smoker: Not reported Recurrent bladder cancer: 31% vs. 18% (p=0.06) Stage: 42% vs. 41% pTaG1, 31% vs. 28% pTaG2, 2.3% vs. 1.0% pTaG3, 7.9% vgs. 13% pT1G2, 11.4% vs. 11.7% pT1G3, 5.7% vs. 4.9% CIS Risk group: 35% vs. 48% low, 46% vs. 34% intermediate, 19% vs. 18% high

Table 19. Fluorescent cystoscopy study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Cystoscopic Followup Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Geavlete, 2010[247]	Romania Single center 2007-2009	A: White light and HAL fluorescent cystoscopy with TURBT (n=223) B: White light cystoscopy (n=223) All patients received single, immediate postoperative MMC instillation	Duration: 6 weeks Method: White light cystoscopy	Age (mean): 64 years (overall) Male: 73% (overall) Race/ethnicity: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage: 10% vs. 8.1% CIS, 51% vs. 47% pTa, 17% vs. 17% pT1, 14% vs. 15% MIBC Grade (for Ta and T1 tumors): 40% vs. 40% G1, 41% vs. 41% G2, 19% vs. 19% G3
Geavlete, 2011[248]	Romania Single center Study years not reported	A: White light and HAL fluorescent cystoscopy with TURBT (n=125) B: White light cystoscopy and TURBT (n=114) All patients received single, immediate postoperative MMC instillation	Duration: 2 years Method: White light cystoscopy	Age (mean): 67 years (overall) Male: 74% (overall) Stage: 11% vs. 8.3% CIS, 45% vs. 41% pTa, 19% vs. 18% pT1 Grade: Not reported
Hermann, 2011[250]	Denmark Multicenter Study years not reported	A: White light and HAL fluorescent cystoscopy with TURBT (n=59) B: White light cystoscopy (n=74)No patient received intravesical therapy immediately after TURBT, 3 patients in each arm had previously received MMC and 21 patients BCG (10 in arm A and 11 in arm B)	Duration: 12 months Method: White light cystoscopy	Age (mean): 71 vs. 69 years Male: 75% Race/ethnicity: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage and grade: 84% vs. 90% Ta low grade, 12% vs. 6% Ta high grade, 0% T1 low grade, 2% vs. 4% T1 high grade

Table 19. Fluorescent cystoscopy study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Cystoscopic Followup Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Karaolides, 2012[251]	Greece Single center 2008-2010	A: White light and HAL fluorescent cystoscopy with TURBT (n=41) B: White light cystoscopy with TURBT (n-45) Patients with moderate and high risk tumors received epirubicin 6 weeks after TURBT, or BCG	Duration: 18 months Method: White light cystoscopy	Age (mean): 66 vs. 64 years Male: 80% vs. 89% Race/ethnicity: Not reported Smoker: Not reported Recurrent bladder cancer: 29% vs. 24% Tumor stage and grade: 12% vs. 6.7% CIS, 22% vs. 31% high grade, 63% vs. 60% low grade, 2.4% vs. 2.2% low malignant potential
Kriegmair, 2002[252]	Austria Multicenter 1997-1998	A: White light and 5-ALA fluorescent cystoscopy with TURBT (n=52) B: White light cystoscopy with TURBT (n=49) Additional treatments not reported	Duration: 10 to 14 days Method: not reported	Age (mean): 69 vs. 70 years Male: 82% vs. 70% Stage: 4.6% vs. 6.2% CIS, 55% vs. 47% Ta, 18% vs. 20% T1, 7.7% vs. 16% T2 Grade: 32% vs. 12% G1, 32% vs. 42% G2, 9.2% vs. 12% G3
Naselli, 2012[254] Italy	Italy Multicenter 2009-2010	A: Narrow band imaging cystoscopy and TURBT (n=76) B: White light cystoscopy and TURBT (n=72) Additional treatments not reported	Duration: 1 year Method: White light cystoscopy	Age (mean): 71 vs. 72 years Male: 16% vs. 24% Stage: 76% vs. 72% Ta or CIS, 24% vs. 28% T1 Grade: 51% vs. 57% low, 49% vs. 43% high (including CIS)
O'Brien, 2013[255]	UK Single center 2005-2010	A: HAL fluorescent cystoscopy with TURBT (n=86) B: White light cystoscopy with TURBT (n=82) All patients received single shot intravesical MMC, BCG for grade tumors or CIS	Duration: 12 months Method: not reported	Age (mean): 68 vs. 68 years Male: 74% vs. 73% Stage and grade: 57% vs. 50% G1pTa or G2 (low grade) pTa/pT1; 17% vs. 13% G2 (high grade) pTa or G3pTa; 25% vs. 36% G2 (high grade) pTa or G3pT1; 14% vs. 26% secondary CIS
Riedl, 2001[256] (also Daniltchenko, 2005[242])	Germany Multicenter 1998-2000	A: 5-ALA fluorescent cystoscopy with TURBT (n=51) B: White light cystoscopy with TURBT (n=51) MMC for pTa and pT1G1-2, BCG for pT1G3, CIS, and failed MMC	Duration: 60 months (median 42 vs. 39 months) Method: ALA fluorescent cystoscopy at 6 weeks	Age (mean): 70 vs. 67 years Male: 71% vs. 73% Stage: 78% vs. 78% Ta, 22% vs. 22% T1 Grade: 18% vs. 14% G1, 69% vs. 76% G2, 14% vs. 9.8% G3

Table 19. Fluorescent cystoscopy study characteristics (continued)

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Cystoscopic Followup Method	Population Characteristics by Treatment Group (age, race/ethnicity, sex, stage of disease, functional status)
Schumacher, 2010[257]	Sweden Multicenter 2002-2005	A: White light and 5-ALA fluorescent cystoscopy with TURBT (n=141) B: White light cystoscopy with TURBT (n=138)Patients received BCG for CIS, pTaG3, and pT1G2-3 starting 4 weeks after TURBT	Duration: 12 months Method: White light cystoscopy	Age (mean): 70 vs. 69 years Male: 73% vs. 75% Stage and grade: 0.7% vs. 4.3% CIS, 55% vs. 48% pTaG1-2, 12% vs. 10% pTaG3 or pT1G1-2, 4.3% vs. 5.1% pT1G3, 0.7% vs. 3.6% pT2
Stenzl, 2010[258] (also Grossman 2012[249])	USA, Canada, and Europe Multicenter Study years not reported	A: White light cystoscopy following instillation of HAL, followed by second randomization: a: Fluorescent cystoscopy and TURBT (n=271) b: TURBT without fluorescent cystoscopy (excluded from recurrence analysis, n unclear) B: White light cystoscopy and TURBT (n=280) Intravesical BCG for high grade T1 or CIS	Duration: 9 months, additional followup to median of 53-55 months Method: White light cystoscopy	Age (mean): 68 vs. 70 years Male: 78% vs. 79% Stage: 72% vs. not reported Ta, 17% vs. not reported T1, 11% vs. not reported CIS Grade: Not reported
Stenzl, 2011[259]	Italy Multicenter 2009-2010	A: White light and fluorescent cystoscopy with TURBT following instillation of 5-ALA (n=183) B: White light and fluorescent cystoscopy with TURBT following instillation of placebo (n=176) CIS, pTaG3, or pT1G2-3 received BCG 4 weeks after TURBT	Duration: 12 months Method: White light cystoscopy	Age (mean): 66 years (overall) Male: 72% (overall) Stage and grade: 33% vs. 28% pTaG1, 19% vs. 20% pTaG2, 1.1% vs. 0% pTaG3, 1.1% vs. 0.6% pT1G1, 8.7% vs. 8.5% pT1G2, 10% vs. 31% pT1G3, 5.5% vs. 4.5% pT2, 1.6% vs. 1.7% isolated CIS

5-ALA = 5-aminolevulinic acid; AUA = American Urological Association; BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; G1 = Grade 1; G2 = Grade 2; G3 = Grade 3; HAL = hexaminolevulinate; MMC = Mitomycin C; pT1 = Tumor stage 1 determined by pathology; pTa = Tumor stage a determined by pathology; T1 = Tumor stage 1; Ta = Tumor stage a; TURBT = transurethral resection of the bladder tumor

Table 20. Fluorescent cystoscopy results summary

Type	Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
5-ALA fluorescent cystoscopy	Babjuk, 2005[241]	A: White light and 5-ALA fluorescent cystoscopy with TURBT (n=60) B: White light cystoscopy with TURBT (n=62)	Short-term: 8.3% (5/60) vs. 37% (23/62) Long-term: 60% (36/60) vs. 73% (45/62)	8.3% (5/60) vs. 8.1% (5/62)	Not reported
	Filbeck, 2002[246] (also Denzinger 2007a, Denzinger 2007b)	A: White light and 5-ALA fluorescent cystoscopy with TURBT (n=88) B: White light cystoscopy with TURBT (n=103) Progression analysis restricted to patients with T1 high grade lesions on initial cystoscopy	Long-term: 20% (18/88) vs. 42% (43/103)	19% (4/21) vs. 12% (3/25)	Not reported
	Kriegmair, 2002[252]	A: White light and 5-ALA fluorescent cystoscopy with TURBT (n=52) B: White light cystoscopy with TURBT (n=49)	Short-term: 52% (27/52) vs. 54% (26/49)	Not reported	Not reported
	Riedl, 2001[256] (also Daniltchenko, 2005[242])	A: 5-ALA fluorescent cystoscopy with TURBT (n=51) B: White light cystoscopy with TURBT (n=51)	Short-term: 20% (10/51) vs. 47% (24/51) Intermediate term: 29% (15/51) vs. 53% (27/51) Long-term: 59% (30/51) vs. 75% (38/51)	7.8% (4/51) vs. 18% (9/51)	Not reported
	Schumacher, 2010[257]	A: White light and 5-ALA fluorescent cystoscopy with TURBT (n=141) B: White light cystoscopy with TURBT (n=138)	Long-term: 45% (63/141) vs. 44% (61/138)	9.2% (13/141) vs. 11% (15/138)	3.5% (5/141) vs. 2.9% (4/138)
	Stenzl, 2011[259]	A: White light and fluorescent cystoscopy with TURBT following instillation of 5-ALA (n=183) B: White light and fluorescent cystoscopy with TURBT following instillation of placebo (n=176)	Short-term: 65% (24/37) vs. 47% (17/36) Long-term: 31% (57/183) vs. 26% (45/176)	7.7% (14/183) vs. 8.5% (15/176)	Not reported

Table 20. Fluorescent cystoscopy results summary (continued)

Type	Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
HAL fluorescent cystoscopy	Dragoescu, 2011[245]	A: White light and HAL fluorescent cystoscopy with TURBT (n=22) B: White light cystoscopy with TURBT (n=22)	Short-term: 4.5% (1/22) vs. 14% (3/22) Intermediate-term: 9.1% (2/22) vs. 23% (5/22) Long-term: 18% (4/22) vs. 45% (10/22)	4.5% (1/22) vs. 9.1% (2/22)	Not reported
	Geavlete, 2010[247]	A: White light and HAL fluorescent cystoscopy with TURBT (n=223) B: White light cystoscopy (n=223)	Short-term: 11% (8/72) vs. 31% (20/64)	Not reported	Not reported
	Geavlete, 2011[248]	A: White light and HAL fluorescent cystoscopy with TURBT (n=125) B: White light cystoscopy and TURBT (n=114)	Short-term: 7.2% (9/125) vs. 16% (18/114) Intermediate term: 12% (15/125) vs. 22% (25/114) Long-term: 31% (39/125) vs. 46% (52/114)	2.4% (3/125) vs. 4.4% (5/114) at 1 year, 4% (5/125) vs. 7% (8/114) at 2 years	Not reported
	Hermann, 2011[250]	A: White light and HAL fluorescent cystoscopy with TURBT (n=59) B: White light cystoscopy (n=74)	Intermediate-term: 17% (10/59) vs. 31% (23/74) Long-term: 31% (18/59) vs. 47% (35/74)	Not reported	Not reported
	Karaolides, 2012[251]	A: White light and HAL fluorescent cystoscopy with TURBT (n=41) B: White light cystoscopy with TURBT (n-45)	Short-term: 2.4% (1/41) vs. 13% (6/45) Long-term: 17% (7/41) vs. 40% (18/45)	0% (0/41) vs. 4.4% (2/45)	Not reported
	O'Brien, 2013[255]	A: HAL fluorescent cystoscopy with TURBT (n=86) B: White light cystoscopy with TURBT (n=82)	Short-term: 20% (17/86) vs. 17% (14/82) Long-term: 31% (27/86) vs. 35% (29/82)	Not reported	5.4% (7/129) vs. 0.8% (1/120)

Table 20. Fluorescent cystoscopy results summary (continued)

Type	Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
	Stenzl, 2010[258] (also Grossman 2012[249]) US, Canada, and Europe	A: White light cystoscopy following instillation of HAL, followed by second randomization: a: Fluorescent cystoscopy and TURBT (n=271) b: TURBT without fluorescent cystoscopy (excluded from recurrence analysis, n unclear) B: White light cystoscopy and TURBT (n=280)	Intermediate-term: 47% (128/271) vs. 56% (157/280) Long-term: 38% (97/255) vs. 32% (83/261)	1.8% (5/271) vs. 2.5% (7/280)	Mortality: 1.4% (5/365) vs. 1.4% (5/361) at 9 months, 14% (39/271) vs. 16% (44/280) at median 53 to 55 months Bladder cancer mortality: 2.2% (6/271) vs. 2.9% (8/280)

5-ALA = 5-aminolevulinic acid; AUA = American Urological Association; BCG = bacillus Calmette Guérin; CI = confidence interval; CIS = carcinoma in situ; G1 = Grade 1; G2 = Grade 2; G3 = Grade 3; HAL = hexaminolevulinate; HR = hazard ratio; ITT = intention to treat; MMC = Mitomycin C; OR = odds ratio; pTa = Tumor stage a determined by pathology; T1 = Tumor stage 1; Ta = Tumor stage a; TURBT = transurethral resection of the bladder tumor

Discussion

Key Findings and Strength of Evidence

The key findings of this review are summarized in the summary of evidence table (Table 21) and the factors used to determine the overall strength of evidence grades are summarized in Appendix G.

Urinary biomarkers were associated with sensitivity for bladder cancer that ranged from 0.57 to 0.82 and specificity that ranged from 0.74 to 0.88, for positive likelihood ratios that ranged from 2.52 to 5.53 and negative likelihood ratios that ranged from 0.21 to 0.48. Findings were robust in sensitivity and stratified analyses., Evidence was strongest for quantitative NMP22, qualitative bladder tumor antigen (BTA), fluorescence in situ hybridization (FISH), and ImmunoCyt (strength of evidence [SOE]: moderate), and relatively sparse for other biomarkers (SOE: low). Across urinary biomarkers, sensitivity was greater for higher stage and higher grade tumors (SOE: high). For qualitative BTA, FISH, and ImmunoCyt sensitivity was somewhat higher for evaluation of patients with signs or symptoms of bladder cancer than for surveillance of patients previously treated for bladder cancer, but for quantitative nuclear matrix protein 22 (NMP22) there was no clear difference in diagnostic accuracy based on reason for obtaining the biomarker. Studies that directly compared the accuracy of quantitative NMP22 and qualitative BTA found no differences in diagnostic accuracy (SOE: moderate). ImmunoCyt was associated with higher sensitivity than FISH (0.71, 95% CI 0.54 to 0.84 vs. 0.61, 95% CI 0.43 to 0.76, for a difference of 0.11, 95% CI 0.001 to 0.21) but lower specificity (0.71, 95% CI 0.62 to 0.79 vs. 0.79, 95% CI 0.71 to 0.85, for a difference of -0.08, 95% CI -0.15 to -0.001), based on three studies (SOE: low). There were too few head-to-head comparisons of other urinary biomarkers to reach firm conclusions regarding comparative accuracy. Sensitivity was increased when urinary biomarkers were used in conjunction with urine cytology than when the biomarker was used alone (SOE: moderate). No study evaluated clinical outcomes associated with use of urinary biomarkers for diagnosis or surveillance of bladder cancer (SOE: insufficient). Urinary biomarkers miss 18 to 43 percent of patients with bladder cancer and are incorrectly positive in 12 to 26 percent of patients without bladder cancer, which could result in delayed diagnosis or unnecessary cystoscopies and other diagnostic procedures, but no study directly measured effects of inaccurate diagnosis on clinical outcomes (SOE: insufficient). Most trials found fluorescent cystoscopy associated with decreased risk of subsequent bladder recurrence versus white light cystoscopy, but there was no difference in risk of progression or mortality, though data for these outcomes was relatively sparse (SOE: low). In addition, evidence on effects on risk of recurrence were inconsistent, and the only trial[259] designed to minimize performance bias (by blinding the cystoscopist to instillation of photosensitizer versus placebo) found no different in risk of bladder cancer recurrence.

Intravesical therapy was effective for reducing risk of bladder cancer recurrence versus no intravesical therapy (Tables 19, 20). Versus no intravesical therapy, bacillus Calmette Guérin (BCG) was associated with decreased risk of bladder cancer recurrence (RR 0.63, 95% CI 0.50 to 0.79) as well as progression (RR 0.50, 95% CI 0.32 to 0.77) (SOE: moderate). mitomycin C (MMC), doxorubicin, and epirubicin were also associated with decreased risk of bladder cancer recurrence versus no intravesical therapy (RR 0.66 to 0.80) but effects on bladder cancer progression were not statistically significant (MMC and epirubicin) or showed no effect (doxorubicin). Although trials varied with respect to doses, instillation regimens, and patient populations evaluated, findings were generally robust in sensitivity and subgroup analyses,

including exclusion of single dose instillation trials. No intravesical agent, including BCG, was associated with decreased risk of all-cause or bladder cancer specific mortality versus no intravesical therapy. However, evidence on the effectiveness of "optimized" MMC regimens on mortality was limited. Evidence on gemcitabine, interferon alpha, and thiotepa was sparse, and we found no randomized trials of valrubicin, paclitaxel, or apaziquone.

Head-to-head trials of intravesical therapy using different drugs showed few clear differences. For BCG versus MMC, the most well-studied comparison, there was no difference on any outcome, including bladder cancer recurrence, progression, or mortality (SOE: moderate). However, BCG was associated with decreased risk of bladder cancer recurrence in the subgroup of trials that evaluated maintenance regimens (SOE: low). Other head-to-head comparisons were evaluated in fewer trials, and showed few differences, though limited evidence suggested that BCG might be associated with decreased risk of bladder cancer recurrence and progression versus epirubicin (SOE: low). Although doxorubicin was associated with increased risk of bladder cancer recurrence versus epirubicin (RR 1.56, 95% CI 1.08 to 2.22), this finding was based on only three trials (SOE: low).[119,195,196]

Evidence to determine the effects of tumor characteristics on estimates of effectiveness of intravesical therapies was limited, but indicated no differences in risk estimates based on factors such as tumor stage, grade, multiplicity, recurrence status, and size (SOE: low). However, even if relative estimates of effectiveness are similar, absolute effects will vary depending on the underlying incidence of recurrence, progression, mortality, or other outcomes. Therefore, patients with higher stage, higher grade, multiple, recurrent, or larger tumors would be expected to experience greater absolute benefits. Evidence to determine the effects of patient characteristics such as age, sex, race/ethnicity, performance status, or comorbidities on estimates of effectiveness of intravesical therapies was not available, and evidence on comparative effectiveness of therapies for patients with recurrence or progression following treatment with BCG was limited to two small trials comparing different intravesical therapies.[184,194]

Trials that compared effects of intravesical therapy using different doses or instillation regimens for the same agent were difficult to interpret due to variability in the patient populations, doses, instillation regimens, and other factors. For BCG, there were no clear difference between standard and lower doses of BCG in risk of bladder cancer recurrence, progression, or mortality, including in patients with higher-risk non–muscle-invasive bladder cancer (NMIBC), but there was some inconsistency between trials (SOE: low). Limited evidence suggested that BCG maintenance regimens (>6 weeks) are more effective than induction regimens (≤6 weeks) at reducing risk of bladder cancer recurrence in responders to induction therapy or in patients with higher risk tumors (SOE: low). Head-to-head trials suggest that BCG TICE may be less effective than other BCG strains at reducing risk of recurrence, with no clear difference between non-TICE strains (SOE: low). Trials on the effects of dose and duration of other intravesical agents on outcomes reported inconsistent results and were clinically heterogeneous, making it difficult to draw strong conclusions (SOE: insufficient to low). However, there was no evidence that prolonging therapy for more than one year is more effective than shorter regimens.

Evidence on harms associated with intravesical therapies was more limited than evidence on benefits. Trials of BCG versus no intravesical therapy found that local and systemic adverse events were relatively common (granulomatous cystitis or irritative symptoms in 27% to 84% of patients, macroscopic hematuria in 21% to 72%, and fever in 27% to 44%) (SOE: low). BCG was also associated with an increased risk of local adverse events and fever versus MMC (SOE:

low). Standard dose BCG was associated with increased risk of local and systemic adverse events versus lower dose BCG. Few trials reported harms of intravesical agents other than BCG versus no intravesical therapy, or against another intravesical agent.

The only randomized trial of radiation therapy found no effects on recurrence, progression, or survival in patients with T1G3 cancers when compared against no radiotherapy (for unifocal cancers and no CIS) or against intravesical therapy (for multifocal disease or CIS) (SOE: low).[239]

Findings in Relationship to What Is Already Known

Our findings on diagnostic accuracy were generally consistent with prior systematic reviews that found urinary biomarkers insufficiently accurate to replace cystoscopy.[263-265] Estimates for sensitivity and specificity were generally similar in our review and prior reviews, even though we excluded case-control studies and included more recently published studies. In addition, prior reviews did not evaluate potential differences in diagnostic accuracy for testing performed for evaluation of signs and symptoms of bladder cancer versus for surveillance.

Prior systematic reviews[266,267] found fluorescent cystoscopy associated with decreased risk of recurrent bladder cancer versus white light cystoscopy, but were published prior to a recent trial that was the only one to blind the cystoscopist to instillation of the photosensitizer and found no effect.[259] Like our report, prior reviews found no effect of fluorescent cystoscopy on risk of progression or mortality. Although prior reviews also found that fluorescent cystoscopy detected more bladder cancers on initial cystoscopy, this was not an assessed outcome for our review.

Our findings regarding the comparative effectiveness and harms of intravesical therapies are generally consistent with prior reviews that found intravesical therapy associated decreased risk of bladder cancer recurrence versus no intravesical therapy,[268,269] and BCG associated with decreased risk of bladder cancer progression. Prior systematic reviews that focused on immediate single instillation therapy also found intravesical therapy to be more effective than no intravesical therapy in reducing risk of bladder cancer recurrence, a conclusion consistent with our finding of no clear difference in risk estimates based on the type of instillation regimen.[270-272] Like our review, prior systematic reviews found maintenance therapy with BCG associated with decreased risk of bladder cancer versus MMC, despite some differences in the trials that were included, definitions of maintenance therapy, and use of individual patient data in the prior review.[273] Our findings are also consistent with prior systematic reviews that found BCG associated with decreased risk of bladder cancer versus epirubicin,[274] that the evidence on intravesical gemcitabine is limited,[275] and that the optimal dose and duration of intravesical therapy cannot be determined based on the available evidence.[276]

Applicability

Some issues could impact the applicability of our findings. Some studies of diagnostic accuracy did not report results separately for patients undergoing evaluation of signs and symptoms of bladder cancer and those undergoing surveillance, though there is some evidence that diagnostic accuracy may vary based on the indication for testing. Studies of intravesical therapy varied in the doses used, the timing, number, frequency, and duration or instillations, and other factors (e.g., the BCG strain), making it difficult to reach conclusions that are widely generalizable. In addition, trials varied with regard to tumor characteristics in the patient populations evaluated. Another factor that potentially impacts applicability is that most studies focused on effects of intravesical therapy on recurrence of bladder cancer. Fewer trials evaluated more potentially serious, distal outcomes such as progression or mortality. A number of studies

were conducted in Japan, where management of bladder cancer may differ from the U.S. Treatment studies tended to exclude patients with significant comorbidities or poor general performance status, which could limit applicability to these populations. Very little information was available to determine whether diagnostic accuracy or treatment effects vary according to patient factors such as age, sex, race/ethnicity, performance status, or comorbidities.

Implications for Clinical and Policy Decisionmaking

Our review has implications for clinical and policy decisionmaking. As there are no studies evaluating effects of using urinary biomarkers for diagnosis or surveillance of bladder cancer on clinical outcomes, decisions regarding their use must necessarily be made on the basis of diagnostic test performance. Table 22 shows estimated probabilities for bladder cancer following use of urinary biomarkers, based on likelihood ratios calculated from pooled sensitivities and specificities. In populations with a pretest probability of 5 percent, the post-test probability increased to 16 to 24 percent following a positive result, and decreased to 1.8 to 2.5 percent following a negative result. In settings with a pretest probability of 20 percent, the post-test probability increased to 37 to 60 percent following a positive results, and decreased to 8.0 to 11 percent following a negative result. Whether urinary biomarkers are sufficiently accurate to rule out bladder cancer and thereby reduce the need for cystoscopy depends on the ability of clinicians to estimate the pretest probability of disease and the acceptable threshold for a missed or delayed diagnosis. Use of urinary biomarkers in combination with urinary cytology increases the sensitivity for bladder cancer, but still misses about 10 percent of cases.

Regarding fluorescent cystoscopy, studies have not shown an effect on progression or mortality and trials that found reduced risk of recurrence may have been affected by performance bias. These findings might inform decisions regarding widespread adoption of fluorescent cystoscopy. Cost may also impact decisions to use fluorescent cystoscopy and urinary biomarkers, but was outside the scope of this report.

Our findings also have implications for use of intravesical therapy. Although intravesical therapy was associated with decreased risk of bladder cancer recurrence, there were no clear effects on bladder cancer-specific or all-cause mortality, and intravesical therapies are associated with local and systemic adverse events. Our findings are consistent with guidelines that recommend BCG as first-line therapy,[13,277] as no intravesical agent was more effective than BCG at reducing risk of bladder cancer recurrence, BCG is the only intravesical agent associated with decreased risk of bladder cancer progression versus no intravesical therapy, and some evidence indicates that BCG is associated with decreased risk of bladder cancer recurrence versus other intravesical agents. However, BCG is also associated with a high risk of adverse events. Some evidence indicates that using lower than standard doses of BCG maintains effectiveness while reducing harms. Other evidence suggests that longer courses of therapy may be necessary for optimal effects, particularly in higher risk patients. Therefore, decisions to use intravesical therapy and regarding the intravesical agent, doses, and regimen selected should take into account the trade-offs between potential benefits, which are likely to be higher in patients at higher risk for disease progression, and harms.

Limitations of the Review Process

Substantial statistical heterogeneity was present in most pooled analyses of diagnostic accuracy; this situation is common in meta-analyses of diagnostic accuracy.[278-280] As noted in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy, “heterogeneity is to

be expected in meta-analyses of diagnostic test accuracy."[280] To address the anticipated heterogeneity, we utilized random effects models to pool studies and stratified studies according to the reason that imaging was performed and the unit of analysis used. We also performed additional stratified and sensitivity analyses based on the reference standard used, study characteristics (such as country in which the study was conducted, factors related to risk of bias), patient characteristics, and technical factors related to the imaging tests under investigation. As noted previously, results were generally robust in sensitivity analyses, despite the heterogeneity. We also focused on evaluations of comparative test performance based on within-study comparisons of imaging modalities, which tended to be associated with less heterogeneity than pooled across-study estimates. A limitation of our analysis of within-group comparisons is that we had to treat the two compared groups as independent, because we had only aggregated data. Individual patient level data would be required to take into account the paired nature of the comparisons. Such correlations are generally positive and would be expected to result in more narrow confidence intervals. Although it is possible that this could have caused us to not detect statistically significant differences, the point estimates indicated very little difference between tests.

We did not construct summary receiver operating characteristic curves. Almost all studies of a specific urinary biomarker used the same definition for a positive test, including tests based on a quantitative threshold. Estimates of sensitivity and specificity at different thresholds are needed to construct informative ROC curves.[25]

Statistical heterogeneity was also present in some analyses of intravesical therapies and fluorescent cystoscopy. To address this, we used the Dersimonian-Laird random effects model to pool studies. The Dersimonian-Laird random effects model may result in confidence intervals that are too narrow when heterogeneity is present, particularly when the number of studies is small.[29] Therefore, we repeated analyses using the profile likelihood method, which resulted in similar findings. Regardless of the method used, meta-analyses based on small numbers of trials can underestimate statistical heterogeneity and must be interpreted with caution.[29] We also stratified trials according to factors such as risk of bias rating, dose, number of instillations, duration of followup, enrollment of patients with high-risk NMIBC, and other factors. Although statistical heterogeneity remained present in some analyses, with some unexplained outlier trials, results were generally robust.

We excluded non-English language articles and did not search for studies published only as abstracts. Because of small numbers of trials for meta-analyses involving intravesical therapies, we did not formally assess for publication bias using statistical or graphical methods for assessing sample size effects because of small numbers of studies, as research indicates that such methods can be seriously misleading in such situations.[281,282] For fluorescent cystoscopy, we found one relatively large trial that showed no effect on risk of recurrence versus white light cystoscopy, suggesting that publication bias could have impacted results.[260]

Limitations of the Evidence Base

Several limitations of the evidence base limited our ability to reach strong conclusions with regard to several aspects of diagnosis and treatment of NMIBC. Other than quantitative NMP22, qualitative BTA, FISH, and ImmunoCyt, urinary biomarkers were assessed in small numbers of studies , resulting in less precise estimates. In addition, almost all studies on diagnostic accuracy of biomarkers had methodological shortcomings. In some studies of urinary biomarkers, patients with positive markers and normal cystoscopy were considered to be positive without biopsy,

which could result in verification bias and overestimation of diagnostic accuracy. In addition, most of the evidence on comparative accuracy was indirect, as relatively few studies directly compared the accuracy of two or more biomarkers against cystoscopy and histopathology.

For fluorescent cystoscopy, a limitation of the evidence base is that few trials reported effects on progression or mortality, and instead mostly focused on evaluating effects on recurrence. In addition, only one trial of fluorescent cystoscopy blinded the cystoscopist to whether the photosensitizer had been instilled, which may have a greater impact on assessments of recurrence due to performance bias related to knowledge of the type of initial cystoscopy performed.

A limitation of the evidence for all Key Questions addressed in our review is that very few trials were assessed as low risk of bias. Methodological shortcomings included failure to adequately describe randomization and allocation concealment methods and unblended design. Findings would be stronger if more high-quality trials were available.

Other limitations include the lack of evidence on how use of urinary biomarkers impacts clinical outcomes (including harms), a single randomized trial on effects of radiation therapy for NMIBC, no trials on effects of using a risk-adapted approach, and no studies on effects of how using different surveillance intervals impacts outcomes. Few studies evaluated effects of patient characteristics such as age, sex, race/ethnicity, performance status, or comorbidities on diagnostic test performance or effectiveness of intravesical therapy.

Research Gaps

We identified a number of important research gaps. Given the increased sensitivity of urinary biomarkers with cytology, studies on how this combination impacts use of cystoscopy and subsequent clinical outcomes might be helpful for determining its role in diagnosis or surveillance and in followup of patients with abnormal cystoscopy or atypical cytology. Randomized trials that adequately safeguard against performance bias associated with use of photosensitizers for fluorescent cystoscopy are needed to determine effects on recurrence, progression, and mortality. Additional head-to-head trials of intravesical therapies that use more standardized instillation regimens and doses, “optimized” instillation of MMC, report outcomes in subgroups stratified by patient and tumor characteristics, include long-term outcomes related to progression and mortality, and assess and report harms using more standardized methods would help clarify optimal treatment strategies. Studies to determine optimal strategies for management of patients with recurrence or progression after standard intravesical therapy are needed. Research is also needed on determine the effectiveness of risk-adapted approaches to guide selection of therapy, including use of nontraditional prognostic markers, effects of different surveillance intervals and protocols, and newer techniques such as electromotive administration of intravesical therapy.

Table 21. Summary of the strength of evidence

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
Key Question 1. What is the diagnostic accuracy of various urinary biomarkers compared with other urinary biomarkers or standard diagnostic methods (cystoscopy, cytology, and imaging) in 1) people with signs or symptoms warranting evaluation for possible bladder cancer or 2) people undergoing surveillance for previously treated bladder cancer?	Quantitative NMP22: sensitivity and specificity	Moderate	Sensitivity was 0.69 (95% CI, 0.62 to 0.75) and specificity 0.77 (95% CI, 0.70 to 0.83), based on 19 studies, for a positive likelihood ratio of 3.05 (95% CI, 2.28 to 4.10) and negative likelihood ratio of 0.40 (95% CI, 0.32 to 0.50).
	Qualitative NMP22: sensitivity and specificity	Low	Sensitivity was 0.58 (95% CI, 0.39 to 0.75) and specificity 0.88 (95% CI, 0.78 to 0.94), based on 4 studies, for a positive likelihood ratio of 4.89 (95% CI, 3.23 to 7.40) and negative likelihood ratio of 0.48 (95% CI, 0.33 to 0.71).
	Qualitative BTA: sensitivity and specificity	Moderate	Sensitivity was 0.64 (95% CI, 0.58 to 0.69; 22 studies) and specificity 0.77 (95% CI, 0.73 to 0.81; 21 studies), for a positive likelihood ratio of 2.80 (95% CI, 2.31 to 3.39) and negative likelihood ratio of 0.47 (95% CI, 0.30 to 0.55).
	Quantitative BTA: sensitivity and specificity	Low	Sensitivity was 0.65 (95% CI, 0.54 to 0.75) and specificity 0.74 (95% CI, 0.64 to 0.82), based on 4 studies, for a positive likelihood ratio of 2.52 (95% CI, 1.86 to 3.41) and negative likelihood ratio of 0.47 (95% CI, 0.37 to 0.61).
	FISH: sensitivity and specificity	Moderate	Sensitivity was 0.63 (95% CI, 0.50 to 0.75) and specificity 0.87 (95% CI, 0.79 to 0.93), based on 11 studies, for a positive likelihood ratio of 5.02 (95% CI, 2.93 to 8.60) and negative likelihood ratio of 0.42 (95% CI, 0.30 to 0.59).
	ImmunoCyt™: sensitivity and specificity	Moderate	Sensitivity was 0.78 (95% CI, 0.68 to 0.85) and specificity 0.78 (95% CI, 0.72 to 0.82), based on 14 studies, for a positive likelihood ratio of 3.49 (95% CI, 2.82 to 4.32) and negative likelihood ratio of 0.29 (95% CI, 0.20 to 0.41).
	CxBladder™: sensitivity and specificity	Low	Sensitivity was 0.82 (95% CI, 0.70 to 0.90) and specificity 0.85 (95% CI, 0.81 to 0.88) for evaluation of symptoms, based on 1 study, for a positive likelihood ratio of 5.53 (95% CI, 4.28 to 7.15) and negative likelihood ratio of 0.21 (95% CI, 0.13 to 0.36).

Table 21. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	Quantitative NMP22 versus qualitative BTA: sensitivity and specificity	Moderate	Based on 7 studies, there was no difference between quantitative NMP22 (cutoff >10 U/mL) and qualitative BTA in sensitivity (0.69; 95% CI, 0.62 to 0.76 vs. 0.66; 95% CI, 0.59 to 0.73, for a difference of 0.03; 95% CI, -0.04 to 0.10) or specificity (0.73; 95% CI, 0.62 to 0.82 vs. 0.76; 95% CI, 0.66 to 0.84, for a difference of 0.03; 95% CI, -0.08 to 0.01).
	ImmunoCyt versus FISH: sensitivity vs. specificity	Low	ImmunoCyt was associated with higher sensitivity than FISH (0.71; 95% CI, 0.54 to 0.84 vs. 0.61; 95% CI, 0.43 to 0.76, for a difference of 0.11; 95% CI, 0.001 to 0.21) but lower specificity (0.71; 95% CI, 0.62 to 0.79 vs. 0.79; 95% CI, 0.71 to 0.85, for a difference of -0.08; 95% CI, -0.15 to -0.001), based on 3 studies.
	Other head-to-head comparisons of urinary biomarkers	Insufficient	Evidence for other head-to-head comparisons of urinary biomarkers was based on small numbers of studies with imprecise estimates and methodological shortcomings, precluding reliable conclusions regarding comparative test performance.
	Various urinary biomarkers plus cytology vs. the urinary biomarker alone: sensitivity and specificity	Moderate	Sixteen studies found various urinary biomarkers plus cytology to be associated with higher sensitivity than the urinary biomarker alone (0.81; 95% CI, 0.75 to 0.86 vs. 0.69; 95% CI, 0.61 to 0.76, for a difference of 0.13; 95% CI, 0.08 to 0.17), with no difference in specificity.
Key Question 1a. Does the diagnostic accuracy differ according to patient characteristics (e.g., age, sex, race/ethnicity), or according to the nature of the presenting signs or symptoms?	Effects of tumor stage: sensitivity	High	Across urinary biomarkers, sensitivity increased with higher tumor stage. Evidence was most robust for quantitative NMP22 (11 studies), qualitative BTA (18 studies), and FISH (8 studies); the association between higher tumor stage and increased sensitivity was least pronounced for ImmunoCyt (10 studies). Sensitivity was generally similar to or slightly lower for CIS tumors than for T1 tumors.

Table 21. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	Effects of tumor grade: sensitivity	High	Across urinary biomarkers, sensitivity increased with higher tumor grade. Evidence was most robust for quantitative NMP22 (12 studies), ImmunoCyt (10 studies), qualitative BTA (18 studies), and FISH (9 studies).
	Effects of tumor size: sensitivity	Low	Two studies found that sensitivity was higher for larger (>1 cm or >2 cm) vs. smaller tumors.
	Effects of patient characteristics (age, sex, smoking status, and presence of other clinical conditions): sensitivity and specificity	Low	Evidence on the effects of patient characteristics, such as age, sex, smoking status, and presence of other clinical conditions, on diagnostic accuracy of urinary biomarkers was limited but did not clearly or consistently indicate effects on sensitivity or specificity.
Key Question 2. For patients with non–muscle-invasive bladder cancer, does the use of a formal risk-adapted assessment approach to treatment decisions (e.g., Guidelines of the European Association of Urology or based on urinary biomarker tests) decrease mortality or improve other outcomes (e.g., recurrence, progression, need for cystectomy, quality of life) compared with treatment not guided by a formal assessed risk-adapted approach?	Mortality, recurrence, progression, need for cystectomy, quality of life	Insufficient	No studies.
Key Question 3. For patients with non–muscle-invasive bladder cancer treated with transurethral resection of bladder tumor (TURBT), what is the effectiveness of various intravesical chemotherapeutic or immunotherapeutic agents for decreasing mortality or improving other outcomes (e.g., recurrence, progression, need for cystectomy, quality of life) compared with TURBT alone?	*BCG vs. no intravesical therapy* : All-cause mortality	Insufficient	No trial evaluated effects of BCG vs. no intravesical therapy on risk of all-cause mortality..
	BCG vs. no intravesical therapy: Bladder cancer specific mortality	Insufficient	One trial found BCG to be associated with decreased risk of bladder cancer specific mortality vs. no intravesical therapy, but the difference was not statistically significant (RR, 0.62; 95% CI, 0.32 to 1.19).
	BCG vs. no intravesical therapy: Recurrence	Low	BCG was associated with decreased risk of bladder cancer recurrence vs. no intravesical therapy (3 trials; RR, 0.56; 95% CI, 0.43 to 0.71; $I^2 = 0\%$).
	BCG vs. no intravesical therapy: Progression	Low	BCG was associated with decreased risk of bladder cancer progression (4 trials; RR, 0.39; 95% CI, 0.24 to 0.64; $I^2 = 40\%$) vs. no intravesical therapy

Table 21. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	MMC vs. no intravesical therapy : All-cause mortality	Low	There was no difference in risk of all cause-mortality for MMC vs. no intravesical therapy (1 trial; HR, 1.17; 95% CI, 0.89 to 1.53).
	MMC vs. no intravesical therapy : Bladder cancer specific mortality	Low	The effects on bladder cancer specific mortality were not statistically significant for MMC vs. no intravesical therapy (1 trial; HR, 0.71; 95% CI, 0.34 to 1.46).
	MMC vs. no intravesical therapy : Recurrence	Moderate	MMC was associated with decreased risk of bladder cancer recurrence vs. no intravesical therapy (8 trials; RR, 0.71; 95% CI, 0.57 to 0.89; $I^2 = 72\%$).
	MMC vs. no intravesical therapy : Progression	Low	Effects of MMC on bladder cancer progression were not statistically significant (5 trials; RR, 0.68; 95% CI, 0.39 to 1.20; $I^2 = 0\%$) vs. no intravesical therapy.
	Doxorubicin vs. no intravesical therapy : All-cause mortality	Low	Doxorubicin was associated with no clear effects on all-cause mortality (2 trials) vs. no intravesical therapy.
	Doxorubicin vs. no intravesical therapy : Bladder cancer specific mortality	Low	Doxorubicin was associated with no clear effects on bladder cancer specific mortality (1 trial) vs. no intravesical therapy.
	Doxorubicin vs. no intravesical therapy : Recurrence	Moderate	Doxorubicin was associated with decreased risk of bladder cancer recurrence vs. no intravesical therapy (10 trials; RR, 0.80; 95% CI, 0.72 to 0.88; $I^2 = 46\%$).
	Doxorubicin vs. no intravesical therapy : Progression	Low	Doxorubicin was associated with no difference in risk of bladder cancer progression (5 trials; RR, 1.03; 95% CI, 0.72 to 1.46; $I^2 = 0.0\%$) vs. no intravesical therapy.
	Epirubicin vs. no intravesical therapy : Recurrence	Moderate	Epirubicin was associated with decreased risk of bladder cancer recurrence (9 trials; RR, 0.63; 95% CI, 0.53 to 0.75; $I^2 = 64\%$) vs. no intravesical therapy.
	Epirubicin vs. no intravesical therapy : Progression	Low	Epirubicin was associated with a non–statistically significant effect on bladder cancer progression (8 trials; RR, 0.79; 95% CI, 0.84 to 1.30; $I^2 = 27\%$).
	Gemcitabine vs. no intravesical therapy : All-cause mortality, bladder cancer specific mortality, progression	Insufficient	Estimates for progression (RR, 3.00; 95% CI, 0.32 to 28.4), all-cause mortality (RR, 0.50; 95% CI, 0.13 to 2.00), and bladder cancer specific mortality (RR, 1.00; 95% CI, 0.06 to 15.81) were very imprecise for gemcitabine vs. no intravesical therapy.

Table 21. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	Gemcitabine vs. no intravesical therapy : Recurrence	Low	One trial found no difference between single-instillation gemcitabine vs. no intravesical therapy in risk of bladder cancer recurrence (RR, 0.98; 95% CI, 0.70 to 1.36).
	Interferon alpha vs. no intravesical therapy : Bladder cancer specific mortality	Low	Interferon alpha was associated with no difference in risk of bladder cancer specific mortality (1 trial; RR, 1.00; 95% CI, 0.15 to 6.75).
	Interferon alpha vs. no intravesical therapy : Recurrence	Low	Interferon alpha was associated with a non–statistically significant reduction in risk for bladder cancer recurrence vs. no intravesical therapy (3 trials; RR, 0.75; 95% CI, 0.53 to 1.06; I^2 = 50%).
	Interferon alpha vs. no intravesical therapy : Progression	Low	Interferon alpha was associated with decreased risk of bladder cancer progression vs. no intravesical therapy (2 trials; RR, 0.33; 95% CI, 0.14 to 0.76; I^2 = 0%).
	Interferon gamma vs. no intravesical therapy : Recurrence	Low	Interferon gamma was associated with decreased risk of bladder cancer recurrence vs. no intravesical therapy (1 trial; RR, 0.72; 95% CI, 0.51 to 1.01).
	Interferon gamma vs. no intravesical therapy : Progression	Low	Interferon gamma was associated with no difference in risk of bladder cancer progression vs. no intravesical therapy (1 trial; RR, 1.08; 95% CI, 0.07 to 16.4).
	Thiotepa vs. no intravesical therapy : Recurrence	Low	Thiotepa was associated with decreased risk of bladder cancer recurrence vs. no intravesical therapy in 5 trials (RR, 0.78; 95% CI, 0.58 to 1.06; I^2 = 69%).
Key Question 3a. What is the comparative effectiveness of various chemotherapeutic or immunotherapeutic agents, as monotherapy or in combination?	*BCG vs. MMC*: All-cause mortality	Moderate	There was no difference in risk of all-cause mortality between BCG and MMC (7 trials; RR, 0.94; 95% CI, 0.83 to 1.06; I^2 = 0%).
	BCG vs. MMC: Bladder cancer specific mortality	Moderate	There was no difference between BCG and MMC in risk of bladder cancer specific mortality (5 trials; RR, 0.77; 95% CI, 0.54 to 1.10; I^2 = 0%).
	BCG vs. MMC: Recurrence	Low	There were no differences between BCG and MMC in risk of bladder cancer recurrence (10 trials; RR, 0.95; 95% CI, 0.81 to 1.11; I^2 = 67%).
	BCG vs. MMC: Progression	Moderate	There was no difference in risk of progression (7 trials; RR, 0.88; 95% CI, 0.66 to 1.17; I^2 = 18%).

Table 21. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	BCG alone vs. BCG plus MMC given sequentially: All-cause mortality, bladder cancer specific mortality, recurrence, progression	Low	There were no differences sequentially in risk of all-cause (1 trial; RR, 1.57; 95% CI, 0.67 to 3.71) or bladder cancer specific mortality (2 trials; RR, 1.10; 95% CI, 0.50 to 2.38; I^2 = 17%), bladder cancer recurrence (4 trials; RR, 1.03; 95% CI, 0.70 to 1.52; I^2 = 75%), progression (3 trials; RR, 0.87; 95% CI, 0.40 to 1.91; I^2 = 22%), or cystectomy (4 trials; RR, 0.87; 95% CI, 0.41 to 1.84; I^2 = 0%).
	BCG plus MMC given sequentially vs. MMC alone: All-cause mortality, bladder cancer specific mortality, recurrence, progression	Low	There were no differences in risk of all-cause (2 trials; RR, 1.53; 95% CI, 0.72 to 1.74 and RR, 0.95; 95% CI, 0.71 to 1.30) or bladder cancer mortality (2 trials; RR, 0.64; 95% CI, 0.22 to 1.88 and RR, 0.95; 95% CI, 0.45 to 1.56), bladder cancer recurrence (2 trials; RR, 0.88; 95% CI, 0.75 to 1.03; I^2 = 0%), or progression (2 trials; RR, 0.82; 95% CI, 0.40 to 1.68 and RR, 1.28; 95% CI, 0.35 to 4.61).
	BCG vs. doxorubicin: All-cause mortality, recurrence, progression	Low	BCG was associated with decreased risk of bladder cancer recurrence vs. doxorubicin (2 trials; RR, 0.31; 95% CI, 0.16 to 0.61 and RR, 0.75; 95% CI. 0.64 to 0.88), but there was no difference in risk of all-cause mortality (2 trials; RR, 0.40; 95% CI, 0.01 to 12 and RR, 1.00; 95% CI, 0.71 to 1.37) or bladder cancer progression (1 trial; RR, 0.20; 95% CI, 0.02 to 1.72).
	BCG vs. epirubicin: All-cause mortality	Low	Estimates favored BCG for all-cause mortality, but differences were not statistically significant (3 trials; RR, 0.72; 95% CI, 0.44 to 1.19; I^2 = 87%).
	BCG vs. epirubicin: Bladder cancer specific mortality	Low	Estimates favored BCG for bladder cancer specific mortality, but differences were not statistically significant (3 trials; RR, 0.72; 95% CI, 0.25 to 2.08; I^2 = 80%).
	BCG vs. epirubicin: Recurrence	Moderate	BCG was associated with reduced risk of bladder cancer recurrence, but statistical heterogeneity was high (5 trials; RR, 0.54; 95% CI, 0.40 to 0.74; I^2 = 76%).

Table 21. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	BCG vs. epirubicin: Progression	Low	Estimates favored BCG for bladder cancer progression, but differences were not statistically significant (5 trials; RR, 0.60; 95% CI, 0.36 to 1.01; I^2 = 47%).
	BCG alone vs. BCG plus epirubicin given sequentially: Recurrence, progression	Low	There were no differences in risk of bladder cancer recurrence (3 trials; RR, 1.25; 95% CI, 0.92 to 1.69; I^2 = 0%). BCG was associated with increased risk of bladder cancer progression, but the difference was not statistically significant (3 trials; RR, 1.92; 95% CI, 0.73 to 5.07; I^2 = 0%).
	BCG vs. epirubicin plus interferon: Bladder cancer specific mortality, progression	Low	One trial found no differences in risk of bladder cancer mortality (RR, 0.79;, 95% CI, 0.32 to 1.63) or progression-free survival, although BCG was associated with decreased risk of bladder cancer recurrence (RR, 0.66; 95% CI, 0.51 to 0.85).
	BCG vs. gemcitabine: All-cause mortality	Low	There were no differences in risk of all-cause mortality (1 trial; RR, 1.20; 95% CI, 0.04 to 34).
	BCG vs. gemcitabine: Recurrence	Insufficient	Evidence from 3 trials was insufficient to determine risk of bladder cancer recurrence because of clinical heterogeneity and inconsistent findings (RR, 1.67; 95% CI, 1.21 to 2.29; RR, 0.53; 95% CI, 0.28 to 1.01; and RR, 0.76; 95% CI, 0.44 to 1.90).
	BCG vs. gemcitabine: Progression	Low	There were no differences in risk of progression (2 trials; RR, 1.11; 95% CI, 0.53 to 2.34 and RR, 0.52; 95% CI, 0.13 to 2.06).
	BCG vs. gemcitabine: Quality of life	Low	There were no differences for BCG vs. gemcitabine in quality of life (1 trial).
	BCG alone vs. BCG plus gemcitabine given sequentially: Recurrence, progression	Low	There were no differences in risk of bladder cancer recurrence (1 trial; RR, 0.86; 95% CI, 0.49 to 1.51) or progression (1 trial; RR, 1.18; 95% CI, 0.30 to 4.61).
	BCG vs. interferon alpha-2a: Recurrence, progression	Low	BCG was associated with reduced risk of bladder cancer recurrence (1 trial; RR, 0.57; 95% CI, 0.39 to 0.82), but the difference in risk of bladder cancer progression was not statistically significant (1 trial; RR, 0.69; 95% CI, 0.25 to 1.92).

Table 21. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	BCG alone vs. alternating BCG and interferon alpha-2b: Recurrence	Low	BCG alone was associated with reduced risk of bladder cancer recurrence (1 trial; RR, 0.42; 95% CI, 0.30 to 0.59).
	BCG alone vs. coadministration of BCG and interferon alpha-2b: Recurrence, progression	Low	Differences in risk of bladder cancer recurrence (1 trial; RR, 0.88; 95% CI, 0.71 to 1.08) or progression (1 trial; RR, 0.76; 95% CI, 0.17 to 3.30) did not reach statistical significance.
	BCG vs. thiotepa: Recurrence	Low	Two trials found maintenance therapy with BCG to be associated with decreased risk of recurrence vs. thiotepa (RR, 0.38; 95% CI, 0.19 to 0.76 and RR, 0.04; 95% CI, 0.00 to 0.63).
	BCG vs. thiotepa: Progression, mortality, and cystectomy	Insufficient	Estimates were too imprecise to evaluate effects.
	MMC vs. doxorubicin: Recurrence, progression	Low	There was no difference in risk of bladder cancer recurrence (6 trials; RR, 1.00; 95% CI, 0.82 to 1.22; I^2 = 44%), but MMC was associated with a non–statistically significant trend toward decreased risk of bladder cancer progression (4 trials; RR, 0.63; 95% CI, 0.37 to 1.08; I^2 = 21%).
	MMC vs. epirubicin: Recurrence	Low	There was no difference in risk of bladder cancer recurrence in 1 trial (RR, 1.16; 95% CI, 0.52 to 2.58).
	MMC vs. gemcitabine: Recurrence, progression	Low	In 1 trial, there was no difference in risk of bladder cancer progression (p = 0.29). MMC was associated with increased risk of recurrence, but the difference was not statistically significant (RR, 1.64; 95% CI, 0.64 to 4.19).
	MMC vs. interferon alpha: Recurrence, progression	Low	One trial found no difference between MMC and interferon alpha in risk of bladder cancer recurrence (RR, 0.77; 95% CI, 0.58 to 1.01) or bladder cancer progression (RR, 1.38; 95% CI, 0.49 to 3.88).
	MMC vs. interferon gamma: Recurrence	Low	MMC was associated with increased risk of bladder cancer recurrence in 1 trial (RR, 1.61; 95% CI, 0.97 to 2.67).
	MMC vs. thiotepa: Recurrence	Low	Two trials found no difference between MMC and thiotepa in risk of recurrence (RR, 1.76; 95% CI, 0.36 to 8.70 and RR, 1.14; 95% CI, 0.60 to 2.16).

Table 21. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	Doxorubicin vs. epirubicin: Recurrence, progression	Low	Doxorubicin was associated with increased risk of bladder cancer recurrence (3 trials; RR, 1.56; 95% CI, 1.08 to 2.22; $I^2 = 0\%$); the difference in risk of progression was not statistically significant (1 trial; RR, 1.32; 95% CI, 0.50 to 3.47).
	Doxorubicin vs. thiotepa: Recurrence	Low	There was no statistically significant difference in risk of bladder cancer recurrence (RR, 1.22; 95% CI, 0.76 to 1.94).
	Doxorubicin vs. thiotepa: Progression, noncancer mortality, cancer specific mortality	Insufficient	Estimates from 1 trial for progression (RR, 2.11; 95% CI, 0.40 to 11.06), noncancer mortality (RR, 0.35; 95% CI, 0.01 to 8.45), and cancer specific mortality (RR, 3.17; 95% CI, 0.13 to 76.1) were very imprecise.
	Epirubicin vs. interferon alpha: Recurrence	Low	Epirubicin was associated with decreased risk of bladder cancer recurrence in 1 trial (RR, 0.67; 95% CI, 0.49 to 0.91).
Key Question 3b. Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?	Stage, grade, tumor multiplicity, primary vs. recurrent	Low	There were no clear differences in estimates of effectiveness of intravesical therapies in subgroups defined by tumor stage, grade, size, multiplicity, recurrence status, or DNA ploidy
Key Question 3c. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, race/ethnicity, performance status, or medical comorbidities?	Age, sex, race/ethnicity, performance status, comorbidities	Insufficient	No studies.
	Recurrence, disease-free survival	Low	In patients with recurrence or progression following prior BCG therapy, 1 trial found maintenance therapy with gemcitabine to be associated with decreased risk of recurrence vs. repeat treatment with BCG, and 1 trial found MMC maintenance therapy to be associated with lower likelihood of disease-free survival than gemcitabine; estimates for progression were imprecise.
Key Question 3d. Does the comparative effectiveness of various chemotherapeutic or immunotherapeutic agents differ according to dosing frequency, duration of treatment, and/or the timing of administration relative to TURBT?	Standard vs. lower dose BCG: recurrence, progression, mortality, adverse events	Low	Six trials found no clear differences in risk of recurrence, progression, or bladder cancer mortality, including in patients with higher risk NMIBC, although there was some inconsistency between trials. Standard therapy was associated with increased risk of local and systemic adverse events vs. lower dose BCG.

Table 21. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	Maintenance vs. induction BCG: recurrence, progression, adverse events	Low	Two trials found more prolonged courses of BCG to be associated with decreased risk of bladder cancer recurrence vs. induction therapy in patients with higher risk NMIBC (RR, 0.54; 95% CI, 0.31 to 0.95) but increased risk of adverse events.
	BCG maintenance for 1 vs. 3 years: recurrence, progression, mortality, adverse events	Low	One trial of patients with solitary T1Grade(G)3 or multiple Ta–T1/G1–G3 tumors found no difference between 1 vs. 3 years of BCG maintenance therapy in risk of recurrence, progression, mortality, or adverse events.
	MMC single vs. 5 instillations: recurrence, progression, mortality, adverse events	Low	One trial of patients with NMIBC (not selected for being at higher risk) found no clear differences in risk of recurrence, progression, or mortality. The single instillation was associated with lower risk of local adverse events.
	MMC induction vs. maintenance: recurrence, adverse events	Low	One trial of patients with higher risk NMIBC found MMC 20 mg induction therapy for 6 weeks to be associated with higher risk of recurrence than maintenance therapy. There were no clear differences in risk of adverse events.
	MMC maintenance therapy with increased frequency and number of instillations vs. fewer instillations: recurrence, progression, adverse events	Low	Two trials of MMC maintenance regimens in patients with NMIBC not selected for being at higher risk found some evidence that a higher total number of instillations and increased frequency during initial therapy were associated with lower risk of recurrence and progression, and might be associated with lower risk of local adverse events.
	MMC optimized through alkalinization of urine vs. nonoptimized administration: recurrence, adverse events	Low	One trial found no difference between “optimized” versus nonoptimized administration of intravesical MMC in risk of recurrence in patients with low-risk NMIBC, but 1 other trial of patients with higher risk NMIBC found optimized administration to be associated with lower risk of recurrence and increased risk of local adverse events.

Table 21. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	Doxorubicin 8 weeks vs. 2 years: recurrence, progression, adverse events	Low	Two trials of patients with NMIBC not selected for being at higher risk found no differences between doxorubicin 30 mg and 20 mg given as short (8 weeks) or long (2 years) regimens in risk of recurrence or progression, with no differences in adverse events.
	Doxorubicin induction vs. maintenance: recurrence, progression, mortality, adverse events	Low	Two trials of patients with NMIBC not selected for being at higher risk found no clear differences between doxorubicin induction therapy and induction plus maintenance in risk of recurrence, progression, or mortality, with no differences in adverse events.
	Doxorubicin prior to vs. after TURBT: recurrence, adverse events	Low	Two trials of doxorubicin found no clear benefits associated with administration prior to TURBT or multiple instillations immediately after TURBT, with some evidence of increased adverse events with multiple immediate post-TURBT instillations.
	Epirubicin higher vs. lower doses: recurrence, progression, adverse events	Moderate	Three trials of epirubicin found no clear evidence that higher doses are associated with reduced risk of recurrence or progression vs. lower doses, with no differences in adverse events.
	Epirubicin single vs. multiple instillations: recurrence, progression, bladder cancer mortality, adverse events	Moderate	Three trials found no clear difference between single-instillation epirubicin and multiple instillations in patients with low- or high-risk NMIBC in risk of recurrence, progression, or bladder cancer mortality, with some evidence of lower risk of local adverse events with single instillation.
	Epirubicin maintenance vs. induction without maintenance: recurrence, progression, adverse events	Moderate	Two trials found no clear differences between epirubicin maintenance therapy and induction without maintenance in risk of recurrence or progression, including 1 trial of patients with higher risk NMIBC. There were no differences in risk of local adverse events.

Table 21. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	Epirubicin, more vs. less intensive therapy: recurrence, adverse events	Low	Five trials that evaluated different epirubicin regimens that included maintenance therapy found some evidence that more intensive therapy is associated with decreased risk of recurrence, but results were inconsistent. There was no difference in risk of adverse events.
	Thiotepa 30 vs. 60 mg: recurrence, adverse events	Low	Two trials found no clear differences between thiotepa 30 mg and 60 mg for maintenance or for treatment of incompletely resected NMIBC or CIS.
	Interferon alpha-2b, high vs. lower doses: recurrence, progression, resolution of bladder cancer marker lesions	Low	Three trials found higher doses of interferon alpha-2b to be associated with improved outcomes related to recurrence, progression, or resolution of bladder cancer marker lesions vs. lower doses, but most estimates were imprecise and did not reach statistical significance. There were no clear differences in risk of local or systemic adverse events.
	MMC or doxorubicin on day of TURBT vs. 1 to 2 weeks after TURBT: recurrence, progression, mortality, adverse events	Low	One trial found no difference between initiation of intravesical therapy (9 instillations over 6 months) with MMC or doxorubicin 50 mg on the day of TURBT versus 1 to 2 weeks after TURBT in risk of recurrence, progression, or mortality.
	MMC or doxorubicin maintenance vs. no maintenance: recurrence, progression, mortality, adverse events	Low	One trial found no difference between maintenance beyond 6 months vs. no additional maintenance therapy. There were no clear differences in local or systemic adverse events.
Key Question 4. For patients with high risk non–-muscle-invasive bladder cancer treated with TURBT, what is the effectiveness of external beam radiation therapy (either alone or with systemic chemotherapy/immunotherapy) for decreasing mortality or improving other outcomes compared with intravesical chemotherapy/immunotherapy alone or cystectomy?	Mortality, recurrence, progression	Low	One randomized trial of patients with T1G3 bladder cancer found no effects of radiation therapy vs. no radiotherapy (for unifocal disease and no CIS) or radiation therapy vs. intravesical therapy (for multifocal disease or CIS) in recurrence-free survival (HR, 0.94; 95% CI, 0.67 to 1.30), progression-free interval (HR, 1.07; 95% CI, 0.65 to 1.74), progression-free survival (HR, 1.35; 95% CI, 0.92 to 1.98), or overall survival (HR, 1.32; 95% CI, 0.86 to 2.04) after 5 years.

Table 21. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
Key Question 5. In surveillance of patients treated for non–muscle-invasive bladder cancer, what is the effectiveness of various urinary biomarkers to decrease mortality or improve other outcomes compared with other urinary biomarkers or standard diagnostic methods (cystoscopy, cytology, and imaging)?	Mortality	Insufficient	No studies.
Key Question 5a. Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?		Insufficient	No studies.
Key Question 5b. Does the comparative effectiveness differ according to the treatment used (i.e., specific chemotherapeutic or immunotherapeutic agents and/or TURBT)?		Insufficient	No studies.
Key Question 5c. Does the comparative effectiveness differ according to the length of surveillance intervals?		Insufficient	No studies.
Key Question 5d. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, or race/ethnicity?		Insufficient	No studies.

Table 21. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
Key Question 6. For initial diagnosis or surveillance of patients treated for non–muscle-invasive bladder cancer, what is the effectiveness of blue light or other methods of augmented cystoscopy compared with standard cystoscopy for recurrence rates, progression of bladder cancer, mortality, or other clinical outcomes?	*Fluorescent cystoscopy vs. white light cystoscopy:* Mortality	Low	There was no difference between fluorescent and white light cystoscopy in risk of mortality (3 trials; RR, 1.28; 95% CI, 0.55 to 2.95; I^2 = 41%).
	Fluorescent cystoscopy vs. white light cystoscopy: Recurrence	Low	Fluorescent cystoscopy with 5-ALA or HAL was associated with decreased risk of bladder cancer recurrence vs. white light cystoscopy at short-term (<3 months; 9 trials, RR 0.58, 95% CI 0.36 to 0.94, I^2=75%), intermediate-term (3 months to <1 year, 5 trials, RR 0.67, 95% CI 0.51 to 0.88, I^2=35%), and long-term followup (≥1 year, 11 trials, RR 0.81, 95% CI 0.68 to 0.98, I^2=64%), but findings were inconsistent and potentially susceptible to performance bias (because of failure to blind the initial cystoscopy) and publication bias.
	Fluorescent cystoscopy vs. white light cystoscopy: Progression	Moderate	There was no difference between fluorescent and white light cystoscopy in risk of progression to muscle-invasive bladder cancer (9 trials; RR, 0.78; 95% CI, 0.55 to 1.12; I^2 = 0%).
	Narrow band imaging vs. white light cystoscopy: Recurrence	Low	Narrow band imaging was associated with lower risk of bladder cancer recurrence at 3 months (3.9% vs. 17%; OR, 0.62; 95% CI, 0.41 to 0.92) and at 12 months (OR, 0.24; 95% CI, 0.07 to 0.81) in 1 trial.
Key Question 7. What are the comparative adverse effects of various tests for diagnosis and post-treatment surveillance of bladder cancer, including urinary biomarkers, cytology, and cystoscopy?	Urinary biomarkers: adverse clinical outcomes	Insufficient	Urinary biomarkers miss 23% to 42% of patients with bladder cancer and are incorrectly positive in 11% to 28% of patients without bladder cancer, but no study directly measured effects of inaccurate diagnosis on clinical outcomes.
	Fluorescent vs. white light cystoscopy: false-positives	Low	There were no clear differences between fluorescent cystoscopy and white light cystoscopy in risk of false-positives in 2 trials.
	Fluorescent vs. white light cystoscopy: renal and genitourinary adverse events	Low	There were no clear differences between fluorescent cystoscopy and white light cystoscopy in risk of renal and genitourinary adverse events in 2 trials.

Table 21. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
Key Question 8. What are the comparative adverse effects of various treatments for non–-muscle-invasive bladder cancer, including intravesical chemotherapeutic or immunotherapeutic agents and TURBT?	BCG vs. no intravesical therapy: local and systemic adverse events	Low	Four trials reported granulomatous cystitis or irritative symptoms in 27% to 84% of patients, macroscopic hematuria in 21% to 72%, and fever in 27% to 44%. Harms were not reported in patients who did not receive intravesical therapy.
	Non-BCG intravesical therapies vs. no intravesical therapy: local and systemic adverse events	Low (local adverse events); insufficient (systemic adverse events)	Evidence on harms was very limited, although some trials reported an increased risk of local adverse events. Evidence was insufficient to determine effects of non-BCG intravesical therapies vs. no intravesical therapy on risk of systemic adverse events.
	BCG vs. MMC: Local adverse events	Low (moderate for cystitis and hematuria)	BCG was associated with increased risk of any local adverse event (2 trials; RR, 2.01; 95% CI, 1.59 to 2.54; I^2 = 0%), granulomatous cystitis (5 trials; RR, 1.71; 95% CI, 1.22 to 2.41; I^2 = 58%), dysuria (3 trials; 48% vs. 32%; RR, 1.23; 95% CI, 1.03 to 1.46; I^2 = 34%), and hematuria (6 trials; RR, 1.78; 95% CI, 1.24 to 2.56; I^2 = 62%) vs. MMC.
	BCG vs. MMC: Systemic adverse events	Low	BCG was associated with increased risk of any systemic adverse event (2 trials; RR, 2.01; 95% CI, 1.59 to 2.54; I^2 = 0%) and fever (4 trials; RR, 4.51; 95% CI, 2.31 to 8.82; I^2 = 25%) vs. MMC.
	BCG alone vs. BCG plus MMC given sequentially: Discontinuation of therapy	Low	BCG alone was associated with increased risk of discontinuation of instillations vs. BCG plus MMC given sequentially (1 trial; RR, 4.06; 95% CI, 2.09 to 7.86).
	BCG plus MMC given sequentially vs. MMC alone: Local adverse events	Low	There was no difference between sequentially administered BCG plus MMC and MMC alone in local adverse events (1 trial; RR, 1.36; 95% CI, 0.60 to 3.08) or risk of granulomatous cystitis (1 trial; RR, 1.30; 95% CI, 0.88 to 1.93).
	BCG plus MMC given sequentially vs. MMC alone: Systemic adverse events	Low	There was no difference between BCG and MMC given sequentially and MMC used alone in systemic adverse events (1 trial; RR, 1.07; 95% CI, 0.63 to 1.84), but BCG plus MMC was associated with increased risk of fever (1 trial; 12% vs. 3%; RR, 3.75; 95% CI, 1.08 to 13).

Table 21. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	BCG plus MMC given sequentially vs. MMC alone: Discontinuation of therapy	Low	There was no difference between alternating BCG plus MMC and MMC alone in risk of discontinuation of instillations in patients with CIS (1 trial; RR, 0.54; 95% CI, 0.16 to 1.84) or in patients with Ta or T1 tumors (1 trial; RR, 0.93; 95% CI, 0.52 to 1.65).
	BCG vs. doxorubicin: Local adverse events	Low (cystitis); insufficient (dysuria and hematuria)	BCG was associated with increased risk of cystitis vs. doxorubicin (1 trial; RR, 17; 95% CI, 1 to 289), but there was insufficient evidence to determine effects on dysuria (3 trials; data not pooled) and hematuria (2 trials; data not pooled) because of small numbers of trials with inconsistent results.
	BCG vs. epirubicin: Local adverse events	Low	BCG was associated with increased risk of local side effects (1 trial; RR, 3.28; 95% CI, 1.26 to 8.53).
	BCG vs. epirubicin: Discontinuation of therapy	Insufficient	Results were mixed for discontinuation of intravesical therapy (2 trials; data not pooled).
	BCG vs. epirubicin: Systemic adverse events	Low	BCG was associated with increased risk of granulomatous cystitis (4 trials; RR, 1.86; 95% CI, 1.35 to 2.56; I^2 = 65%), dysuria (1 trial; RR, 2.43; 95% CI, 1.13 to 5.24), hematuria (4 trials; RR, 1.77; 95% CI, 1.41 to 2.22; I^2 = 0%), and fever (2 trials; RR, 9.73; 95% CI, 2.72 to 35; I^2 = 0%).
	BCG alone vs. BCG plus epirubicin given sequentially: Local adverse events	Low	There was no difference in risk of dysuria (1 trial; RR, 1.22; 95% CI, 0.56 to 2.66) or hematuria (2 trials; RR, 2.27; 95% CI, 0.86 to 6.00; I^2 = 0%).
	BCG alone vs. BCG plus epirubicin given sequentially: Systemic adverse events	Low	BCG was associated with increased risk of systemic adverse events (1 trial; RR, 5.97; 95% CI, 2.18 to 16) and granulomatous cystitis (1 trial; RR, 2.28; 95% CI, 1.46 to 3.54) but no difference in risk of fever (2 trials; RR, 2.09; 95% CI, 0.48 to 9.02; I^2 = 0%).
	BCG alone vs. BCG plus epirubicin given sequentially: Discontinuation of therapy	Low	BCG was associated with increased risk of discontinuation of instillations (1 trial; RR, 4.56; 95% CI, 1.35 to 15).

Table 21. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	BCG vs. gemcitabine: Local adverse events	Low	There were no differences between BCG and gemcitabine in risk of local adverse events requiring postponement or discontinuation of intravesical therapy (1 trial; RR, 1.33; 95% CI, 0.32 to 5.49).
	BCG vs. gemcitabine: Systemic adverse events	Low	There were no differences in systemic adverse events (1 trial; RR, 0.50; 95% CI, 0.10 to 2.5), dysuria (2 trials; RR, 1.51; 95% CI, 0.92 to 2.50; I^2 = 0%), or hematuria (2 trials; RR, 4.62; 95% CI, 0.78 to 27; I^2 = 29%), but BCG was associated with increased risk of fever (2 trials; RR, 6.24; 95% CI, 1.03 to 38; I^2 = 5%).
	BCG alone vs. BCG plus gemcitabine given sequentially: Local adverse events	Low	One trial found no difference in risk of dysuria (RR, 0.92; 95% CI, 0.52 to 1.65) or hematuria (RR, 0.30; 95% CI, 0.08 to 1.09).
	BCG vs. interferon alpha-2a: Local adverse events	Low	BCG was associated with increased risk of dysuria (1 trial; RR, 84; 95% CI, 5.29 to 1,319).
	BCG vs. interferon alpha-2a: Systemic adverse events	Low	There was no difference in risk of fever (1 trial; RR, 4.82; 95% CI, 0.25 to 94).
	BCG alone vs. coadministration of BCG and interferon alpha-2b: Systemic adverse events	Low	BCG was associated with increased risk of constitutional symptoms (1 trial; RR, 1.63; 95% CI, 1.12 to 2.38) and fever (1 trial; RR, 2.26; 95% CI, 1.30 to 3.95).
	BCG vs. thiotepa: Local adverse events	Low	BCG was associated with increased risk of bladder irritability (1 trial; RR, 2.93; 95% CI, 1.45 to 5.90) and cystitis (1 trial; RR, 18; 95% CI, 1.11 to 306).
	BCG vs. thiotepa: Systemic adverse events	Low	BCG was associated with increased risk of fever (1 trial; RR, 8.36; 95% CI, 0.47 to 150).
	MMC vs. doxorubicin: Local adverse events	Insufficient	Evidence was insufficient to determine effects of MMC vs. doxorubicin on risk of local adverse events, based on inconsistent results from 6 trials.
	MMC vs. epirubicin: Local adverse events	Low	One small trial found no difference between MMC and epirubicin 80 mg in risk of urinary symptoms.
	MMC vs. interferon alpha: Local adverse events	Low	One trial found MMC to be associated with greater risk of hematuria vs. interferon alpha (RR, 2.00; 95% CI, 1.09 to 3.65) and no difference in risk of dysuria or urinary frequency.

Table 21. Summary of the strength of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	MMC vs. interferon alpha: Systemic adverse events	Low	One trial found MMC to be associated with decreased risk of fever (RR, 0.13; 95% CI, 0.03 to 0.55).
	MMC vs. gemcitabine: Local adverse events	Low	One trial found MMC to be associated with increased risk of chemical cystitis (RR, 3.93; 95% CI, 1.17 to 13.14), with no difference in risk of dysuria or hematuria.
	Doxorubicin vs. epirubicin: Local adverse events	Low	Doxorubicin was associated with increased risk of chemical cystitis (1 trial; RR, 1.85; 95% CI, 1.13 to 3.03), with no clear difference in risk of dysuria or urinary frequency (2 trials) or hematuria (3 trials; RR, 1.53; 95% CI, 0.50 to 4.66; I^2 = 0%).
	Doxorubicin vs. thiotepa: Local adverse events	Low	One trial found no difference in risk of bladder irritability (RR, 0.92; 95% CI, 0.36 to 2.37).
	Epirubicin vs. interferon alpha: Local adverse events	Low	One trial found no difference in risk of dysuria.
	Epirubicin vs. interferon alpha: Systemic adverse events	Low	One trial found no difference in risk of fever.
Key Question 8a. How do adverse effects of treatment vary by patient characteristics, such as age, sex, race/ethnicity, performance status, or medical comorbidities such as chronic kidney disease?	Adverse effects	Insufficient	No studies

5-ALA = 5-aminolevulinic acid; BCG = bacillus Calmette–Guérin; BTA = bladder tumor antigen; CI = confidence interval; CIS = carcinoma in situ; FISH = fluorescence in situ hybridization; G1 = Grade 1; G3 = Grade 3; HAL = hexaminolevulinate; HR = hazard ratio; MMC = Mitomycin C; mg = milligram; NMP22 = nuclear matrix protein-22; NMIBC = non-muscle-invasive bladder cancer; OR = odds ratio; RR = risk ratio; T1 = Tumor stage 1; Ta = Tumor stage a; TURBT = transurethral resection of bladder tumor

Table 22. Post-test probability of bladder cancer using different biomarkers

Urinary Biomarker	Pretest Probability of Bladder Cancer	Positive Likelihood Ratio (95% CI)	Post-Test Probability of HCC Following a Positive Test	Negative Likelihood Ratio (95% CI)	Post-Test Probability of HCC Following a Negative Test
Quantitative NMP22	5%	3.05 (2.28 to 4.10)	14%	0.40 (0.32 to 0.50)	2.1%
	20%	3.05 (2.28 to 4.10)	43%	0.40 (0.32 to 0.50)	9.1%
Qualitative NMP22	5%	4.89 (3.23 to 7.40)	20%	0.48 (0.33 to 0.71)	2.5%
	20%	4.89 (3.23 to 7.40)	55%	0.48 (0.33 to 0.71)	11%
Qualitative BTA	5%	2.80 (2.31 to 3.39)	13%	0.47 (0.30 to 0.55)	2.4%
	20%	2.80 (2.31 to 3.39)	41%	0.47 (0.30 to 0.55)	11%
Quantitative BTA	5%	2.52 (1.86 to 3.41)	12%	0.47 (0.37 to 0.61)	2.4%
	20%	2.52 (1.86 to 3.41)	39%	0.47 (0.37 to 0.61)	11%
FISH	5%	5.02 (2.93 to 8.60)	21%	0.42 (0.30 to 0.59)	2.2%
	20%	5.02 (2.93 to 8.60)	56%	0.42 (0.30 to 0.59)	9.5%
ImmunoCyt™	5%	3.49 (2.82 to 4.32)	16%	0.29 (0.20 to 0.41)	1.5%
	20%	3.49 (2.82 to 4.32)	47%	0.29 (0.20 to 0.41)	6.8%

BTA = bladder tumor antigen; FISH = fluorescence in situ hybridization; HCC = hepatocellular carcinoma; NMP22 = nuclear matrix protein-22

Conclusions

Urinary biomarkers are falsely negative in a substantial proportion of patients with bladder cancer and additional research is needed to clarify advantages of fluorescent cystoscopy over white light cystoscopy. Intravesical therapy reduces risk of bladder cancer recurrence versus no intravesical therapy. Bacillus Calmette-Guérin (BCG) is the only intravesical therapy shown to be associated with decreased risk of bladder cancer progression, but is associated with a high rate of adverse events.

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Abbreviations

AHRQ	Agency for Healthcare Research and Quality
BCG	Bacillus Calmette-Guèrin
CER	Comparative Effectiveness Review
CI	Confidence interval
ECOG	Eastern Cooperative Oncology Group
FDA	U.S. Food and Drug Administration
HAL	Hexaminolevulinate
LR-	Negative likelihood ratio
LR+	Positive likelihood ratio
MMC	Mitomycin C
NMIBC	Non-muscle-invasive bladder cancer
PICOTS	Populations, interventions, comparators, outcomes, timing, and study designs
ROC	Receiver operating characteristic
SRC	Scientific Research Center
TEP	Technical Expert Panel
TOO	Task Order Officer
TURBT	Transurethral resection of the bladder tumor
WHO	World Health Organization

Emerging Approaches to Diagnosis and Treatment of Non-Muscle-Invasive Bladder Cancer: Addendum

This addendum details updated results for Key Question 3 (comparative effectiveness of intravesical therapies) and Key Question 6 (comparative effectiveness of fluorescent versus white light cystoscopy). An updated search using the same search strategy from the original report was conducted in September 2015. The methods used for this update were the same as in the original report.

Key Question 3

We identified two additional trials (n=43 and 63) of adjuvant intravesical therapy versus TURBT alone.[1, 2] One trial was rated medium risk of bias[1] and the other high risk of bias.[2] Both trials evaluated single dose therapy with MMC in patients with lower-risk NMIBC.

We updated the meta-analyses of MMC versus TURBT alone with the new trials. For recurrence, we also added data from a previously included trial that was omitted in the original report.[3] The only outcomes that were affected in the new analysis were bladder cancer recurrence and progression; updated estimates and conclusions were generally similar to those in the original report (Table 1).

Table 1. Updated results for MMC versus no intravesical therapy (TURBT alone)

Intravesical Therapy	All-Cause Mortality	Bladder Cancer-Specific Mortality	Bladder Cancer Recurrence	Bladder Cancer Progression
MMC	1 trial, HR 1.17, 95% CI 0.89 to 1.53	1 trial, HR 0.71, 95% CI 0.34 to 1.46	11 trials, RR 0.68, 95% CI 0.55 to 0.83, I^2=74%	7 trials, RR 0.65, 95% CI 0.38 to 1.11, I^2=0%

BCG = bacillus Calmette Guérin; CI = confidence interval; RR = relative risk; HR = hazard ratio

Regarding head-to-head comparisons of intravesical therapies, we identified one additional trial (n=407, medium risk of bias) of intravesical BCG versus BCG plus MMC given sequentially.[4] We updated the meta-analyses with the new study; we also added data on progression from a previously included trial[5] that was omitted from the original report. Updated estimates and conclusions were similar to those in the original report (Table 2)

Table 2. Updated results for BCG versus BCG plus MMC given sequentially

Comparison	All-Cause Mortality	Bladder Cancer-Specific Mortality	Bladder Cancer Recurrence	Bladder Cancer Progression
BCG vs. BCG plus MMC given sequentially	2 trials, RR 1.15, 95% CI 0.84 to 1.57, I^2=0%	3 trials, RR 1.27, 95% CI 0.76 to 2.12, I^2=0%	5 trials, RR 1.17, 95% CI 0.77 to 1.77, I^2=77%	5 trials, RR 0.86, 95% CI 0.61 to 1.22, I^2=0%

BCG = bacillus Calmette Guérin; CI = confidence interval; MMC = mitomycin C; RR = risk ratio

For comparisons involving dose or duration, we identified one additional trial (n=166, medium risk of bias) that compared BCG Tokyo strain 40 mg versus 80 mg (each administered once weekly for eight weeks).[6] It was consistent with two trials in the original report that found no clear difference between higher and lower doses of BCG. In the new trial, there was no clear

difference between the lower and higher dose in risk of complete response (78% vs. 85%, p=0.12), recurrence-free survival (p=0.94), or progression (6.2% vs. 5.8%).[6]

Key Question 6

We identified one new trial (n=85, medium risk of bias) of fluorescent cystoscopy plus white light cystoscopy versus white light cystoscopy alone that reported effects on bladder cancer recurrence.[7] It found no clear difference between fluorescent plus white light cystoscopy versus white light cystoscopy alone in risk of recurrence through up to 40 months of follow-up (38% vs. 46%, RR 0.82, 95% CI 0.49 to 1.35), though results slightly favored fluorescent cystoscopy. All patients received a single instillation of epirubicin immediately following TURBT. There were also no differences between fluorescent versus white light cystoscopy when patients were stratified according to tumor risk category. The trial did not evaluate effects on progression or mortality. Patients were randomized to intravesical HAL or placebo administered one hour prior to white light cystoscopy, which was performed in all patients. Surgeons were blinded to treatment allocation until after white light cystoscopy was completed; only patients randomized to HAL underwent fluorescent cystoscopy.

We updated the meta-analyses on recurrence with data from the new trial. We also found errors in the data used for long-term recurrence and progression for one trial[8] included in the original report and used corrected data in the updated meta-analysis. The updated analyses resulted in similar estimates and conclusions and are shown in Table 3. Estimates and overall conclusions were similar to those in the original report.

Table 3. Updated results for fluorescent cystoscopy versus white light cystoscopy

Outcome	Number of trials	Relative risk, fluorescent cystoscopy versus white light cystoscopy (95% confidence interval)*	I^2
Short-term (<3 months) recurrence	9	0.59 (0.40 to 0.88)	69%
HAL	6	0.62 (0.38 to 1.00)	51%
5-ALA	4	0.57 (0.28 to 1.16)	84%
Intermediate-term (3 months to <1 year) recurrence	6	0.70 (0.56 to 0.88)	19%
Long-term (≥1 year) recurrence	12	0.81 (0.70 to 0.93)	49%
HAL	7	0.75 (0.62 to 0.92)	41%
5-ALA	5	0.86 (0.68 to 1.08)	65%
Progression	9	0.74 (0.52 to 1.03)	0%
HAL	4	0.51 (0.28 to 0.96)	0%
5-ALA	5	0.86 (0.57 to 1.28)	0%
Mortality	3	1.28 (0.55 to 2.95)	43%

HAL=hexaminolevulinate, 5-ALA=aminolevulinic acid

*p for interaction based on photosensitizer used 0.97 for short-term recurrence, 0.41 for long-term recurrence, and 0.18 for progression

Study characteristics and risk of bias ratings for the additional studies are shown in Tables 4, 5 and 6.

Table 4. Characteristics and results of additional trials of intravesical therapy

Author, Year Risk of Bias	Inclusion Criteria	Population Characteristics	Intervention	Followup Duration	Main Results
Barghi, 2006[1] Medium	Primary or papillary tumors, single tumors of 3 cm or less in size, and low-grade superficial tumors (TaG1, TaG2, T1G1)	Age, mean (years): 56 vs. 54 Male: 77% vs. 81% Recurrent bladder cancer: NR Ta: 73% vs. 71% T1: 28% vs. 29% G1: 91% vs. 91% G2: 9% vs. 9%	A: Mitomycin C 30 mg (in 30mL distilled water). Single instillation 6 to 24 hours after TURBT. Catheter clamped for 2 hours (n=22). B: Placebo (distilled water). Single instillation 6 to 24 hours after TURBT. Catheter clamped for 2 hours (n=21).	24 months	Recurrence within 1 year: 4.5% (1/22) vs. 38.1% (8/21), p=0.007 Progression within 1 year: 0% (1/22) vs. 14.3% (3/21), p=0.06
El-Ghobashy, 2007[2] High	2 cm or less, single, papillary, primary or recurrent transitional cell carcinoma of the urinary bladder, who were disease free for more than 1 year.	Age, mean (years): 62.2 vs. 59.9 Sex: NR Recurrent bladder cancer: 9.7% vs. 13% Ta: 18% vs. 50% T1: 52% vs. 50% G1: 48% vs. 53% G2: 52% vs. 47%	A: Mitomycin, 30mg (in 50mL saline), instilled when hematuria stopped, usually within 6 hours of TURBT. Catheter clamped for 1 hour (n=31). B: No adjuvant treatment. TURBT alone (n=32).	Mean (months): 44 vs. 43	Recurrence within two years: 16.1% (5/31) vs. 34.3% (11/32), p<0.05 Recurrence after 2 years: 26.9% (7/31) vs. 28.6% (6/32), non significant Progression: 3.2% (1/31) vs. 3.1% (1/32), non significant

Solsona, 2015[4] Medium	Papillary NMIBC, TaG3 or T1G1-3 tumors, and Tis alone or associated with papillary tumors Ta-1G1-3	Age: 65 vs. 66 years Male: 91% vs. 89% Recurrent bladder cancer: 29% vs. 35% Stage Ta: 17% vs. 16% Stage T1: 77% vs. 74% Grade G1: 16% vs. 10% Grade G2: 64% vs. 59% Grade G3: 20% vs. 31%	A: MMC, 30 mg (in 50 mL water), later reduced to 10 mg due to adverse effects one day prior to BCG Connaught, 1.5-5 x 108 CFU (in 50 mL water). Total 9 instillations; 6 weekly instillations starting 14 to 28 days after TURBT, then 3 instillations every 2 weeks (n=211). B: BCG Connaught, 1.5-5 x 108 CFU (in 50 mL water). Total 9 instillations; 6 weekly instillations starting 14 to 28 days after TURBT, then 3 instillations every 2 weeks (n=196).	Median (years): 7.1 years	Bladder cancer mortality: 4.7% (10/211) vs. 7.6% (15/196), RR 0.62 (95% CI 0.28 to 1.35) All-cause mortality: 24% (51/211) vs. 26% (52/196), RR 0.91 (95% CI 0.65 to 1.27) Recurrence (Ta, T1, or Tis tumor): 18% (38/211) vs. 33% (64/196), RR 0.55 (95% CI 0.39 to 0.78) Relapse (Ta, T1, Tis, or upper urinary tract tumor, prostatic urethral involvement, T2 or higher tumor, nodal involvement or metastasis): 21% (44/211) vs. 35% (68/196), RR 0.60 (95% CI 0.43 to 0.83)
Yokomizo, 2015[6] Medium	CIS or unresectable NMIBC with CIS, age 20-85	Age: 68 vs. 68 (CIS, n=155), 67 vs. 72 (no CIS, n=21) Male: 80% vs. 85% (CIS), 91% vs. 70% (no CIS) Race/ethnicity: Not reported Recurrent bladder cancer: 13% vs. 13% (CIS), 14% vs. 20% (no CIS) Stage Tis, pure (CIS): 49% vs. 36%, Stage Ta + Tis (CIS): 26% vs. 33% Stage T1 + Tis (CIS): 26% vs. 19% Stage Ta (no CIS): 55% vs. 70% Stage T1 (no CIS): 45% vs. 30%	A: BCG Tokyo strain, 40 mg once weekly for 8 weeks (n=81) B: BCG Tokyo strain, 80 mg once weekly for 8 weeks (n=85)	Median 3.6 years	Complete response (no residual tumor): 78% vs. 85% (p=0.12) Recurrence-free survival: p=0.94 Progression: 5/81 vs. 5/86

Table 5. Characteristics and selected results of an additional trial of fluorescent cystoscopy

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Cystoscopic Followup Method	Population Characteristics by Treatment Group	Main Results
Gkritsios, 2014[7] Medium	Greece Single center Study years not reported	A: White light and HAL fluorescent cystoscopy with TURBT (n=48) B: White light cystoscopy (n=37) All patients received single instillation of epirubicin 50 mg immediately following TURBT	Duration: up to 40 months (mean not reported) Method: White light cystoscopy	Age (mean): 66 vs. 68 years Male: 80% vs. 73% Stage: 76% vs. 70% Ta, 24% vs. 30% T1 and CIS Grade: 85% vs. 73% low grade, 15% vs. 27% high grade and CIS	Recurrence: Intermediate-term: 8.3% (4/48) vs. 11% (4/37) Long-term: 38% (18/48) vs. 46% (17/37)

Table 6. Risk of bias of additional trials

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline? (age, sex, race, smoking status-if available, bladder cancer stage)	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?	Patient Masked?
Barghi, 2006[1]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear
El-Ghobashy, 2007[2]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear
Gkritsios, 2014[7]	Yes	Unclear	Yes	Yes	Unclear	Yes	Unclear

Solsona, 2015[4]	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear
Yokomizo, 2016[6]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear

Author, Year	Attrition Reported?	Overall loss to followup <20%? Differential attrition <10%?	Intention-to-Treat Analysis (analyzed by groups they were assigned to)	Postrandomization Exclusions	Outcomes Prespecified	Risk of Bias
Barghi, 2006[1]	Yes	Overall: Yes Differential: Unclear	Yes	Yes	Yes	Medium
El-Ghobashy, 2007[2]	No	Unclear	Yes	Unclear	Yes	High
Gkritsios, 2014[7]	Yes	Overall: Yes Differential: No	Yes	Yes	Yes	Medium
Solsona, 2015[4]	Yes	Yes	Yes	Yes (36/443)	Yes	Medium
Yokomizo, 2016[6]	Yes	Yes	Yes	Yes (13/171)	Yes	Medium

References

1. Barghi MR, Rahmani MR, Hosseini Moghaddam SM, et al. Immediate intravesical instillation of mitomycin C after transurethral resection of bladder tumor in patients with low-risk superficial transitional cell carcinoma of bladder. Urol J. 2006; 3(4):220-4. PMID: 17559045.
2. El-Ghobashy S, El-Leithy TR, Roshdy MM, et al. Effectiveness of a single immediate mitomycin C instillation in patients with low risk superficial bladder cancer: short and long-term follow-up. J Egypt Natl Canc Inst. 2007 Jun; 19(2):121-6. PMID: 19034342.
3. Tolley DA, Parmar MK, Grigor KM, et al. The effect of intravesical mitomycin C on recurrence of newly diagnosed superficial bladder cancer: a further report with 7 years of follow up. J Urol. 1996 Apr; 155(4):1233-8. PMID: 8632538.
4. Solsona E, Madero R, Chantada V, et al. Sequential combination of mitomycin C plus bacillus Calmette-Guerin (BCG) is more effective but more toxic than BCG alone in patients with non-muscle-invasive bladder cancer in intermediate- and high-risk patients: final outcome of CUETO 93009, a randomized prospective trial. Eur Urol. 2015 Mar;67(3):508-16. doi: http://dx.doi.org/10.1016/j.eururo.2014.09.026. PMID: 25301758.
5. Mohsen MAE, Shelbaia A, Ghobashy SE, et al. Sequential chemoimmunotherapy using mitomycin followed by bacillus Calmette-Guerin (MCC + BCG) versus single-agent immunotherapy (BCG) for recurrent superficial bladder tumors. UIJ. 2010; 3(3).
6. Yokomizo A, Kanimoto Y, Okamura T, et al. Randomized controlled study of the efficacy, safety and quality of life with low dose bacillus Calmette-Guerin instillation therapy for nonmuscle invasive bladder cancer. J Urol. 2016;195(1):41-6. doi: 10.1016/j.juro.2015.08.075.
7. Gkritsios P, Hatzimouratidis K, Kazantzidis S, et al. Hexaminolevulinate-guided transurethral resection of non-muscle-invasive bladder cancer does not reduce the recurrence rates after a 2-year follow-up: a prospective randomized trial. International Urology & Nephrology. 2014 May;46(5):927-33. doi: http://dx.doi.org/10.1007/s11255-013-0603-z. PMID: 24249423.
8. Stenzl A, Burger M, Fradet Y, et al. Hexaminolevulinate guided fluorescence cystoscopy reduces recurrence in patients with nonmuscle invasive bladder cancer. J Urol. 2010 Nov; 184(5):1907-13. doi: 10.1016/j.juro.2010.06.148. PMID: 20850152.

Appendix A. Search Strategies

Primary Search Strategy (Ovid MEDLINE)

1. exp Urinary Bladder Neoplasms/
2. ((((non or "not") adj (invas$ or invad$ or infiltrat$)) or noninvas$ or noninvad$ or noninfiltrat$) adj5 muscle$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3. (cis or Tis or ta or t1$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4. 2 or 3
5. ((sign or signs or symptom$ or possib$ or suspect$ or potential$) adj5 (bladder$ adj3 (cancer$ or tumor$ or tumour$ or neoplas$ or carcino$ or malig$ or adenocarcin$))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
6. 4 or 5
7. 1 and 6
8. exp Biological Markers/
9. 7 and 8
10. ((urin$ adj3 biomark$) or bladder tumor associated antigen$ or nuclear matrix protein or nmp22 or fluorescence in situ hybrid$ or (fish adj assay$) or fibroblast growth factor receptor 3 or fgfr3 or cxbladder or immunocyt or cytokeratin fragment$ or cyfra 21-1 or (cytokerat$ adj3 (tpa or tps)) or survivin or telomeras$ or vascular endothelial growth factor$ or vegf or metalloproteinas$ or mmp-2 or mmp-9 or twist homolog$ or twist1 or nidogen-2 or nid2).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
11. 7 and 10
12. ((assess$ or analyz$ or judg$ or consider$ or quantif$ or predict$ or identif$ or adapt$) adj7 risk$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
13. exp Surgical Procedures, Operative/
14. exp Drug Therapy/
15. exp Antineoplastic Agents/
16. exp Radiotherapy/
17. (th or su or rt or dh or dt).fs.
18. 13 or 14 or 15 or 16 or 17
19. 12 and 18
20. 7 and 19
21. (mitomycin$ or apaziquone or paclitaxel or gemcitabine or thiotepa or valrubicin or doxorubicin or bacillus calmette guerin or bcg or interferon$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word,

protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
22. 7 and 21
23. (electromotiv$ or emda).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
24. 1 and 23
25. (blue adj5 cystoscop$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
26. 1 and 25
27. exp Radiotherapy/
28. rt.fs.
29. 27 or 28
30. 7 and 29
31. 9 or 11 or 20 or 22 or 24 or 26 or 30
32. exp Urinary Bladder Neoplasms/
33. ((invas$ or invad$ or infiltrat$) adj5 muscl$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
34. (t2$ or t3$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
35. 33 or 34
36. 32 and 35
37. cystectom$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
38. ((excis$ or remov$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 bladder$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
39. 37 or 38
40. (bladder$ adj5 (spare or sparing or spares or spared or preserv$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
41. (avoid$ adj7 cystectom$).mp.
42. 40 or 41
43. exp Lymph Node Excision/
44. ((excis$ or remov$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 (lymph$ or node or nodes)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
45. 43 or 44

46. (adjuvant$ or neoadjuvant$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
47. (abraxane or carboplatin$ or cisplatin$ or docetaxel or doxorubicin or epirubicin or 5-fluorouracil or gemcitabine or methotrexate or mitomycin or paclitaxel or valrubicin or vinblastin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
48. 46 or 47
49. 39 or 42 or 45 or 48
50. 36 and 49
51. 31 or 50
52. limit 51 to yr="1990 -Current"
53. limit 52 to english language
54. limit 52 to abstracts
55. 53 or 54

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

1. ((Urinar$ or urothel$) adj5 (bladder$ adj3 (neoplas$ or cancer$ or tumor$ or tumour$ or carcino$ or adenocarcin$ or malig$))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
2. ((((non or "not") adj (invas$ or invad$ or infiltrat$)) or noninvas$ or noninvad$ or noninfiltrat$) adj5 muscle$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3. (cis or Tis or ta or t1$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4. 2 or 3
5. ((sign or signs or symptom$ or possib$ or suspect$ or potential$) adj5 (bladder$ adj3 (cancer$ or tumor$ or tumour$ or neoplas$ or carcino$ or malig$ or adenocarcin$))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6. 4 or 5
7. 1 and 6
8. ((urin$ adj3 biomark$) or bladder tumor associated antigen$ or nuclear matrix protein or nmp22 or fluorescence in situ hybrid$ or (fish adj assay$) or fibroblast growth factor receptor 3 or fgfr3 or cxbladder or immunocyt or cytokeratin fragment$ or cyfra 21-1 or (cytokerat$ adj3 (tpa or tps)) or survivin or telomeras$ or vascular endothelial growth factor$ or vegf or metalloproteinas$ or mmp-2 or mmp-9 or twist homolog$ or twist1 or nidogen-2 or nid2).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
9. 7 and 8
10. ((assess$ or analyz$ or judg$ or consider$ or quantif$ or predict$ or identif$ or adapt$) adj7 risk$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

11. (surger$ or surgic$ or surgeon$ or cystectom$ or excis$ or (remov$ adj3 bladder$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
12. ((drug$ adj3 (therap$ or treat$ or regimen$ or protocol$)) or pharmacother$ or chemother$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
13. Antineoplastic$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
14. (Radiother$ or ((radio$ or irradiat$ or radiat$ or x-ray or gamma) adj3 (treat$ or therap$ or protocol$))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
15. 11 or 12 or 13 or 14
16. 10 and 15
17. 7 and 16
18. (mitomycin$ or apaziquone or paclitaxel or gemcitabine or thiotepa or valrubicin or doxorubicin or bacillus calmette guerin or bcg or interferon$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
19. 7 and 18
20. (electromotiv$ or emda).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
21. 1 and 20
22. (blue adj5 cystoscop$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
23. 1 and 22
24. 9 or 17 or 19 or 21 or 23
25. ((Urinar$ or urothel$) adj5 (bladder$ adj3 (neoplas$ or cancer$ or tumor$ or tumour$ or carcino$ or adenocarcin$ or malig$))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
26. ((invas$ or invad$ or infiltrat$) adj5 muscl$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
27. (t2$ or t3$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
28. 26 or 27
29. 25 and 28
30. cystectom$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
31. ((excis$ or remov$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 bladder$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
32. 30 or 31
33. (bladder$ adj5 (spare or sparing or spares or spared or preserv$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
34. (avoid$ adj7 cystectom$).mp.
35. 33 or 34
36. ((excis$ or remov$ or biops$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 (lymph$ or node or nodes)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

37. (adjuvant$ or neoadjuvant$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
38. (abraxane or carboplatin$ or cisplatin$ or docetaxel or doxorubicin or epirubicin or 5-fluorouracil or gemcitabine or methotrexate or mitomycin or paclitaxel or valrubicin or vinblastin).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
39. 37 or 38
40. 32 or 35 or 36 or 39
41. 29 and 40
42. 24 or 41
43. limit 42 to yr="1990 -Current"

Database: EBM Reviews – Cochrane Database of Systematic Reviews

1. ((Urinar$ or urothel$) adj5 (bladder$ adj3 (neoplas$ or cancer$ or tumor$ or tumour$ or carcino$ or adenocarcin$ or malig$))).mp. [mp=title, abstract, full text, keywords, caption text]

Database: EBM Reviews – Database of Abstracts of Reviews of Effects

1. ((Urinar$ or urothel$) adj5 (bladder$ adj3 (neoplas$ or cancer$ or tumor$ or tumour$ or carcino$ or adenocarcin$ or malig$))).mp. [mp=title, full text, keywords]
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3. (cis or Tis or ta or t1$).mp. [mp=title, full text, keywords]
4. 2 or 3
5. ((sign or signs or symptom$ or possib$ or suspect$ or potential$) adj5 (bladder$ adj3 (cancer$ or tumor$ or tumour$ or neoplas$ or carcino$ or malig$ or adenocarcin$))).mp. [mp=title, full text, keywords]
6. 4 or 5
7. 1 and 6
8. ((urin$ adj3 biomark$) or bladder tumor associated antigen$ or nuclear matrix protein or nmp22 or fluorescence in situ hybrid$ or (fish adj assay$) or fibroblast growth factor receptor 3 or fgfr3 or cxbladder or immunocyt or cytokeratin fragment$ or cyfra 21-1 or (cytokerat$ adj3 (tpa or tps)) or survivin or telomeras$ or vascular endothelial growth factor$ or vegf or metalloproteinas$ or mmp-2 or mmp-9 or twist homolog$ or twist1 or nidogen-2 or nid2).mp. [mp=title, full text, keywords]
9. 7 and 8
10. ((assess$ or analyz$ or judg$ or consider$ or quantif$ or predict$ or identif$ or adapt$) adj7 risk$).mp. [mp=title, full text, keywords]
11. (surger$ or surgic$ or surgeon$ or cystectom$ or excis$ or (remov$ adj3 bladder$)).mp. [mp=title, full text, keywords]

12. ((drug$ adj3 (therap$ or treat$ or regimen$ or protocol$)) or pharmacother$ or chemother$).mp. [mp=title, full text, keywords]
13. Antineoplastic$.mp. [mp=title, full text, keywords]
14. (Radiother$ or ((radio$ or irradiat$ or radiat$ or x-ray or gamma) adj3 (treat$ or therap$ or protocol$))).mp. [mp=title, full text, keywords]
15. 11 or 12 or 13 or 14
16. 10 and 15
17. 7 and 16
18. (mitomycin$ or apaziquone or paclitaxel or gemcitabine or thiotepa or valrubicin or doxorubicin or bacillus calmette guerin or bcg or interferon$).mp. [mp=title, full text, keywords]
19. 7 and 18
20. (electromotiv$ or emda).mp. [mp=title, full text, keywords]
21. 1 and 20
22. (blue adj5 cystoscop$).mp. [mp=title, full text, keywords]
23. 1 and 22
24. 9 or 17 or 19 or 21 or 23
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26. ((invas$ or invad$ or infiltrat$) adj5 muscl$).mp. [mp=title, full text, keywords]
27. (t2$ or t3$).mp. [mp=title, full text, keywords]
28. 26 or 27
29. 25 and 28
30. cystectom$.mp. [mp=title, full text, keywords]
31. ((excis$ or remov$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 bladder$).mp. [mp=title, full text, keywords]
32. 30 or 31
33. (bladder$ adj5 (spare or sparing or spares or spared or preserv$)).mp. [mp=title, full text, keywords]
34. (avoid$ adj7 cystectom$).mp.
35. 33 or 34
36. ((excis$ or remov$ or biops$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 (lymph$ or node or nodes)).mp. [mp=title, full text, keywords]
37. (adjuvant$ or neoadjuvant$).mp. [mp=title, full text, keywords]
38. (abraxane or carboplatin$ or cisplatin$ or docetaxel or doxorubicin or epirubicin or 5-fluorouracil or gemcitabine or methotrexate or mitomycin or paclitaxel or valrubicin or vinblastin).mp. [mp=title, full text, keywords]
39. 37 or 38
40. 32 or 35 or 36 or 39
41. 29 and 40
42. 24 or 41

Database: EBM Reviews – Health Technology Assessment

1. ((Urinar$ or urothel$) adj5 (bladder$ adj3 (neoplas$ or cancer$ or tumor$ or tumour$ or carcino$ or adenocarcin$ or malig$))).mp. [mp=title, text, subject heading word]

Database: EBM Reviews – NHS Economic Evaluation Database

1. ((Urinar$ or urothel$) adj5 (bladder$ adj3 (neoplas$ or cancer$ or tumor$ or tumour$ or carcino$ or adenocarcin$ or malig$))).mp. [mp=title, text, subject heading word]
2. ((((non or "not") adj (invas$ or invad$ or infiltrat$)) or noninvas$ or noninvad$ or noninfiltrat$) adj5 muscle$).mp. [mp=title, text, subject heading word]
3. (cis or Tis or ta or t1$).mp. [mp=title, text, subject heading word]
4. 2 or 3
5. ((sign or signs or symptom$ or possib$ or suspect$ or potential$) adj5 (bladder$ adj3 (cancer$ or tumor$ or tumour$ or neoplas$ or carcino$ or malig$ or adenocarcin$))).mp. [mp=title, text, subject heading word]
6. 4 or 5
7. 1 and 6
8. ((urin$ adj3 biomark$) or bladder tumor associated antigen$ or nuclear matrix protein or nmp22 or fluorescence in situ hybrid$ or (fish adj assay$) or fibroblast growth factor receptor 3 or fgfr3 or cxbladder or immunocyt or cytokeratin fragment$ or cyfra 21-1 or (cytokerat$ adj3 (tpa or tps)) or survivin or telomeras$ or vascular endothelial growth factor$ or vegf or metalloproteinas$ or mmp-2 or mmp-9 or twist homolog$ or twist1 or nidogen-2 or nid2).mp. [mp=title, text, subject heading word]
9. 7 and 8
10. ((assess$ or analyz$ or judg$ or consider$ or quantif$ or predict$ or identif$ or adapt$) adj7 risk$).mp. [mp=title, text, subject heading word]
11. (surger$ or surgic$ or surgeon$ or cystectom$ or excis$ or (remov$ adj3 bladder$)).mp. [mp=title, text, subject heading word]
12. ((drug$ adj3 (therap$ or treat$ or regimen$ or protocol$)) or pharmacother$ or chemother$).mp. [mp=title, text, subject heading word]
13. Antineoplastic$.mp. [mp=title, text, subject heading word]
14. (Radiother$ or ((radio$ or irradiat$ or radiat$ or x-ray or gamma) adj3 (treat$ or therap$ or protocol$))).mp. [mp=title, text, subject heading word]
15. 11 or 12 or 13 or 14
16. 10 and 15
17. 7 and 16
18. (mitomycin$ or apaziquone or paclitaxel or gemcitabine or thiotepa or valrubicin or doxorubicin or bacillus calmette guerin or bcg or interferon$).mp. [mp=title, text, subject heading word]
19. 7 and 18
20. (electromotiv$ or emda).mp. [mp=title, text, subject heading word]
21. 1 and 20 (0)
22. (blue adj5 cystoscop$).mp. [mp=title, text, subject heading word]
23. 1 and 22
24. 9 or 17 or 19 or 21 or 23
25. ((Urinar$ or urothel$) adj5 (bladder$ adj3 (neoplas$ or cancer$ or tumor$ or tumour$ or carcino$ or adenocarcin$ or malig$))).mp. [mp=title, text, subject heading word]
26. ((invas$ or invad$ or infiltrat$) adj5 muscl$).mp. [mp=title, text, subject heading word]
27. (t2$ or t3$).mp. [mp=title, text, subject heading word]

28. 26 or 27
29. 25 and 28
30. cystectom$.mp. [mp=title, text, subject heading word]
31. ((excis$ or remov$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 bladder$).mp. [mp=title, text, subject heading word]
32. 30 or 31
33. (bladder$ adj5 (spare or sparing or spares or spared or preserv$)).mp. [mp=title, text, subject heading word]
34. (avoid$ adj7 cystectom$).mp.
35. 33 or 34
36. ((excis$ or remov$ or biops$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 (lymph$ or node or nodes)).mp. [mp=title, text, subject heading word]
37. (adjuvant$ or neoadjuvant$).mp. [mp=title, text, subject heading word]
38. (abraxane or carboplatin$ or cisplatin$ or docetaxel or doxorubicin or epirubicin or 5-fluorouracil or gemcitabine or methotrexate or mitomycin or paclitaxel or valrubicin or vinblastin).mp. [mp=title, text, subject heading word]
39. 37 or 38
40. 32 or 35 or 36 or 39
41. 29 and 40
42. 24 or 41

Appendix B. PICOTS

Table B1. PICOTS

PICOT	Inclusion and Exclusion Criteria
Populations	Include: Patients with signs or symptoms of possible bladder cancer [KQ 1; KQ 6; KQ7] Patients with non-muscle invasive bladder cancer (stages Ta, Tis, or T1) [KQ 2] Adults with non-muscle invasive bladder cancer treated with TURBT [KQ 3; KQ 8] Adults with high-risk non-muscle invasive bladder cancer treated with TURBT [KQ4; KQ8] Adults undergoing surveillance following treatment for non-muslce invasive bladder cancer [KQ 1; KQ 5; KQ 6; KQ 7]
Interventions	Include: Urinary biomarkers [KQ 1; KQ 5; KQ 7] Risk-adapted treatment approaches [KQ 2] Intravesical chemotherapeutic or immunotherapeutic agents [KQ 3; KQ 8] External beam radiation therapy, with or without systemic chemotherapy or immunotherapy [KQ 4] Blue light cystoscopy or other methods of augmented cystoscopy Biomarkers included are: BTAstat® [BTA], Alere NMP22®, BladderChek® [NMP22], UroVysion® [FISH] and ImmunoCyt™ [immunocytology], CxBladder™ Chemotherapeutic and immunotherapeutic agents of interest include: mitomycin; apaziquone; paclitaxel; gemcitabine; thiotepa; valrubicin; doxorubicin; epirubicin; bacillus Calmette-Guérin (BCG); and interferon Exclude: Electromotive drug administration
Comparators	Include: Other urinary biomarkers or standard diagnostic methods (cystoscopy, cytology and imaging) [KQ 1; KQ 5; KQ 7] Treatment not guided by risk-adapted approach [KQ 2] Other Intravesical chemotherapeutic or immunotherapeutic agent, different dose or duration of intravesical chemotherapy or immunotherapy, or TURBT alone [KQ 3; KQ 8] Intravesical chemotherapeutic or immunotherapeutic agents or cystectomy. [KQ 4]
Outcomes	Include: Diagnostic accuracy, using cystoscopy with biopsy as the reference standard [KQ 1; KQ 5] Mortality, disease specific and all-cause [KQ 2; KQ 3; KQ 4; KQ 5] Need for cystectomy [KQ 2; KQ 3; KQ 4; KQ 5] Recurrence of cancer [KQ 2; KQ 3;' KQ 4; KQ 5; KQ 6] Progression of cancer [KQ 2; KQ 3; KQ 4; KQ 5] Quality of life [KQ 2; KQ 3; KQ 4; KQ 5] Adverse effects of diagnostic testing [KQ 7] Adverse effects of treatment [KQ 8] Exclude: Prediction of treatment response
Timing	Include: Any duration of followup
Setting	Include: Inpatient or outpatient settings
Study Design	Include: RCTs, Cohort Studies Must be comparative Systematic reviews must evaluate quality of individual studies

KQ = key question; PICOTS = populations, interventions, comparators, outcomes, timing, setting; RCT = randomized controlled trial; T1 = Tumor stage 1; Ta = Tumor stage a; Tis = carcinoma in situ; TURBT = transurethral resection of bladder tumor

Appendix C. Included Studies

Please refer to this section as a reference list for Appendixes E and F.

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Appendix E. Data Abstraction of Included Studies

Table E1. Key Question 1: Diagnostic accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Cha, 2012 Germany Medium	ImmunoCyt	Prospective	Cystoscopy with pathological confirmation and imaging	Patients with painless hematuria (microscopic or gross) and no prior bladder cancer	Median age: 65 years Male: 78% Race: NR Smoker: NR Signs or symptoms: 68% microscopic hematuria and 32% gross hematuria Prior bladder cancer stage/grade: None with prior bladder cancer
Chahal, 2001 United Kingdom Medium	NMP22 (quantitative)	Prospective	Cystoscopy with pathological Confirmation	Patients with hematuria or irritative symptoms (n=96) or undergoing surveillance for treated bladder cancer (n=115)	Age: NR Sex: NR Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: NR
Feil, 2003 Germany Medium	ImmunoCyt	Unclear	Cystoscopy with pathological Confirmation	Patients suspected of having TCC (n=41), symptoms suggestive of tumor recurrence (n=46), or undergoing surveillance (n=34)	Mean age: 62 years Male: 82% Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: NR

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Cha, 2012 Germany Medium	202/1182 (21%) Tumor stage: 160 Ta, 44 T1, 26 T2-T4 Tumor grade: 138 low grade, 97 high grade	ImmunoCyt: Positive (≥1 fluorescent cell)	23 with inconclusive ImmunoCyt results (excluded)	None reported
Chahal, 2001 United Kingdom Medium	16/96 (17%) primary Tumor stage: 7 Ta, 5 T1, 3 T2, 1 T1 Tumor grade: 6 G1, 3 G2, 7 G3 17/115 (16%) recurrent Tumor stage: 15 Ta, 2 T1 Tumor grade: 13 G1, 3 G2, 1 G3	NMP22 (quantitative): >10 U/mL (also >3.75, >6.4, >10, >15.25)	NR	None reported
Feil, 2003 Germany Medium	26/113 (23%) Tumor stage: 11 Ta, 8 T1, 7 T2 Tumor grade: 7 G1, 19 G2/G3	ImmunoCyt: Positive (≥1 fluorescent cell)	8 specimens "could not be evaluated"	None reported

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Cha, 2012 Germany Medium	0.82 (202/245)	0.87 (811/937)	6.3	0.21
Chahal, 2001 United Kingdom Medium	Overall: 0.33 (11/33) Ta: 0.09 (2/22) T1: 0.43 (3/7) T2: 0.33 (1/3) T3: 1.0 (1/1) G1: 0.05 (1/19) G2: 0.33 (2/6) G3: 0.50 (4/8) Primary: 0.44 (7/16) Recurrent: 0.24 (4/17) NMP22 >1.5, >3.75, >4.75 >6.4, >7.25, >10, >15.25, >22.5 Overall: 0.49 (16/33), 0.42 (14/33), 0.42 (14/33), 0.39 (13/33), 0.33 (11/33), 0.33 (11/33), 0.33 (11/33), 0.30 (10/33)	Overall: 0.92 (164/178) NMP22 >1.5, >3.75, >4.75 >6.4, >7.25, >10, >15.25, >22.5 Overall: 0.64 (114/178), 0.80 (142/178), 0.81 (144/178), 0.86 (153/178), 0.89 (158/178), 0.92 (164/178), 0.92 (164/178), 0.93 (166/178)	Overall: 4.1 Primary: Recurrent: NMP22 >1.5, >3.75, >4.75 >6.4, >7.25, >10, >15.25, >22.5 Overall: 1.4, 2.1, 2.2, 2.8, 3.0, 4.1, 4.1, 4.3	Overall: 0.73 Primary: 0.62 Recurrent: 0.83 NMP22 >1.5, >3.75, >4.75 >6.4, >7.25, >10, >15.25, >22.5 Overall: 0.80, 0.72, 0.72, 0.71, 0.75, 0.73, 0.73, 0.75
Feil, 2003 Germany Medium	Overall: 0.38 (10/26) Ta: 0.18 (2/11) T1: 0.38 (3/8) T2: 0.71 (5/7) G1: 0.14 (1/7) G2: 0.43 (can't calculate n/N) G3: 0.60 (can't calculate n/N) ImmunoCyt + cytology Overall: 0.54 (14/26)	Overall: 0.84 (73/87) ImmunoCyt + cytology Overall: 0.82 (71/87)	Overall: 2.4 ImmunoCyt + cytology Overall: 3.0	Overall: 0.74 ImmunoCyt + cytology Overall: 0.56

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Cha, 2012 Germany Medium	0.62 (202/328)	0.95 (811/854)	NR	No funding reported	May have some overlap with populations in Schmitz-Drager 2007a and 2007b
Chahal, 2001 United Kingdom Medium	Overall: 0.44 (11/25) Primary: 0.50 (7/14) Recurrent: 0.33 (4/12) NMP22 >1.5, >3.75, >4.75 >6.4, >7.25, >10, >15.25, >22.5 Overall: 0.20 (16/80), 0.28 (14/50), 0.29 (14/48), 0.34 (13/38), 0.44 (11/25), 0.44 (11/25), 0.45 (10/22)	Overall: 0.88 (164/186) Primary: 0.89 (73/82) Recurrent: 0.87 (90/103) NMP22 >1.5, >3.75, >4.75 >6.4, >7.25, >10, >15.25, >22.5 Overall: 0.86 (114/133), 0.88 (142/161), 0.88 (144/163), 0.88 (153/173), 0.88 (164/186), 0.88 (164/186), 0.88 (166/189)	NR	NR; NMP22 kits provided by MAST Diagnostics	
Feil, 2003 Germany Medium	Overall: 0.42 (10/24) ImmunoCyt + cytology Overall: 0.47 (14/30)	Overall: 0.47 (14/30) ImmunoCyt + cytology Overall: 0.86 (71/83)	NR	NR	

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Friedrich, 2002 Germany Medium	BTA stat NMP22	Unclear	Cystoscopy with pathological Confirmation	Patients with symptoms suggestive of bladder cancer (hematuria or irritative voiding symptoms) (n=70) or undergoing surveillance for superficial bladder cancer (n=45)	Age: NR Sex: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: 30 Ta, 15 T1

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Friedrich, 2002 Germany Medium	54/115 (47%) Tumor stage 25 Ta, 20 T1, 8 ≥T2, 1 CIS Tumor grade: 7 G1, 31 G2, 16 G3	BTA stat: Positive NMP22 quantitative: >10 U/mL	NR	None reported

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Friedrich, 2002 Germany Medium	BTA Overall: 0.70 (38/54) Ta: 0.52 (13/25) T1: 0.85 (17/20) ≥T2: 1.00 (8/8) CIS: 0.0 (0/1) G1: 0.43 (3/7) G2: 0.68 (21/31) G3: 0.88 (14/16) NMP22 Overall: 0.69 (37/54) Ta: 0.52 (13/25) T1: 0.90 (18/20) ≥T2: 0.75 (6/8) CIS: 0.0 (0/1) G1: 0.43 (3/7) G2: 0.71 (22/31) G3: 0.75 (12/16)	BTA Overall: 0.64 (39/61) NMP22 Overall: 0.59 (36/61)	BTA Overall: 1.9 NMP22 Overall: 1.7	BTA Overall: 0.47 NMP22 Overall: 0.53

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Friedrich, 2002 Germany Medium	BTA Overall: 0.63 (38/60) NMP22 Overall: 0.60 (37/62)	BTA Overall: 0.71 (39/55) NMP22 Overall: 0.68 (36/53)	BTA Trak: NR NMP22: 0.68 (0.95 CI 0.59 to 0.77)	NR	

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Giannopoulos, 2001 Greece Medium	NMP22 (BladderChek) BTA stat	Unclear	Cystoscopy with pathological confirmation	Patients suspected of having bladder cancer based on clinical signs, symptoms, or recent imaging results (n=118) or undergoing surveillance for superficial bladder cancer (n=95)	Mean age: 66 years Male: 85% Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: NR
Gibanel, 2002 Spain Medium	BTA TRAK	Unclear	Cystoscopy with pathological confirmation	Patients with symptoms suspicious for bladder cancer or undergoing surveillance for bladder cancer (n=65) Excluded patients with BCG therapy, radiotherapy, or intravesical mitomycin	Age: NR Sex: NR Race: NR Smoker: NR Signs or symptoms: NR Previous bladder cancer stage/grade: NR

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Giannopoulos, 2001 Greece Medium	118/234 (50%) Tumor stage: 57 Ta, 32 T1, 20 T2-4, 6 CIS, 3 Tx Tumor grade: 30 G1, 45 G2, 43 G3	NMP22 quantitative: >8 U/mL BTA stat: Positive	NR	None reported
Gibanel, 2002 Spain Medium	21/65 (32%) Tumor stage: 2 Tis, 12 Ta, 2 T1, 5 T2-4 Tumor grade: 9 G1, 4 G2, 6 G3	BTA TRAK: >18 U/mL	NR	None reported

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Giannopoulos, 2001 Greece Medium	NMP22 Overall: 0.64 (75/118) Ta: 0.53 (30/57) T1: 0.66 (21/32) T2-4: 0.90 (18/20) CIS: 0.83 (5/6) G1: 0.50 (15/30) G2: 0.56 (25/45) G3: 0.81 (35/43) Primary: 0.69 (47/68) Recurrent: 0.56 (28/50) BTA stat Overall: 0.73 (86/118) Ta: 0.58 (33/57) CIS: 1.00 (6/6) T1: 0.78 (25/32) T2-4: 0.95 (19/20) G1: 0.50 (15/30) G2: 0.73 (33/45) G3: 0.88 (38/43) Primary: 0.74 (50/68) Recurrent: 0.72 (36/50) NMP22 + BTA stat Overall: 0.90 (106/118)	NMP22 Overall: 0.75 (87/116) BTA stat Overall: 0.65 (75/116) NMP22 + BTA stat: NR	NMP22 Overall: 2.6 BTA stat Overall: 2.1	NMP22 Overall: 0.48 BTA stat Overall: 0.42
Gibanel, 2002 Spain Medium	Overall: 0.52 (11/21) Ta: 0.33 (4/12) T1: 0.50 (1/2) T2-4: 1.00 (5/5) CIS: 0.50 (1/2) G1: 0.22 (2/9) G2: 0.60 (3/5) G3: 1.00 (5/5) BTA TRAK + cytology Overall: 0.81 (17/21)	Overall: 0.86 (31/36) BTA TRAK + cytology Overall: 0.83 (30/36)	Overall: 3.7 BTA TRAK + cytology Overall: 4.8	Overall: 0.56 BTA TRAK + cytology Overall: 0.23

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Giannopoulos, 2001 Greece Medium	NMP22 Overall: 0.72 (75/104) BTA stat Overall: 0.68 (86/127)	NMP22 Overall: 0.67 (87/130) BTA stat Overall: 0.70 (75/107)	NR	NR	
Gibanel, 2002 Spain Medium	Overall: 0.69 (11/16) BTA TRAK + cytology Overall: 0.74 (17/23)	Overall: 0.76 (31/41) BTA TRAK + cytology Overall: 0.88 (30/34)	Overall: 0.68 +/- 0.079 BTA TRAK + cytology Overall: NR	NR	

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Grossman, 2005 United States (also Lotan 2009) Low	NMP22 (qualitative, BladderChek)	Prospective	Cystoscopy with pathological confirmation	Patients with risk factors or symptoms associated with bladder cancer (e.g. smoking, hematuria, dysuria) (n=1331)	Mean age: 59 years Male: 57% Race: 82% White, non-Hispanic; 9% Smoker: NR Signs or symptoms: NR

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Grossman, 2005 United States (also Lotan 2009) Low	79/1331 (5.9%) Tumor stage: 30 Ta, 27 T1, 6 T2 or T2a, 4 T3a or T3b, 7 Tx, 5 CIS Tumor grade: 27 well differentiated, 18 moderately differentiated, 25 poorly differentiated, 9 grade unknown	NMP22 qualitative: Positive	16 patients did not undergo NMP22	49 patients did not undergo cystoscopy (excluded)

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Grossman, 2005 United States (also Lotan 2009) Low	Overall: 0.56 (44/79) Ta: 0.47 (14/30) T1: 0.48 (13/27) T2, T2a: 1.00 (6/6) T3a, T3b: 0.75 (3/4) Tx: 0.57 (4/7) Ta-T1: 0.50 (31/62) T2-T3: 0.90 (9/10) CIS: 0.80 (4/5) Well-differentiated: 0.48 (13/27) Moderately differentiated: 0.50 (9/18) Poorly differentiated: 0.72 (18/25) Gx: 0.44 (4/9) Men: 0.59 (34/58) Women: 0.50 (9/18) <65 years: 0.63 (17/27) >65 years: 0.53 (26/49) Smoker: 0.50 (18/36) Nonsmoker: 0.62 (25/40) Microhematuria: 0.47 (17/36) Gross hematuria: 0.44 (26/59)	Overall: 0.86 (1073/1252) Men: 0.84 (556/665) Women: 0.88 (466/531) <65 years: 0.89 (679/766) >65 years: 0.80 (343/430) Smoker: 0.86 (367/425) Nonsmoker: 0.85 (655/771) Microhematuria: 0.86 (799/924) Gross hematuria: 0.79 (133/168)	Overall: 4.0	Overall: 0.51

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Grossman, 2005 United States (also Lotan 2009) Low	Overall: 0.20 (44/223) Men: 0.24 (34/143) Women: 0.12 (9/74) <65 years: 0.16 (17/104) >65 years: 0.23 (26/113) Smoker: 0.24 (18/76) Nonsmoker: 0.18 (25/141) Microhematuria: 0.12 (17/142) Gross hematuria: 0.98 (799/818)	Overall: 0.97 (1073/1108) Men: 0.96 (556/580) Women: 0.98 (466/475) <65 years: 0.99 (679/689) >65 years: 0.94 (343/366) Smoker: 0.95 (367/385) Nonsmoker: 0.98 (655/670) Microhematuria: 0.98 (799/818) Gross hematuria: 0.80 (133/166)	NR	Matritech Inc.	

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Grossman, 2006 United States Low	NMP22 (qualitative, BladderChek)	Prospective	Cystoscopy with pathological confirmation	Patients undergoing surveillance for bladder cancer (n=668)	Mean age: 71 years Male: 75% Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: NR
Gudjonsson, 2008 Sweden Medium	FISH (UroVysion)	Prospective	Cystoscopy with pathological confirmation	Patients under surveillance for Ta, T1, and CIS (n=156)	Mean age: NR Sex: NR Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: All Ta, T1, or CIS; otherwise NR
Gupta, 2009 India Medium	NMP22 (qualitative, BladderChek)	Prospective	Cystoscopy with pathological confirmation	Patients under surveillance for NMIBC (n=145) Excluded patients with active UTI	Mean age: 57 years Male: 87% Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: 91 Ta, 45 T1, 9 CIS; 18 low malignant potential, 83 low grade, 44 high grade

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Grossman, 2006 United States Low	103/668 (15%) Tumor stage: 50 Ta, 17 T1, 8 T2, 1 T3, 2 T4, 8 CIS, 17 Tx Tumor grade: 38 well differentiated, 16 moderately differentiated, 32 poorly differentiated	NMP 22 qualitative: Positive	None reported	None
Gudjonsson, 2008 Sweden Medium	27/152 (18%) Tumor stage/grade: 1 low malignant potential, 16 TaG1-G2, 1 TaG1 + CIS, 5 Tis, 4 T1G2-G3	FISH: Positive (>16% cells with multiple chromosomes or >48% cells with 9p21 homozygous loss)	16 patients had insufficient amounts of urothelial cells, or other technical factors	4 patients underwent electrocauterization without biopsy
Gupta, 2009 India Medium	56/145 (39%) Tumor stage: 31 Ta, 13 T1, 3 CIS Tumor grade: 6 low malignant potential, 27 low grade, 14 high grade	NMP22 qualitative: Positive	NR	None reported

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Grossman, 2006 United States Low	NMP22 Overall: 0.50 (51/103) Ta: 0.36 (18/50) T1: 0.65 (11/17) T2-T4: 0.91 (10/11) Tx: 0.47 (8/17) Well differentiated: 0.32 (12/38) Moderately differentiated: 0.44 (7/16) Poorly differentiated: 0.75 (24/32) NMP22 + cytology Overall: 0.99 (102/103)	NMP22 Overall: 0.87 (493/565) No evidence of urinary tract disease: 0.89 (236/264) Benign prostatic hyperplasia/prostatitis: 0.86 (103/120) Erythema/cystitis/inflammation: 0.85 (70/82) Urinary tract infection: 0 (0/3) Hyperplasia/squamous metaplasia/cyst/polyp/caruncle: 0.91 (21/23) Calculi: 0.83 (5/6) Trabeculations: 0.88 (43/49) Diverticulum/pouch/cellule: 0.83 (15/18) NMP22 + cytology Overall: NR	NMP22 Overall: 3.8	NMP22 Overall: 0.57
Gudjonsson, 2008 Sweden Medium	Overall: 0.30 (8/27) Low malignant potential: 0.0 (0/1) TaG1-G2: 0.06 (1/16) TaG1 + CIS: 1.00 (1/1) T1G2-G3: 0.25 (1/4) CIS: 1.00 (5/5)	Overall: 0.95 (119/125)	Overall: 6.0	Overall: 0.74
Gupta, 2009 India Medium	Overall: 0.86 (48/56) Low malignant potential: 1.00 (7/7) Low grade: 0.81 (29/36) High grade: 0.85 (11/13) NMP22 + cytology Overall: 0.93 (52/56)	Overall: 0.78 (69/89) LMP: 0.55 Low grade: 0.65 High grade: 0.57 NMP22 + cytology Overall: 0.75 (67/89)	Overall: 3.9 LMP: 2.2 Low grade: 2.3 High grade: 2.0 NMP22 + cytology Overall: 3.7	Overall: 0.18 LMP: 0 Low grade: 0.29 High grade: 0.26 NMP22 + cytology Overall: 0.09

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Grossman, 2006 United States Low	NMP22 Overall: 0.41 (51/123)	NMP22 Overall: 0.90 (493/545)	NR	Matritech Inc.	Cases include 9 patients diagnosed after initial cystoscopy at 1-5 months (7 at 1-3 months)
Gudjonsson, 2008 Sweden Medium	Overall: 0.57 (8/14)	Overall: 0.86 (119/138)	NR	NR	
Gupta, 2009 India Medium	Overall: 0.71 (48/68) LMP: 0.088 Low grade: 0.44 High grade: 0.16	Overall: 0.90 (69/77) LMP: 1.00 Low grade: 0.91 High grade: 0.97	NR	NR	Unable to calculate n/N for specificity and PPV/NPV stratified by tumor grade

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Gutierrez Banos, 2001 Spain Medium	NMP22 (quantitative) BTA stat	Unclear	Cystoscopy with pathological confirmation	Patients with signs and symptoms suspicious for bladder cancer (n=64) or undergoing surveillance for bladder cancer (n=86) Excluded patients with recent systemic chemotherapy, renal disease (stones, nephritis, or kidney cancer), recent bladder trauma, radiation therapy, or gross hematuria and UTI	Mean age: 68 years Sex: NR Race: NR Smoker: NR Signs or symptoms (n=64): 88% macroscopic hematuria, 6.2% irritative symptoms, 6.2% other Prior bladder cancer stage/grade: NR

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Gutierrez Banos, 2001 Spain Medium	76/150 (51%) Tumor stage: 16 Ta, 46 T1, 14 T2-T4 Tumor grade: 16 G1, 29 G2, 31 G3	NMP22 quantitative: >10 U/mL (also >6 U/mL) BTA stat: Positive	NR	None reported

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Gutierrez Banos, 2001 Spain Medium	NMP22 >10 U/mL Overall: 0.76 (58/76) Ta: 0.50 (8/16) T1: 0.80 (37/46) T2-T4: 0.93 (13/14) G1: 0.50 (8/16) G2: 0.69 (20/29) G3: 0.97 (30/31) NMP22 >6 U/mL Overall: 0.84 (64/76) Ta: 0.69 (11/16) T1: 0.85 (39/46) T2-T4: 1.00 (14/14) G1: 0.69 (11/16) G2: 0.76 (22/29) G3: 1.00 (31/31) BTA stat Overall: 0.72 (55/76) Ta: 0.50 (8/16) T1: 0.74 (34/46) T2-T4: 0.93 (13/14) G1: 0.56 (9/16) G2: 0.62 (18/29) G3: 0.90 (28/31)	NMP22 >10 U/mL Overall: 0.91 (67/74) NMP22 >6 U/mL Overall: 0.86 (64/74) BTA stat Overall: 0.89 (66/74)	NMP22 >10 U/mL Overall: 8.1 NMP22 >6 U/mL Overall: 6.2 BTA stat Overall: 6.7	NMP22 >10 U/mL Overall: 0.26 NMP22 >6 U/mL Overall: 0.18 BTA stat Overall: 0.31

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Gutierrez Banos, 2001 Spain Medium	NMP22 >10 U/mL Overall: 0.89 (58/65) NMP22 >6 U/mL Overall: 0.86 (64/74) BTA stat Overall: 0.87 (55/63)	NMP22 >10 U/mL Overall: 0.79 (67/85) NMP22 >6 U/mL Overall: 0.84 (64/76) BTA stat Overall: 0.76 (66/87)	NR	NR	

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Halling, 2002 USA High	BTA stat FISH (UroVysion)	Unclear	Cystoscopy with pathological confirmation	Patients undergoing surveillance for bladder cancer (n=146) or with signs and symptoms (n=119)	Mean age: 70 years Male: 75% Race: NR Smoker: NR Signs and symptoms: NR Prior bladder cancer stage/grade: NR
Horstmann, 2009 Germany Medium	NMP22 (quantitative) ImmunoCyt FISH (UroVysion)	Unclear	Cystoscopy with pathological confirmation	Patients with prior bladder cancer undergoing surveillance or TURBT for suspected recurrence	Mean age: 77 years Male: 82% Race: NR Smoker: NR Signs and symptoms: NR Prior bladder cancer stage/grade: NR

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Halling, 2002 USA High	75/265 (28%) Tumor stage: 38 Ta, 19 T1-T4, 17 CIS Tumor grade: 12 G1, 25 G2, 37 G3	BTA stat: positive FISH: Positive (>5 cells with gains of ≥2 chromosomes or ≥10 cells with gains of 1 chromosome, or >20% cells with 9p21 homozygous loss)	Unclear, diagnostic accuracy only assessed in 155/265 of patients	None reported
Horstmann, 2009 Germany Medium	113/221 (51%) Tumor stage: 69 Ta, 15 T1, 11 T2-T4, 18 CIS Tumor grade: 32 G1, 53 G2, 28 G3	NMP22 quantitative: >10 U/mL ImmunoCyt: Positive (≥1 fluorescent cell) FISH: Positive (≥4 cells with gains of ≥2 chromosomes or ≥12 cells with one signal for 9p21)	NR	None reported

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Halling, 2002 USA High	BTA stat Overall: 0.78 (56/72) Ta: 0.63 (24/38) T1-T4: 0.94 (16/17) CIS: 0.94 (16/17) G1: 0.50 (6/12) G2: 0.72 (18/25) G3: 0.91 (32/35) FISH (UroVysion) Overall: 0.81 (59/73) Ta: 0.65 (24/37) T1-T4: 0.95 (18/19) CIS: 1.0 (17/17) G1: 0.36 (4/11) G2: 0.76 (19/25) G3: 0.97 (36/37)	BTA stat Overall: 0.74 (59/80) FISH (UroVysion) Overall: 0.96 (75/78)	BTA stat Overall: 3.0 FISH (UroVysion) Overall: 20	BTA stat Overall: 0.30 FISH (UroVysion) Overall: 0.20
Horstmann, 2009 Germany Medium	NMP22 Overall:0.68 (77/113) G1: 0.62 (20/32) G2: 0.64 (34/53) G3: 0.79 (22/28) ImmunoCyt Overall: 0.73 (83/113) G1: 0.62 (20/32) G2: 0.81 (43/53) G3: 0.71 (20/28) FISH Overall: 0.76 (86/113) G1: 0.53 (17/32) G2: 0.83 (44/53) G3: 0.89 (25/28)	NMP22 Overall: 0.49 (53/108) ImmunoCyt Overall: 0.72 (78/108) FISH Overall: 0.63 (68/108)	NMP22 Overall:1.3 ImmunoCyt Overall: 2.6 FISH Overall: 2.0	NMP22 Overall: 0.65 ImmunoCyt Overall: 0.38 FISH Overall: 0.38

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Halling, 2002 USA High	BTA stat Overall: 0.73 (56/77) FISH (UroVysion) Overall: 0.95 (59/62)	BTA stat Overall: 0.79 (59/75) FISH (UroVysion) Overall: 0.84 (75/89)	NR	NR	265 patients evaluated, sensitivity evaluated in 75 patients with bladder cancer but specificity only evaluated in 80 patients without bladder cancer
Horstmann, 2009 Germany Medium	NMP22 Overall:0.58 (77/132) ImmunoCyt Overall: 0.73 (83/113) FISH Overall: 0.68 (86/126)	NMP22 Overall: 0.60 (53/89) ImmunoCyt Overall: 0.72 (78/108) FISH Overall: 0.72 (68/95)	NR	Reports no funding	Slight discrepancies between reported and calculated results for diagnostic accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Ianari, 1997 Italy Medium	BTA stat	Prospective	Cystoscopy with pathological confirmation	Patients undergoing surveillance for bladder cancer (n=75)	Median age: 66 years Male: 83% Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: NR
Irani, 1999 France Medium	BTA stat BTA TRAK	Prospective	Cystoscopy with pathological confirmation	Patients with or without a history of bladder cancer with symptoms suspicious for bladder cancer (n=81)	Mean age: NR Male: 83% Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: NR
Junker 2006 Germany Medium	FISH (UroVysion)	Unclear	Cystoscopy with pathological confirmation	Patients undergoing evaluation for bladder cancer	Mean age: NR Male: NR Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: NR
Karnwal, 2010 USA Medium	FISH (UroVysion)	Retrospective	Cystoscopy with pathological confirmation	Patients undergoing surveillance for NMIBC (n=59)	Mean age: 56 years Male: 68% Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: 33 Ta, 22 T1, 2 T1 and CIS; 23 G1, 20 G2, 16 G3

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Ianari, 1997 Italy Medium	13/75 (17%) Tumor stage: 18 Ta, 4 T1 and CIS, 13 T2, 4 T3, 1 T4, 3 CIS Tumor grade: 1 G1, 2 G2, 3 G3, 7 Gx	BTA stat: positive	NR	None reported
Irani, 1999 France Medium	49/81 (60%) Tumor stage: 28 Ta, 11 T1, 10 ≥T2 Tumor grade: 19 G1, 18 G2, 12 G3	BTA stat: positive BTA TRAK: >14 U/mL	NR	None reported
Junker 2006 Germany Medium	112/141 (79%) Tumor stage: 76 Ta, 24 T1, 11 T2-T3, 1 CIS Tumor grade: NR	FISH: Positive (≥5 cells with gain of >1 chromosome, ≥10 cells with gain of 1 chromosome, ≥10 cells loss of 9p21 locus)	20	None reported
Karnwal, 2010 USA Medium	48/59 (81%) Tumor stage: 33 Ta, 24 T1, 4 CIS Tumor grade: 23 G1 or G2, 25 G3	FISH: Positive (criteria NR)	NR	None reported

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Ianari, 1997 Italy Medium	Overall: 0.54 (7/13) G1: 0.00 (0/1) G2: 0.50 (1/2) G3: 1.00 (3/3) (excludes 7 cases with unknown grade)	Overall: 0.85 (53/62)	Overall: 3.6	Overall: 0.54
Irani, 1999 France Medium	BTA stat Overall: 0.65 (32/49) Ta: 0.50 (14/28) T1: 0.73 (8/11) ≥T2: 1.0 (10/10) G1: 0.53 (10/19) G2: 0.72 (13/18) G3: 0.92 (11/12) BTA TRAK Overall: 0.78 (38/49) Ta: 0.68 (19/28) T1: 0.82 (9/11) ≥T2: 1.0 (10/10) G1: 0.74 (14/19) G2: 0.72 (13/18) G3: 0.92 (11/12)	BTA stat Overall: 0.72 (23/32) BTA TRAK Overall: 0.62 (20/32)	BTA stat Overall: 2.3 BTA TRAK Overall: 2.1	BTA stat Overall: 0.49 BTA TRAK Overall: 0.35
Junker 2006 Germany Medium	Overall: 0.60 (57/95) Ta: 0.35 (22/62) T1: 0.65 (15/23) T2-T3: 1.0 (11/11) G1: 0.38 (n/N NR) G2: 0.65 G3: 0.92	Overall: 0.83 (19/23)	Overall: 3.53	Overall: 0.48
Karnwal, 2010 USA Medium	Overall: 0.62 (30/48)	Overall: 0.65 (30/46)	Overall: 1.8	Overall: 0.57

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Ianari, 1997 Italy Medium	Overall: 0.44 (7/16)	Overall: 0.90 (53/59)	NR	NR, BTA tests provided by Bard Diagnostic Sciences	Reports specificity of 91% based on per-cystoscopy evaluation; results reported here as per patient
Irani, 1999 France Medium	BTA stat Overall: 0.78 (32/41) BTA TRAK Overall: 0.76 (38/50)	BTA stat Overall: 0.58 (23/40) BTA TRAK Overall: 0.65 (20/31)	NR	NR	
Junker 2006 Germany Medium	Overall: 0.93 (57/61)	Overall: 0.33 (19/57)	NR	NR	
Karnwal, 2010 USA Medium	Overall: 0.65 (30/46)	Overall: 0.63 (30/48)	NR	NR	

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Leyh, 1997a Germany, UK, and France Medium	BTA stat	Prospective	Cystoscopy with pathological confirmation	Patients with (n=69) or without (n=345) a history of bladder cancer suspected of having bladder cancer based on signs, symptoms, recent intravenous urography, or recent cystoscopy	Mean age: 60 years Male: 64% Race: NR Smoker: NR Signs or symptoms (n=413): 122 gross hematuria, 323 microscopic hematuria, 75 dysuria, 148 bladder irritability, 77 urinary urgency, 39 flank pain, 44 suspicious cystoscopy, 21 abnormal intravenous urography Prior bladder cancer stage/grade: NR
Leyh, 1997b Germany and France Medium	BTA stat	Prospective	Cystoscopy with pathological confirmation	Patients undergoing surveillance for bladder cancer (n=164)	Mean age: 67 years Male: 77% Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: NR

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Leyh, 1997a Germany, UK, and France Medium	71/414 (17%) Tumor stage: 28 Ta, 23 T1, 18 ≥T2, 4 CIS Tumor grade: 6 G1, 36 G2, 25 G3	BTA stat: Positive	NR	None reported
Leyh, 1997b Germany and France Medium	39/164 (24%) Tumor stage: 15 Ta, 10 T1, 10 ≥T2 Tumor grade: 10 G1, 16 G2, 12 G3	BTA stat: Positive	NR	14 patients excluded from analysis with "suspicion" of bladder cancer but no confirmed diagnosis

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Leyh, 1997a Germany, UK, and France Medium	Overall: 0.70 (50/71) Ta: 0.38 (9/24) T1: 0.87 (20/23) ≥T2: 0.89 (16/18) G1: 0.17 (1/6) G2: 0.64 (23/36) G3: 0.92 (23/25) Primary: 0.80 (33/41) Recurrent: 0.57 (17/30)	Overall: 0.90 (304/337) Primary: 0.91 (277/304) Recurrent: 0.82 (27/33)	Overall: 7.0 Primary: 8.0 Recurrent: 3.2	Overall: 0.33 Primary: 0.21 Recurrent: 0.52
Leyh, 1997b Germany and France Medium	BTA STAT Overall: 0.54 (21/39) Ta: 0.33 (5/15) T1: 0.60 (6/10) ≥T2: 0.80 (8/10) G1: 0.30 (3/10) G2: 0.44 (7/16) G3: 0.92 (11/12) BTA STAT plus cytology Overall: 0.64 (25/39)	BTA STAT Overall: 0.92 (102/111) BTA STAT plus cytology Overall: NR	BTA STAT Overall: 6.8 BTA STAT plus cytology Overall: Not calculable	BTA STAT Overall: 0.50 BTA STAT plus cytology Overall: Not calculable

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Leyh, 1997a Germany, UK, and France Medium	Overall: 0.60 (50/83) Primary: 0.55 (33/60) Recurrent: 0.74 (17/23)	Overall: 0.94 (304/325) Primary: 0.97 (277/285) Recurrent: 0.68 (27/40)	NR	Bard Diagnostic Sciences	0.15 with suspicious cystoscopy or abnormal intravenous urography
Leyh, 1997b Germany and France Medium	BTA STAT Overall: 0.70 (21/30) BTA STAT plus cytology Overall: NR	BTA STAT Overall: 0.85 (102/120) BTA STAT plus cytology Overall: NR	NR	Bard Diagnostic Sciences	

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Leyh, 1999 Austria, France, Germany, and Italy High	BTA stat	Prospective	Cystoscopy with pathological confirmation	Patients with (n=134) or without (n=106) a history of bladder cancer suspected of having bladder cancer based on signs, symptoms, recent intravenous urography, or recent cystoscopy	Mean age: 64 years Male: 72% Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: NR

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Leyh, 1999 Austria, France, Germany, and Italy High	107/231 (46%) Tumor stage: 58 Ta, 27 T1, 17 T2-T4, 5 CIS Tumor grade: 26 G1, 45 G2, 36 G3	BTA stat: Positive	18 excluded for "protocol violation"	9 patients excluded from analysis with "suspicion" of bladder cancer but no confirmed diagnosis

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Leyh, 1999 Austria, France, Germany, and Italy High	BTA stat Overall: 0.65 (70/107) Ta: 0.53 (31/58) T1: 0.70 (19/27) T2-T4: 0.88 (15/17) CIS: 1.0 (5/5) G1: 0.39 (10/26) G2: 0.67 (30/45) G3: 0.83 (30/36) Primary: 0.73 (40/55) Recurrent: 0.58 (30/52) BTA stat plus cytology Overall: 0.71 (76/107)	BTA stat Overall: 0.64 (79/124) Primary: 0.52 (26/50) Recurrent: 0.72 (53/74) No genitourinary disease: 0.71 (63/89) Benign renal disease: 0.33 (2/6) Tumors other than bladder cancer: 0.17 (1/6) UTI: 0.50 (4/8) Other genitourinary disease: 0.60 (9/15) BTA stat plus cytology Overall: 0.64 (79/124)	BTA stat Overall: 1.8 BTA stat plus cytology Overall: 2.0	BTA stat Overall: 0.55 BTA stat plus cytology Overall: 0.45

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Leyh, 1999 Austria, France, Germany, and Italy High	BTA stat: Overall: 0.61 (70/115) BTA stat plus cytology Overall: 0.63 (76/121)	BTA stat Overall: 0.68 (79/116) BTA stat plus cytology Overall: 0.72 (79/110)	NR	Bard Diagnostic Sciences	

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Lodde, 2003 Italy Medium	ImmunoCyt (uCyt+)	Prospective	Cystoscopy with pathological confirmation	Patients with signs and symptoms suspicious for bladder cancer (e.g., microhematuria or gross hematuria and/or irritative symptoms) (n=98) or surveillance after TURBT (n=137)	Mean age: NR Sex: NR Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: NR

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Lodde, 2003 Italy Medium	51/91 (56%) primary Tumor stage: 29 Ta, 13 T1, 6 ≥T2, 3 CIS Tumor grade: 20 G1, 18 G2, 13 G3 51/134 (38%) recurrent Tumor stage: 33 Ta, 3 T1, 5 ≥T2, 10 CIS Tumor grade: 23 G1, 10 G2, 18 G3	ImmunoCyt: Positive (≥1 fluorescent cell)	10 patients had too few cells for uCyt+	None reported

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Lodde, 2003 Italy Medium	Overall: 0.87 (89/102) Ta: 0.81 (50/62) T1: 0.94 (15/16) ≥T2: 0.91 (10/11) CIS: 1.0 (13/13) G1: 0.81 (35/43) G2: 0.89 (25/28) G3: 0.94 (29/31) Primary: 0.92 (47/51) Ta: 0.86 (25/29) T1: 1.00 (13/13) ≥T2: 0.83 (5/6) CIS: 1.00 (3/3) G1: 0.85 (17/20) G2: 1.00 (18/18) G3: 0.92 (12/13) Recurrent: 0.82 (42/51) Ta: 0.76 (25/33) T1: 0.67 (2/3) ≥T2: 1.00 (5/5) CIS: 1.00 (10/10) G1: 0.78 (18/23) G2: 0.70 (7/10) G3: 0.94 (17/18)	Overall: 0.67 (83/123) Primary: 0.75 (30/40) Recurrent: 0.64 (53/83)	Overall: 2.6 Primary: 3.7 Recurrent: 2.3	Overall: 0.19 Primary: 0.11 Recurrent: 0.28

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Lodde, 2003 Italy Medium	Overall: 0.69 (89/129) Primary: 0.82 (47/57) Recurrent: 0.53 (42/79)	Overall: 0.86 (83/96) Primary: 0.88 (30/34) Recurrent: 0.90 (53/59)	NR	NR	

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Messing, 2005 USA Medium	ImmunoCyt	Unclear	Cystoscopy with pathological confirmation	Patients undergoing surveillance for completed resected stage T1 or less urothelial cancer, focus on grade 1 and 2 cancer (n=327)	Age: NR Sex: NR Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: All T1 or less; no other data provided

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Messing, 2005 USA Medium	61/327 (19%) Tumor stage: 35 Ta, 8 T1, 2 T2, 5 CIS, 9 Tx Tumor grade: 28 G1, 10 G2, 6 G3	ImmunoCyt: Positive (≥1 fluorescent cell)	14 patients had too few cells for ImmunoCyt	9 patients had cystoscopically evident tumors that were fulgurated, with no tissue for histology

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Messing, 2005 USA Medium	ImmunoCyt Overall: 0.81 (42/52) Ta: 0.83 (29/35) T1: 0.75 (6/8) T2: 1.00 (2/2) CIS: 1.00 (5/5) G1: 0.79 (22/28) G2: 0.90 (9/10) G3: 0.67 (4/6) ImmunoCyt + cytology Overall: 0.81 (42/52) Ta: 0.83 (29/35) T1: 0.75 (6/8) T2: 1.00 (2/2) CIS: 1.00 (5/5) G1: 0.79 (22/28) G2: 0.90 (9/10) G3: 0.67 (4/6)	ImmunoCyt Overall: 0.75 (206/274) ImmunoCyt + cytology: Overall: 0.73 (201/274)	ImmunoCyt Overall: 3.2 ImmunoCyt + cytology Overall: 3.0	ImmunoCyt Overall: 0.25 ImmunoCyt + cytology Overall: 0.26

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Messing, 2005 USA Medium	ImmunoCyt Overall: 0.38 (42/110) ImmunoCyt + cytology Overall: 0.37 (42/115)	ImmunoCyt Overall: 0.95 (206/216) ImmunoCyt + cytology Overall: 0.95 (206/216)	NR	NR	

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Mian, 1999 Italy Medium	ImmunoCyt	Prospective	Cystoscopy with pathological confirmation	Patients undergoing surveillance (n=142) or with signs and symptoms (n=107)	Mean age: 66 years Male: 77% Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: NR
Mian, 2000 Italy and Austria Medium	BTA stat	Retrospective	Cystoscopy with pathological confirmation	Patients with symptoms suggestive of bladder cancer (n=57) or undergoing surveillance for bladder cancer (n=123)	Mean age: 66 years Sex: NR Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: NR
Nasuti, 1999 USA Medium	BTA stat	Unclear	Cystoscopy with pathological confirmation	Patients with dysuria, incontinence, gross hematuria, or microscopic hematuria (n=100)	Age: NR Sex: NR Race: NR Smoker: NR Signs or symptoms: NR

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Mian, 1999 Italy Medium	56/142 (39%) primary, 23/107 (21%) recurrent Tumor stage: 43 Ta, 20 T1, 12 ≥T2, 4 CIS Tumor grade: 25 G1, 25 G2, 29 G3	ImmunoCyt: Positive (≥1 fluorescent cell)	15 had fewer than 500 cells/slide	None reported
Mian, 2000 Italy and Austria Medium	53/180 (29%) Tumor stage: 28 Ta, 13 T1, 7 ≥T2, 1 CIS Tumor grade: 18 G1, 19 G2, 16 G3	BTA stat: Positive	NR	None reported
Nasuti, 1999 USA Medium	3/100 (3%) Tumor stage: 2 noninvasive, 1 invasive Tumor grade: 2 G2, 1 G3	BTA stat: Positive	NR	None reported

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Mian, 1999 Italy Medium	ImmunoCyt Overall: 0.86 (68/79) Ta: 0.86 (37/43) T1: 0.85 (17/20) ≥T2: 0.83 (10/12) CIS: 1.0 (4/4) G1: 0.84 (21/25) G2: 0.84 (21/25) G3: 0.90 (26/29) Primary: 0.91 (21/23) Recurrent: 0.84 (47/56) ImmunoCyt + cytology Overall: 0.90 (71/79) Ta: 0.88 (38/43) T1: 0.90 (18/20) ≥T2: 0.92 (11/12) CIS: 1.0 (4/4) G1: 0.84 (21/25) G2: 0.88 (22/25) G3: 0.97 (28/29) Primary: 0.96 (22/23) Recurrent: 0.88 (49/56)	ImmunoCyt Overall: 0.79 (135/170) Primary: 0.79 (66/84) Cystitis: 0.60 (6/10) Urolithiasis: 0.92 (22/24) Benign lower urinary tract lesion: 0.50 (8/16) Microhematuria: 0.85 (23/27) Renal, prostate, or cervical cancer: 1.0 (7/7) Recurrent: 0.80 (69/86) ImmunoCyt + cytology Overall: 0.79 (135/170) Primary: 0.79 (66/84) Cystitis: 0.60 (6/10) Urolithiasis: 0.92 (22/24) Benign lower urinary tract lesion: 0.50 (8/16) Microhematuria: 0.85 (23/27) Renal, prostate, or cervical cancer: 1.0 (7/7) Recurrent: 0.80 (69/86)	ImmunoCyt Overall: 4.1 Primary: 4.3 Recurrent: 4.2 ImmunoCyt + cytology Overall: 4.3 Primary: 4.6 Recurrent: 4.4	ImmunoCyt Overall: 0.18 Primary: 0.11 Recurrent: 0.20 ImmunoCyt + cytology Overall: 0.13 Primary: 0.05 Recurrent: 0.15
Mian, 2000 Italy and Austria Medium	Overall: 0.53 (28/53) Ta: 0.43 (12/28) T1: 0.62 (8/13) ≥T2: 0.70 (7/10) CIS: 0.50 (1/2) G1: 0.39 (7/18) G2: 0.53 (10/19) G3: 0.69 (11/16)	Overall: 0.70 (89/127)	Overall: 1.8	Overall: 0.67
Nasuti, 1999 USA Medium	1.0 (3/3)	0.84 (81/97)	6.2	0

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Mian, 1999 Italy Medium	ImmunoCyt Overall: 0.66 (68/103) Primary: 0.54 (21/39) Recurrent: 0.73 (47/64) ImmunoCyt + cytology Overall: 0.67 (71/106) Primary: 0.55 (22/40) Recurrent: 0.74 (49/66)	ImmunoCyt Overall: 0.92 (135/146) Primary: 0.97 (66/68) Recurrent: 0.88 (69/78) ImmunoCyt + cytology Overall: 0.94 (135/143) Primary: 0.99 (66/67) Recurrent: 0.91 (69/76)	NR	DiagnoCure, Inc.	
Mian, 2000 Italy and Austria Medium	Overall: 0.42 (28/66)	Overall: 0.78 (89/114)	NR	NR	Studies reports PPV of 0.43 and 0.79, results reported here are based on 2 x 2 tables
Nasuti, 1999 USA Medium	0.16 (3/19)	1.0 (81/81)	NR	NR	

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Olsson, 2001 Sweden Medium	ImmunoCyt	Unclear	Cystoscopy with pathological confirmation	Patients undergoing surveillance for bladder cancer (n=61) or with gross or microscopic hematuria (n=60)	Mean age: 68 years Male: 79% Race: NR Smoker: NR Signs or symptoms: 50% with hematuria Prior bladder cancer stage/grade: NR
O'Sullivan, 2012 New Zealand Medium	Cxbladder NMP22 (qualitative, Bladderchek) NMP22 (quantitative)	Prospective	Cystoscopy with pathological confirmation	Patients with recent gross hematuria, no prior history of bladder cancer (n=485)	Median age: 69 years Male: 80% Race: 87% European, 6.8% Maori Smoker: 16% current, 44% ex-smoker, 40% never smoker Signs or symptoms: 100% gross hematuria

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Olsson, 2001 Sweden Medium	31/114 (27%) Tumor stage: 18 Ta, 7 T1, 4 T2, 2 CIS Tumor grade: 8 G1, 14 G2, 8 G3	ImmunoCyt: Positive (≥1 fluorescent cell)	7 excluded due to too few cells	None reported
O'Sullivan, 2012 New Zealand Medium	66/485 (14%) Tumor stage: 38 Ta, 16 T1, 9 T2, 2 ≥T3, 2 CIS Tumor grade: 3 G1, 38 G2, 24, G3 (WHO 1973); 32 low, 4 mixed, 29 high (WHO ISUP 1998)	Cxbladder: At values giving 85% or 90% specificity NMP22 qualitative (Bladderchek): positive NMP22 quantitaive: >7.5 U/mL	1 patient Bladderchek failed; 3 missing uRNA	9 patients did not have cystoscopy performed, 1 missing cytology

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Olsson, 2001 Sweden Medium	Overall: 1.0 (31/31) Primary: NR Recurrent: NR	Overall: 0.69 (57/83) Primary: 0.72 (33/46) Recurrent: 0.71 (32/45)	Overall: 3.2	Overall: 0
O'Sullivan, 2012 New Zealand Medium	Cxbladder (85% specificity) Overall: 0.82 (54/66) Ta: 0.68 (25/37) T1: 1.0 (16/16) T2: 1.0 (9/9) ≥T3: 1.0 (2/2) CIS: 1.0 (2/2) G1: 0.33 (1/3) G2: 0.76 (29/38) G3: 0.96 (23/24) Unifocal: 0.79 (41/52) Multifocal: 0.92 (12/13) Male: 0.80 (49/61) Female: 1.0 (5/5) Cxbladder (95% specificity) Overall: 0.73 (48/66) NMP22 >7.5 U/mL Overall: 0.50 (33/66) Ta: 0.35 (13/37) T1: 0.75 (12/16) T2: 0.67 (6/9) ≥T3: 1.0 (2/2) CIS: 0 (0/2) G1: 0.33 (1/3) G2: 0.39 (15/38) G3: 0.71 (17/24) Unifocal: 0.44 (23/52) Multifocal: 0.77 (10/13) Male: 0.48 (29/61) Female: 0.80 (4/5)	Cxbladder (85% specificity) Overall: 0.85 (357/419) No diagnosis: 0.88 (144/164) BPH/prostatitis: 0.85 (110/130) UTI or inflammation of urinary tract: 0.82 (32/39) Calculi: 0.68 (19/28) Hematuria due to warfarin: 0.80 (8/10) Other urological cancer: 0.80 (4/5) Cxbladder (95% specificity) Overall: 0.90 (377/419) NMP22 >7.5 U/mL Overall: 0.88 (369/419) No diagnosis: 0.88 (144/164) BPH/prostatitis: 0.90 (117/130) UTI or inflammation of urinary tract: 0.87 (34/39) Calculi: 0.82 (23/28) Hematuria due to warfarin: 0.90 (9/10) Other urological cancer: 0.80 (4/5)	Cxbladder (85% specificity) Overall: 0.47 (54/116) Cxbladder (95% specificity) Overall: 0.53 (48/90) NMP22 >7.5 U/mL Overall: 0.40 (33/83) NMP22 Bladderchek Overall: 0.62 (25/40)	Cxbladder (85% specificity) Overall: 0.97 (357/369) Cxbladder (95% specificity) Overall: 0.95 (377/395) NMP22 >7.5 U/mL Overall: 0.92 (369/402) NMP22 Bladderchek Overall: 0.91 (404/445)

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Olsson, 2001 Sweden Medium	Overall: 0.54 (31/57)	Overall: 1.0 (57/57)	NR	Stiftelsen Boras Forskningns- och Utvecklingsfond mot cancer	
O'Sullivan, 2012 New Zealand Medium	Cxbladder (85% specificity) Overall: 5.5 Cxbladder (95% specificity) Overall: 7.3 NMP22 >7.5 U/mL Overall: 4.2 NMP22 Bladderchek Overall: 9.5	Cxbladder (85% specificity) Overall: 0.21 Cxbladder (95% specificity) Overall: 0.30 NMP22 >7.5 U/mL Overall: 0.23 NMP22 Bladderchek Overall: 0.65	Cxbladder: 0.87 (CI NR) NMP22 ELISA: 0.73 NMP22 Bladderchek: NR	NR	

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
O'Sullivan, 2012 New Zealand Medium Continued					
Paoluzzi, 1999 Italy Medium	NMP22 (quantitative)	Unclear	Cystoscopy with pathological confirmation	Patients with gross or microscopic hematuria (n=90)	Age: NR Male: 85% Race: NR Smoker: NR Signs or symptoms: 100% gross or microscopic hematuria

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
O'Sullivan, 2012 New Zealand Medium Continued				
Paoluzzi, 1999 Italy Medium	32/90 (36%) Tumor stage: NR Tumor grade: NR	NMP22 quantitative: >10 U/mL	NR	None reported

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
O'Sullivan, 2012 New Zealand Medium Continued	NMP22 Bladderchek Overall: 0.38 (25/66) Ta: 0.38 (14/37) T1: 0.50 (8/16) T2: 0.22 (2/9) ≥T3: 0.50 (1/2) CIS: 0 (0/2) G1: 0.33 (1/3) G2: 0.34 (13/38) G3: 0.46 (11/24) Unifocal: 0.33 (17/52) Multifocal: 0.62 (8/13) Male: 0.38 (23/61) Female: 0.40 (2/5)	NMP22 Bladderchek Overall: 0.96 (404/419) No diagnosis: 0.98 (161/164) BPH/prostatitis: 0.98 (121/130) UTI or inflammation of urinary tract: 0.87 (34/39) Calculi: 0.96 (27/28) Hematuria due to warfarin: 1.0 (10/10) Other urological cancer: 1.0 (5/5)		
Paoluzzi, 1999 Italy Medium	NMP22: 0.84 (27/32) NMP22 + cytology: 0.91 (29/32)	NMP22: 0.62 (36/58) NMP22 + cytology: 0.83 (48/58)	NMP22: 2.2 NMP22 + cytology: 5.4	NMP22: 0.26 NMP22 + cytology: 0.11

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
O'Sullivan, 2012 New Zealand Medium Continued					
Paoluzzi, 1999 Italy Medium	NMP22: 0.55 (27/49) NMP22 + cytology: 0.74 (29/39)	NMP: 0.88 (36/41) NMP + cytology: 0.94 (48/51)	NR	NR	Discrepancies between reported PPV of 0.30 and NPV of 0.40 and calculated 0.55 and 0.88 based on 2 x 2 table

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Piaton, 2003 France Medium Pfister, 2003	ImmunoCyt	Prospective	Cystoscopy with pathological confirmation	Patients with symptoms suggestive of bladder cancer (n=236) or undergoing surveillance after TURBT for bladder cancer (n=458)	Mean age: 66 years Male: 79% Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: NR
Placer, 2002 Spain Medium	FISH (UroVysion)	Unclear	Cystoscopy with pathological confirmation	Patients undergoing surveillance for bladder cancer (n=34), with symptoms suggestive of bladder cancer (n=42), or undergoing transurethral resection of prostate (n=10)	Mean age: 70 years Male: 88% Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: NR

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Piaton, 2003 France Medium Pfister, 2003	57/236 (24%) primary; 85/458 (19%) recurrent Tumor stage: 75 Ta, 28 T1, 28 T2 or greater, 8 CIS Tumor grade: 31 G1, 40 G2, 68 G3	ImmunoCyt: Positive (≥1 fluorescent cell)	14 patients ImmunoCyt not performed	52 patients did not have cystoscopy performed, 8 missing clinical pathology data
Placer, 2002 Spain Medium	47/86 (55%) Tumor stage: 26 Ta, 12 T1, 9 T2-T4 Tumor grade: 16 G1, 12 G2, 19 G3	FISH: Positive (five or more cells with polysomy, or >50% of cells with loss of two 9p21 signals)	FISH not interpretable in 6 patients	None reported

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Piaton, 2003 France Medium Pfister, 2003	ImmunoCyt Overall: 0.73 (106/146) Ta-T1: 0.63 (65/103) T2-T4: 0.67(18/27) CIS: 0.64 (7/11) G1: 0.55 (17/31) G2: 0.76 (31/41) G3: 0.77 (53/69) Primary: 0.75 (44/59) Recurrent: 0.71 (62/87) ImmunoCyt + cytology Overall: 0.82 (120/146) Ta-T1: 0.81 (83/103) T2-T4: 0.81 (22/27) CIS: 1.0 (11/11) G1: 0.58 (18/31) G2: 0.85 (35/41) G3: 0.90 (62/69) Primary: 0.86 (51/59) Recurrent: 0.79 (69/87)	ImmunoCyt Overall: 0.82 (416/505) Primary: 0.83 (130/156) Recurrent: 0.82 (286/349) ImmunoCyt + cytology NR	ImmunoCyt Primary: 4.1 Recurrent: 4.4 ImmunoCyt + cytology Not calculable	ImmunoCyt Primary: 0.33 Recurrent: 0.36 ImmunoCyt + cytology Not calculable
Placer, 2002 Spain Medium	FISH (UroVysion) Overall: 0.80 (37/46) Ta: 0.64 (16/25) T1: 1.0 (12/12) T2-T4: 1.0 (9/9) G1: 0.53 (8/15) G2: 0.83 (10/12) G3: 1.0 (19/19) Primary: 0.86 (25/29) Recurrent: 0.71 (12/17) <10 mm: 0.46 (6/13) 10-30 mm: 0.93 (14/15) >30 mm: 0.94 (17/18) FISH (UroVysion) + cytology Overall: 0.83 (38/46)	FISH (UroVysion) Overall: 0.85 (29/34) Primary: 1.0 Recurrent: 0.88 FISH (UroVysion) + cytology Overall: 0.79 (27/34)	FISH (UroVysion) Overall: 5.3 Primary: Not calculable Recurrent: 5.9	FISH (UroVysion) Overall: 0.24 Primary: 0.14 Recurrent: 0.33

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Piaton, 2003 France Medium Pfister, 2003	ImmunoCyt Overall: 0.54 (106/195) Primary: 0.63 (44/70) Recurrent: 0.50 (62/125) ImmunoCyt + cytology NR	ImmunoCyt Overall: 0.91 (416/456) Primary: 0.90 (130/145) Recurrent: 0.92 (286/311) ImmunoCyt + cytology NR	NR	Ferring Laboratories provided ImmunoCyt tests; otherwise NR	Data taken from Piaton; discrepancies in Pfister in reported true negatives; discrepancies between reported sensitivities and calculated 2 x 2 tables and unable to calculate most n/N
Placer, 2002 Spain Medium	FISH (UroVysion) Overall: 0.88 (37/42)	FISH (UroVysion) Overall: 0.76 (29/38)	NR	Spanish Urological Association	Unable to calculate n/N for specificity stratified according to primary and recurrent tumors

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Pode, 1999 Israel Medium	BTA stat	Prospective	Cystoscopy with pathological confirmation	Patients with symptoms of bladder cancer (n=88) or undergoing surveillance for bladder cancer (n=162)	Mean age: NR Male: 83% Race: NR Smoker: NR Signs or symptoms of bladder cancer: 88 with hematuria or irritative voiding symptoms, otherwise NR Prior bladder cancer stage/grade: NR
Ponsky, 2001 USA Medium	NMP22 (quantitative)	Prospective	Cystoscopy with pathological confirmation	Patients with symptoms suggestive of bladder cancer (n=529) or undergoing surveillance for bladder cancer (n=79)	Mean age: 70 years in patients with cancer 61 years in patients without cancer 72% male Race: NR Smoker: NR Signs or symptoms: 143 gross hematuria, 226 microscopic hematuria, 239 urinary frequency or dysuria Prior bladder cancer stage: NR
Quek, 2002 Singapore Medium	BTA stat	Prospective	Cystoscopy and intravenous urogram with pathological confirmation	Patients with symptoms suggestive of bladder cancer (n=106) or undergoing surveillance for bladder cancer (n=13)	Mean age: 54 years 68% male Race: NR Smoker: NR Signs or symptoms: 60 gross hematuria, 29 microhematuria, 13 vesical irritability Prior bladder cancer stage: NR

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Pode, 1999 Israel Medium	71/88 (81%) primary; 57/162 (35%) recurrent Tumor stage: 72 Ta, 29 T1, 13 T2 or T3a, 14 T3b or higher Tumor grade: 25 G1, 58 G2, 45 G3	BTA stat: Positive	NR	None reported
Ponsky, 2001 USA Medium	52/608 (8.6%) Tumor stage and grade: 30 Ta and grade 1 to 2, 12 T1 and grade 2 to 3, 7 T2 and grade 3 or greater, 3 Tis	NMP22: >10 U/mL	NR	None reported
Quek, 2002 Singapore Medium	15% (16/106) primary; 31% (4/13) recurrent Tumor stage: 4 Ta, 10 T1, 6 T2-T4 Tumor grade: 7 G1, 6 G2, 7 G3	BTA stat: Positive	NR	None reported

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Pode, 1999 Israel Medium	Overall: 0.83 (106/128) <2 cm: 0.60 (32/53) 2-5 cm: 0.96 (53/55) >5: 1.0 (20/20) G1: 0.40 (10/25) G2: 0.84 (49/58) G3: 1.0 (45/45) Ta: 0.72 (52/72) T1: 0.90 (26/29) T2 or T3a: 1.0 (13/13) T3b or higher: 1.0 (14/14) Primary: 0.90 (64/71) Recurrent: 0.74 (42/57)	Overall: 0.69 (84/122) Primary: 0.76 (13/17) Recurrent: 0.68 (71/105)	Overall: 2.7 Primary: 3.8 Recurrent: 2.3	Overall: 0.25 Primary: 0.13 Recurrent: 0.38
Ponsky, 2001 USA Medium	0.88 (46/52)	0.84 (467/556)	5.5	0.14
Quek, 2002 Singapore Medium	Overall: 0.85 (17/20) Ta: 0.25 (1/4) T1: 1.00 (10/10) T2- T4: 1.00 (6/6) G1: 0.57 (4/7) G2: 1.00 (6/6) G3: 1.00 (7/7)	Overall: 0.63 (62/99) Less than 40 years old: 0.78 (14/18) More than 40 years old: 0.59 (47/80)	2.3	0.24

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Pode, 1999 Israel Medium	Overall: 0.74 (106/144) Primary: 0.94 (64/68) Recurrent: 0.55 (42/76)	Overall: 0.79 (84/106) Primary: 0.65 (13/20) Recurrent: 0.83 (71/86)	NR	NR	
Ponsky, 2001 USA Medium	0.34 (46/135)	0.99 (467/473)	NR	NR	
Quek, 2002 Singapore Medium	0.31 (17/54)	0.95 (62/65)	NR	NR	Specificity reported by presenting symptom but does not match data provided

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Raitanen, 2001a and 2001b Finland Medium	BTA stat	Prospective	Cystoscopy with pathological confirmation, urography or renal ultrasound if positive BTA stat and negative cystoscopy	Patient undergoing surveillance for bladder cancer (n=501)	Mean age: 69 years 79% male Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: 242 Ta, 187 T1, 20 CIS, 52 Tx; 220 G1, 215 G2, 52 G3, 14 Gx
Saad, 2002 UK Medium	NMP22 (quantitative) BTA stat	Prospective	Cystoscopy with pathological confirmation	Referred for evaluation of various urological conditions (n=120)	Mean age: 70 years Male: 83% Race: NR Smoker: NR Signs or symptoms: NR

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Raitanen, 2001a and 2001b Finland Medium	131/501 (26%) Tumor stage: 56 Ta, 23 T1, 3 T2-3, 12 CIS, 37 Tx Tumor grade: 52 G1, 37 G2, 8 G3, 34 Gx	BTA stat: Positive	NR	55 did not undergo reference standard and other testing and excluded from analysis
Saad, 2002 UK Medium	52/73 (71%) with bladder cancer Tumor stage: 23 Ta, 20 T1, 8 T2, 6 CIS Tumor grade: 13 G1, 22 G2, 17 G3	NMP22 quantitative: ≥10 U/mL BTA stat: Positive	NR	None reported

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Raitanen, 2001a and 2001b Finland Medium	Overall: 0.57 (74/131) No prior intravesical therapy: 0.53 (95% CI 0.32 to 0.76) Past intravesical therapy: 0.55 (95% CI 0.32 to 0.76) Present intravesical therapy: 0.82 (95% CI 0.57 to 0.96)	Overall: 0.75 (270/359) No prior intravesical therapy: 0.81 (95% CI 0.76 to 0.86) Past intravesical therapy: 0.71 (95% CI 0.59 to 0.81) Present intravesical therapy: 0.65 (95% CI 0.50 to 0.78)	Overall: 2.3 No prior intravesical therapy: 2.8 Past intravesical therapy: 1.9 Present intravesical therapy: 2.3	Overall: 0.57 No prior intravesical therapy: 0.58 Past intravesical therapy: 0.63 Present intravesical therapy:0.28
Saad, 2002 UK Medium	BTA stat Overall: 0.63 (33/52) Ta: 0.48 (11/23) T1: 0.80 (16/20) T2: 1.0 (8/8) CIS: 1.0 (6/6) G1: 0.23 (3/13) G2: 0.68 (15/22) G3: 0.88 (15/17) NMP22 Overall: 0.81 (42/52) Ta: 0.70 (16/23) T1: 0.90 (18/20) T2: 1.0 (8/8) CIS: 1.0 (6/6) G1: 0.62 (8/13) G2: 0.86 (19/22) G3: 0.88 (15/17)	BTA stat Overall: 0.82 (56/68) NMP22 Overall: 0.87 (59/68)	BTA stat Overall: 3.5 NMP22 Overall: 6.2	BTA stat Overall: 0.45 NMP22 Overall: 0.22

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Raitanen, 2001a and 2001b Finland Medium	Overall: 0.45 (74/163)	Overall: 0.83 (270/327)	NR	Tampere University Hospital	9/61 patients without bladder tumor on initial cystoscopy had bladder cancer at subsequent followup; results taken from Raitanen 2001b, some slight discrepancies between reported results and results calculated based on 2 x 2 data, also some discrepancies between Raitanen 2001a and 2001b (specificity)
Saad, 2002 UK Medium	BTA stat Overall: 0.73 (33/45) NMP22 Overall: 0.82 (42/51)	BTA stat Overall: 0.75 (56/75) NMP22 Overall: 0.86 (59/69)	NR	NR	

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Sanchez-Carbayo, 2001 Spain Medium	NMP22 (quantitative)	Prospective	Cystoscopy with pathological confirmation	Patients with microscopic hematuria (n=112)	Mean age: 66 years 65% male Race: NR Smoker: NR Signs or symptoms: All had microscopic hematuria
Sarosdy, 2002 USA Medium	FISH (UroVysion) BTA stat	Prospective	Cystoscopy with pathological confirmation or underwent ablation	Patients undergoing surveillance for bladder cancer (n=176)	Mean age: 71 years 75% male Nonwhite race: 13% Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: 118 Ta, 20 T1, 4 T2, 29 CIS, 5 Tx; 70 G1, 56 G2, 46 G3, 4 Gx

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Sanchez-Carbayo, 2001 Spain Medium	43/112 (38%) Tumor stage: 5 Ta, 28 T1, 7 T2, 2 T3, 1 CIS Tumor grade: 11 G1, 15 G2, 17 G3	NMP22 quantitative: >10 U/mL	NR	None reported
Sarosdy, 2002 USA Medium	62/176 (35%) Tumor stage: 32 Ta, 6 T1, 3 T2, 7 CIS, 11 Tx Tumor grade: 22 G1, 9 G2, 18 G3	FISH: Positive (Criteria NR) BTA stat: Positive	Unclear	Unclear (58 excluded due to no specimen, insufficient urine volume, suspicious cystoscopy but no pathology)

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Sanchez-Carbayo, 2001 Spain Medium	Overall: 0.58 (25/43) T1: 0.57 (16/28) T2: 0.86 (6/7) T3: 1.00 (2/2) CIS: 0.0 (0/1) G1: 0.18 (2/11) G2: 0.60 (9/15) G3: 0.82 (14/17)	Overall: 0.90 (62/69)	Overall: 5.8	Overall: 0.47
Sarosdy, 2002 USA Medium	FISH (UroVysion) Overall: 0.71 (44/62) Ta: 0.66 (21/32) T1: 0.83 (5/6) T2: 1.0 (3/3) CIS: 1.0 (7/7) G1: 0.55 (12/22) G2: 0.78 (7/9) G3: 1.0 (7/7) Prior BCG: 0.85 (22/26) BTA stat Overall: NR Ta: 0.50 (16/32) T1: 0.83 (5/6) T2: 0.67 (2/3) CIS: 0.43 (3/7) G1: 0.27 (6/22) G2: 0.78 (7/9) G3: 0.72 (13/18) Prior BCG: 0.69 (18/26)	FISH (UroVysion) Overall: 0.66 (75/114) Prior BCG: 0.70 (38/54) BTA stat Overall: NR Prior BCG: 0.55 (30/55)	FISH (UroVysion) Overall: 2.1 Prior BCG: 2.8 BTA stat Overall: NR Prior BCG: 1.5	FISH (UroVysion) Overall: 0.44 Prior BCG: 0.21 BTA stat Overall: NR Prior BCG: 0.56

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Sanchez-Carbayo, 2001 Spain Medium	Overall: 0.78 (25/32)	Overall: 0.78 (62/80)	NR	IDL and Roche Diagnostics supplied materials, otherwise NR	Discrepancies between reported measures for diagnostic accuracy and calculated measures from 2 x 2 tables based on data provided; number of cancers 25 when reported by tumor grade and 24 when reported by tumor stage; results based on accuracy reported by tumor grade
Sarosdy, 2002 USA Medium	FISH (UroVysion) Overall: 0.53 (44/83) Prior BCG: 0.58 (22/38) BTA stat Overall: NR Prior BCG: 0.42 (18/43)	FISH (UroVysion) Overall: 0.81 (75/93) Prior BCG: 0.90 (38/42) BTA stat Overall: NR Prior BCG: 0.79 (30/38)	NR	NR	

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Sawczuk, 2000 USA Medium	NMP22 (quantitative)	Unclear	Cystoscopy with pathological confirmation	Patients undergoing surveillance for bladder cancer (n=56)	Mean age: 69 years Sex: NR Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: 35 Ta, 14 T1, 2 T2, 5 T3-4; 31 G1 or G2, 25 G3 or G4 (7 with associated CIS)
Schamhart, 1998 the Netherlands Medium	BTA stat	Prospective	Cystoscopy with pathological confirmation	Patients with history of bladder cancer undergoing surveillance or with symptoms suspicious for bladder cancer (n=149)	Mean age: 66 years 81% male Nonwhite race: 0% Smoker: NR Signs and symptoms: 10% gross hematuria, 4.7% microscopic hematuria, 0.5% flank pain, 2.6% dysuria, 4.7% dysuria, 2.6% urgency, 5.2% other symptoms Prior bladder cancer stage/grade: NR
Schmitz-Drager, 2007a Germany Medium	ImmunoCyt	Unclear	Cystoscopy with pathological confirmation and imaging	Patients with painless microscopic hematuria and without prior bladder cancer	Mean age: 57 years Male: 77% Race: NR Smoker: NR Signs or symptoms: All had painless microscopic hematuria Prior bladder cancer stage/grade: No prior bladder cancer
Schmitz-Drager, 2007b Germany Medium	ImmunoCyt	Unclear	Cystoscopy with pathological confirmation and imaging	Patients with painless gross hematuria and without prior bladder cancer	Mean age: 58 years Male: 89% Race: NR Smoker: NR Signs or symptoms: All had painless gross hematuria Prior bladder cancer stage/grade: No prior bladder cancer

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Sawczuk, 2000 USA Medium	34/56 (61%) Tumor stage: 27 Ta, 4 T1, 3 T3b or 4 Tumor grade: 22 G1-2, 12 G3-4	NMP quantitative: >10 U/mL	NR	None reported
Schamhart, 1998 the Netherlands Medium	62/149 (42%) Tumor stage: 42 Ta, 6 T1, 5 ≥T2, 3 CIS Tumor grade: 5 G1, 32 G2, 17 G3, 20 G3 + CIS	BTA stat: Positive	Unclear, 43 excluded for "protocol violations"	Unclear
Schmitz-Drager, 2007a Germany Medium	8/189 (4.2%) Tumor stage: 5 Ta, 1 T1, 2 T2-T3 Tumor grade: 5 low malignant potential, 3 high grade	ImmunoCyt: Positive (≥1 fluorescent cell)	11 not assessable by ImmunoCyt and cytology (excluded)	None reported
Schmitz-Drager, 2007b Germany Medium	15/59 (25%) Tumor stage: 5 Ta, 3 T1, 6 T2-T4 Tumor grade: 5 low-grade, 9 high-grade	ImmunoCyt: Positive (≥1 fluorescent cell)	2 not assessable by ImmunoCyt and cytology (excluded)	None reported

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Sawczuk, 2000 USA Medium	Overall: 0.62 (21/34) G1-2: 0.55 (12/22) G3-4: 0.75 (9/12)	Overall: 0.77 (17/22)	Overall: 2.7	Overall: 0.49
Schamhart, 1998 the Netherlands Medium	Overall: 0.32 (20/62) Ta: 0.24 (10/42) T1: 0.33 (2/6) ≥T2: 1.0 (5/5) CIS: 0.0 (0/3) G1: 0.60 (3/5) G2: 0.22 (7/32) G3 (no Tis): 0.41 (7/17) G3 + Tis: 0.35 (7/20) Low risk (TaG1/TaG2): 0.27 (9/33) High risk (TaG3/T1G2/T1G3/≥T2/Tis): 0.35 (8/23)	Overall: 0.82 (71/87)	Overall: 1.8	Overall: 0.83
Schmitz-Drager, 2007a Germany Medium	Overall: 0.87 (7/8) Ta: 0.80 (4/5) T1: 1.0 (1/1) T2-T3: 1.0 (2/2) Low malignant potential: 0.80 (4/5) High grade: 1.0 (3/3)	Overall: 0.91 (154/170) Papilloma: 1.0 (2/2) Nonurothelial tumor: 0.67 (2/3) BPH: 0.94 (48/51) Urolithiasis: 1.0 (16/16) UTI: 0.84 (16/19) Other conditions: 0.83 (20/24) Hematuria of unknown origin: 0.91 (50/55)	Overall: 9.7	Overall: 0.14
Schmitz-Drager, 2007b Germany Medium	Overall: 0.87 (13/15) Ta: 1.0 (5/5) T1: 0.67 (2/3) T2-T4: 0.83 (5/6) Low grade: 1.0 (5/5) High grade: 0.78 (7/9)	Overall: 0.79 (33/42) BPH: 0.84 (16/19) Urolithiasis: 0.50 (1/2) UTI: 1.0 (4/4) Other conditions: 0.86 (6/7) Hematuria of unknown origin: 0.60 (6/10)	Overall: 4.1	Overall: 0.16

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Sawczuk, 2000 USA Medium	Overall: 0.81 (21/26)	Overall: 0.57 (17/30)	NR	NR	Study appeared to reverse PPV and NPV (Table 1).
Schamhart, 1998 the Netherlands Medium	Overall: 0.56 (20/36)	Overall: 0.63 (71/113)	NR	Test supplied by Bard Diagnostics; otherwise NR	
Schmitz-Drager, 2007a Germany Medium	Overall: 0.30 (7/23)	Overall: 0.99 (154/155)	NR	NR	
Schmitz-Drager, 2007b Germany Medium	Overall: 0.59 (13/22)	Overall: 0.94 (33/35)	NR	NR	Excluded 2 upper tract urothelial cancers when abstracting data

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Serretta, 1998 Italy Medium	NMP22 (quantitative)	Unclear	Cystoscopy and intravenous urogram with pathological confirmation	Patients undergoing surveillance for bladder cancer (n=137)	Mean age: 65 years Male: 89% Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage and grade: 7 Tis, 49 Ta, 71 T1, 10 T2-3; 12 G1, 74 G2, 51 G3
Serretta, 2000 Italy High	NMP22 (quantitative) BTA Stat BTA TRAK	Unclear	Cystostcopy with pathological confirmation	Patients undergoing surveillance for bladder cancer Excluded: Urinary tract infection, other urological diseases, and other malignancies	Mean age: 65 years Male: 84% Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage and grade: 53 Ta, 107 T1, 12 T2-3, 7 CIS, 16 G1, 93 G2, 70 G3

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Serretta, 1998 Italy Medium	42/137 (31%) Tumor stage: NR Tumor grade: NR	NMP22 quantitative: >10 U/mL	NR	None reported
Serretta, 2000 Italy High	55/179 (31%) Tumor stage: 13 Ta, 27 T1, 12 T2-3, 3 CIS, 7 G1, 19 G2, 29 G3 Tumor grade: 7 G1, 19 G2, 29 G3	NMP22 quantitative: >10 U/mL BTA Stat: Positive BTA TRAK: >14 U/mL	All patients underwent NMP22, 92/179 underwent BTA Stat, and 74/179 underwent BTA TRAK	None reported

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Serretta, 1998 Italy Medium	Overall: 0.72 (30/42)	Overall: 0.61 (58/95) Prior intravesical chemotherapy: 0.56 (27/48) No prior intravesical chemotherapy: 0.66 (31/47)	Overall: 1.8	Overall: 0.46
Serretta, 2000 Italy High	NMP22 Overall: 0.75 (41/55) Ta: 0.54 (7/13) T1: 0.74 (20/27) T2-T3: 0.83 (10/12) G1: 0.43 (3/7) G2: 0.63 (12/19) G3: 0.90 (26/29) Subgroup that underwent all tests: 0.70 (14/20) BTA Stat Overall: 0.57 (16/28) Ta: 0.33 (2/6) T1: 0.55 (10/18) T2-T3: 1.0 (4/4) G1: 0.50 (2/4) G2: 0.50 (6/12) G3: 0.67 (8/12) Subgroup that underwent all tests: 0.61 (14/23) BTA TRAK Overall: 0.62 (10/16) Ta: 0.50 (2/4) T1: 0.75 (6/8) T2-T3: 0.50 (2/4) G1: 0.50 (2/4) G2: 1.0 (2/2) G3: 0.60 (6/10) Subgroup that underwent all tests: 0.62 (10/16)	NMP22 Overall: 0.55 (68/124) Subgroup that underwent all tests: 0.56 (30/54) BTA Stat Overall: 0.62 (40/64) Subgroup that underwent all tests: 0.65 (33/51) BTA TRAK Overall: 0.79 (46/58) Subgroup that underwent all tests: 0.79 (46/58)	NMP22 Overall: 1.7 Subgroup that underwent all tests: 1.6 BTA Stat Overall: 1.5 Subgroup that underwent all tests: 1.7 BTA TRAK Overall: 3.0 Subgroup that underwent all tests: 3.0	NMP22 Overall: 0.45 Subgroup that underwent all tests: 0.54 BTA Stat Overall: 0.69 Subgroup that underwent all tests: 0.60 BTA TRAK Overall: 0.48 Subgroup that underwent all tests: 0.48

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Serretta, 1998 Italy Medium	Overall: 0.45 (30/67)	Overall: 0.83 (58/70)	NR	NR	
Serretta, 2000 Italy High	NMP22 Overall: 0.42 (41/97) Subgroup that underwent all tests: 0.37 (14/38) BTA Stat Overall: 0.40 (16/40) Subgroup that underwent all tests: 0.44 (14/32) BTA TRAK Overall: 0.45 (10/22) Subgroup that underwent all tests: 0.45 (10/22)	NMP22 Overall: 0.83 (68/82) Subgroup that underwent all tests: 0.83 (30/36) BTA Stat Overall: 0.77 (40/52) Subgroup that underwent all tests: 0.79 (33/42) BTA TRAK Overall: 0.88 (46/52) Subgroup that underwent all tests: 0.88 (46/52)	NR	NR	Only a subgroup of patients underwent all 3 tests

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Shariat, 2006 USA, Europe, Japan, Canada Medium	NMP22 (quantitative)	Prospective	Cystoscopy with pathological confirmation	Patients undergoing surveillance for bladder cancer (Ta, T1, and/or Tis) (n=2,871)	Median age: 68 years Male: 76% Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: NR
Sharma, 1999 USA Medium	NMP22 (quantitative) BTA stat	Unclear	Cystoscopy with pathological confirmation	Patients with symptoms of bladder cancer (n=278); 199 without prior cancer and 79 with prior cancer	Mean age: NR Sex: NR Race: NR Smoker: NR Signs or symptoms: 40% microscopic hematuria, 28% gross hematuria, 32% chronic irritative voiding symptoms Prior bladder cancer stage/grade: NR

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Shariat, 2006 USA, Europe, Japan, Canada Medium	1045/2871 (36%) Tumor stage: 448 Ta, 276 T1, 220 ≥T2 Tumor grade: 233 G1, 420 G2, 329 G3	NMP22 quantitative: >10 U/mL; also various cutoffs from 1 to 30 U/mL	NR	None reported
Sharma, 1999 USA Medium	34/278 (12%) with bladder cancer; 6/199 (3.0%) in persons without prior bladder cancer; 28/79 (35%) in persons with prior cancer Tumor stage: NR Tumor grade: NR	BTA stat: Positive NMP22 quantitative: >10 U/mL for primary, >6 U/mL for recurrent	NR	None reported

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Shariat, 2006 USA, Europe, Japan, Canada Medium	Overall: 0.57 (596/1045) ≥T2: 0.83 (183/220) G3: 0.75 (247/329) NMP >2, >6.5, >15, >20, >25, >30: 0.90 (940/1045), 0.68 (711/1045), 0.48 (502/1045), 0.42 (439/1045), 0.38 (397/1045), 0.36 (376/1045)	Overall: 0.81 (1479/1826) NMP >2, >6.5, >15, >20, >25, >30: 0.26 (475/1826), 0.67 (1223/1826), 0.88 (1607/1826), 0.92 (1680/1826), 0.94 (1716/1826), 0.95 (1735/1826)	Overall: 3.0 NMP >2, >6.5, >15, >20, >25, >30: 1.2, 2.1, 4.0, 5.2, 6.3, 7.2	Overall: 0.53 NMP >2, >6.5, >15, >20, >25, >30: 0.38, 0.48, 0.59, 0.63, 0.66, 0.67
Sharma, 1999 USA Medium	BTA stat Overall: 0.68 (23/34) Primary: 0.67 (4/6) Recurrent: 0.68 (19/28) NMP22 Overall: 0.82 (28/34) Primary: 0.67 (4/6) Recurrent: 0.86 (24/28)	BTA stat Overall: 0.82 (201/244) Primary: 0.82 Recurrent: 0.82 Benign inflammatory: 0.75 (47/63) Renal/bladder calculi: 0.57 (4/7) Foreign body: 0 (0/2) Bowel interposition segment: 0 (0/8) Other genitourinary cancer: 0.92 (54/59) Instrumentation: 0.60 (9/15) NMP22 Overall: 0.82 (200/244) Primary: 0.86 Recurrent: 0.67 Benign inflammatory: 0.78 (40/51) Renal/bladder calculi: 0.67 (4/6) Foreign body: 0 (0/2) Bowel interposition segment: 0 (0/6) Other genitourinary cancer: 0.82 (40/49) Instrumentation: 0.75 (9/12)	BTA stat Overall: 3.8 Primary: 3.7 Recurrent: 3.8 NMP22 Overall: 4.6 Primary: 4.8 Recurrent: 2.6	BTA stat Overall: 0.39 Primary: 0.40 Recurrent: 0.39 NMP22 Overall: 0.22 Primary: 0.38 Recurrent: 0.21

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Shariat, 2006 USA, Europe, Japan, Canada Medium	Overall: 0.63 (596/943) NMP >2, >6.5, >15, >20, >25, >30: 0.41 (940/2291), 0.54 (711/1314), 0.70 (502/721), 0.75 (439/585), 0.78 (397/507), 0.81 (376/467)	Overall: 0.77 (1479/1928) NMP >2, >6.5, >15, >20, >25, >30: 0.82 (475/580), 0.79 (1223/1557), 0.75 (1607/2150), 0.73 (1680/2295), 0.73 (1716/2364), 0.72 (1735/2404)	Overall: 0.74 (95% CI 0.72 to 0.76)	NR	AUC for G3 vs. G1/2 or no cancer 0.81 (95% CI 0.78 to 0.83) AUC for ≥T2 vs. <T2 or no cancer 0.86 (95% CI 0.84 to 0.89)
Sharma, 1999 USA Medium	BTA stat Overall: 0.35 (23/66) Primary: 0.68 Recurrent: 0.10 NMP22 Overall: 0.39 (28/72) Primary: 0.58 Recurrent: 0.13	BTA stat Overall: 0.95 (201/212) Primary: 0.82 Recurrent: 0.99 NMP22 Overall: 0.97 (200/206) Primary: 0.90 Recurrent: 0.99	NR	NR	Unable to calculate n/N for specificity or generate 2 x 2 table

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Song, 2010 South Korea Medium	FISH (UroVysion)	Prospective	Cystoscopy with pathological confirmation	Patients with hematuria	Mean age: 62 years Male: 82% Race: NR Smoker: NR Signs or symptoms: Hematuria Prior bladder cancer stage/grade: NR
Sullivan, 2009 USA Medium	FISH (UroVysion) ImmunoCyt	Unclear	Cystoscopy with pathological confirmation	Patients undergoing surveillance for bladder cancer	Mean age: NR Male: NR Race: NR Smoker: NR Signs or symptoms: All undergoing surveillance Prior bladder cancer stage/grade: NR

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Song, 2010 South Korea Medium	95/602 (16%) Tumor stage: 38 Ta, 29 T1, 24 T2-T3, 4 CIS Tumor grade: 20 G1, 35 G2, 16 G3	FISH: ≥5 cells with gains of 2 or more chromosomes or ≥3 cells with homozygous deletion of 9p21	NR	None reported
Sullivan, 2009 USA Medium	25/100 (12%) Tumor stage: 19 Ta, 4 T1, 2 T2 Tumor grade: 13 low grade, 11 high grade	ImmunoCyt: Positive (≥1 fluorescent cell) FISH: ≥4 cells with gains of 2 or more chromosomes or ≥12 cells with homozygous deletion of 9p21	2 for ImmunoCyt and 12 for UroVysion	5 lesions were fulgurated with no pathologic specimen and excluded

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Song, 2010 South Korea Medium	Overall: 0.60 (57/95) Ta: 0.34 (13/38) T1: 0.79 (23/29) T2-T3: 0.79 (19/24) CIS: 0.50 (2/4) G1: 0.20 (4/20) G2: 0.51 (18/35) G3: 1.0 (16/16))	Overall: 0.95 (481/507)	Overall: 12.0	Overall: 0.42
Sullivan, 2009 USA Medium	ImmunoCyt Overall: 0.76 (19/25) Ta: 0.68 (13/19) T1: 1.0 (4/4) T2: 1.0 (2/2) Low grade: 0.62 (8/13) High grade: 0.91 (10/11) UroVysion Overall: 0.12 (3/25) Ta: 0.11 (2/19) T1: 0.25 (1/4) T2: 0 (0/2) Low grade: 0.08 (1/13) High grade: 0.18 (2/11) ImmunoCyt plus cytology Overall: 0.76 (19/25) Ta: 0.68 (13/19) T1: 1.0 (4/4) T2: 1.0 (2/2) Low grade: 0.62 (8/13) High grade: 0.91 (10/11)	ImmunoCyt Overall: 0.63 (46/73) UroVysion Overall: 0.90 (57/63) ImmunoCyt plus cytology Overall: 0.63 (46/73)	ImmunoCyt Overall: 2.1 UroVysion Overall: 1.2 ImmunoCyt plus cytology: Overall: 2.1	ImmunoCyt Overall: 0.38 UroVysion Overall: 0.98 ImmunoCyt plus cytology Overall: 0.38

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Song, 2010 South Korea Medium	Overall: 0.69 (57/83)	Overall: 0.93 (481/519)	NR	NR	
Sullivan, 2009 USA Medium	ImmunoCyt Overall: 0.41 (19/46) UroVysion Overall: 0.33 (3/9) ImmunoCyt plus cytology Overall: 0.41 (19/46)	ImmunoCyt Overall: 0.88 (46/52) UroVysion Overall: 0.72 (57/79) ImmunoCyt plus cytology Overall: 0.88 (46/52)	NR	DiagnoCure, Inc.	Slight discrepancies between calculated results for diagnostic accuracy

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Tetu, 2005 Canada Medium	ImmunoCyt	Retrospective	Cystoscopy with pathological confirmation or visualization with fulguration	Patients undergoing surveillance for bladder cancer or undergoing evaluation for urinary symptoms	Mean age: NR Male: NR Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: NR
Thomas, 1999 Europe Medium	BTA TRAK	Prospective	Cystoscopy with pathological confirmation	Patients with signs, symptoms, or imaging or cystoscopic findings suggestive of bladder cancer (n=96) or undergoing surveillance for bladder cancer (n=124)	Mean age: 64 years Male: 70% Caucasian: 98% Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: NR

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Tetu, 2005 Canada Medium	136/870 (16%) Tumor stage: 65 Ta, 6 T1, 19 T2-T4, 14 CIS Tumor grade: 31 low malignant potential, 33 low-grade papillary carcinoma, 40 high grade papillary carcinoma	ImmunoCyt: Positive (≥1 fluorescent cell)	34 (excluded)	None reported
Thomas, 1999 Europe Medium	100/220 (45%) overall; 49/96 (51%) primary; 51/124 (41%) recurrent Tumor stage: 55 Ta, 24 T1, 16 T2-T4, 5 CIS Tumor grade: 25 G1, 41 G2, 34 G3	BTA TRAK: >14 kilounits/L	NR	None reported

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Tetu, 2005 Canada Medium	ImmunoCyt Overall: 0.74 (100/136) Ta: 0.79 (51/65) T1: 0.83 (5/6) T2-T4: 0.68 (13/19) CIS: 0.93 (13/14) Low malignant potential: 0.71 (22/31) Low-grade papillary carcinoma: 0.79 (26/33) High-grade papillary carcinoma: 0.85 (34/40) ImmunoCyt plus cytology Overall: 0.84 (114/136) Ta: 0.79 (51/65) T1: 0.83 (5/6) T2-T4: 0.79 (15/19) CIS: 1.0 (14/14) Low malignant potential: 0.71 (22/31) Low-grade papillary carcinoma: 0.79 (26/33) High-grade papillary carcinoma: 0.93 (37/40)	ImmunoCyt Overall: 0.62 (453/734) ImmunoCyt plus cytology Overall: 0.61 (450/734)	ImmunoCyt Overall: 2.0 ImmunoCyt plus cytology Overall: 2.2	ImmunoCyt Overall: 0.42 ImmunoCyt plus cytology Overall: 0.26
Thomas, 1999 Europe Medium	BTA TRAK Overall: 0.66 (66/100) Ta: 0.51 (28/55) T1: 0.88 (21/24) T2-T4: 0.88 (14/16) CIS: 0.60 (3/5) G1: 0.48 (12/25) G2: 0.59 (24/41) G3: 0.88 (30/34) Primary: 0.76 (37/49) Recurrent: 0.57 (29/51) BTA TRAK plus cytology (either positive) Overall: 0.71 (71/100)	BTA TRAK Overall: 0.69 (83/120) Primary: 0.53 (25/47) Primary, no GU disease: 0.64 (16/25) Primary, GU disease: 0.41 (9/22) Recurrent: 0.79 (58/73) Recurrent, no genitourinary disease: 0.81 (52/64) Recurrent, GU disease: 0.48 (15/31) No GU disease: 0.76 (68/89) GU disease: 0.48 (15/31) BTA TRAK plus cytology (either positive) Overall: 0.69 (83/120)	BTA TRAK Overall: 2.1 BTA TRAK plus cytology Overall: 2.3	BTA TRAK Overall: 0.49 BTA TRAK plus cytology Overall: 0.20

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Tetu, 2005 Canada Medium	ImmunoCyt Overall: 0.26 (100/382) ImmunoCyt plus cytology Overall: 0.29 (114/398)	ImmunoCyt Overall: 0.93 (453/488) ImmunoCyt plus cytology Overall: 0.94 (450/472)	NR	NR	
Thomas, 1999 Europe Medium	BTA TRAK Overall: 0.64 (66/103) Primary: 0.63 (37/59) Recurrent: 0.66 (29/44) BTA TRAK plus cytology (either positive) Overall: 0.66 (71/108)	BTA TRAK Overall: 0.71 (83/117) Primary: 0.68 (25/37) Recurrent: 0.72 (58/80) BTA TRAK plus cytology (either positive) Overall: 0.74 (83/112)	NR	Bard Diagnostic Sciences	

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Toma, 2004 Germany Medium	NMP22 (quantitative) ImmunoCyt BTA stat FISH (UroVysion)	Unclear	Cystoscopy with pathological confirmation	Patients with suspected bladder cancer (n=47) or undergoing surveillance for bladder cancer (n=79) Excluded urinary infection	Age: NR Sex: NR Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: NR

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Toma, 2004 Germany Medium	42/126 (33%) Tumor stage: 21 Ta, 15 T1, 6 T2-T4, 2 CIS Tumor grade: 7 G1, 23 G2, 12 G3	NMP22: >10 U/mL ImmunoCyt: Positive (≥1 fluorescent cell) BTA stat: Positive FISH: ≥20% cells with gains of 2 or more chromosomes or ≥40% cells with gain of 1 chromosome, or ≥40% deletion of 9p21	2 did not have ImmunoCyt performed due to too few cells	None reported

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Toma, 2004 Germany Medium	NMP22 Overall: 0.69 (29/42) Ta: 0.52 (11/21) T1: 0.93 (14/15) T2-T4: 0.83 (5/6) CIS: 1.0 (2/2) G1: 0.43 (3/7) G2: 0.70 (16/23) G3: 0.83 (10/12) ImmunoCyt Overall: 0.79 (33/42) Ta: 0.71 (15/21) T1: 0.87 (13/15) T2-T4: 0.83 (5/6) CIS: 1.0 (2/2) G1: 0.86 (6/7) G2: 0.74 (17/23) G3: 0.83 (10/12) BTA stat Overall: 0.67 (28/42) Ta: 0.57 (12/21) T1: 0.80 (12/15) T2-T4: 1.0 (6/6) CIS: 0 (0/2) G1: 0.43 (3/7) G2: 0.70 (16/23) G3: 0.83 (10/12)	NMP22 Overall: 0.65 (51/78) ImmunoCyt Overall: 0.74 (58/78) BTA stat Overall: 0.78 (61/78) FISH Overall: 0.89 (69/78) ImmunoCyt plus cytology Overall: 0.73 (57/78)	NMP22 Overall: 2.0 ImmunoCyt Overall: 3.0 BTA stat Overall: 3.0 FISH Overall: 6.3 ImmunoCyt plus cytology Overall: 3.3	NMP22 Overall: 0.48 ImmunoCyt Overall: 0.28 BTA stat Overall: 0.42 FISH Overall: 0.35 ImmunoCyt plus cytology Overall: 0.16

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Toma, 2004 Germany Medium	NMP22 Overall: 0.52 (29/56) ImmunoCyt Overall: 0.62 (33/53) BTA stat Overall: 0.62 (28/45) FISH Overall: 0.76 (29/38) ImmunoCyt plus cytology Overall: 0.64 (37/58)	NMP22 Overall: 0.80 (51/64) ImmunoCyt Overall: 0.87 (58/67) BTA stat Overall: 0.81 (61/75) FISH Overall: 0.84 (69/82) ImmunoCyt plus cytology Overall: 0.79 (57/72)	NR	NR	Several discrepancies between reported diagnostic accuracy and results calculated from 2 x 2 tables

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Toma, 2004 Germany Medium					
United Kingdom and Eire Bladder Tumouir Antigen Study Group, 1997 UK Medium	BTA stat	Prospective	Cystoscopy with pathological confirmation	Patients undergoing surveillance for bladder cancer (n=272) Excluded urinary infection or gross hematuria	Age: NR Sex: NR Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: NR
van Der Poel, 1998 the Netherlands Medium	BTA stat	Unclear	Cystoscopy with pathological confirmation	Patients undergoing surveillance for bladder cancer (n=88) or undergoing cystoscopy with no prior bladder cancer (n=50) Excluded urinary tract infection	Age: NR Sex: NR Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: NR

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Toma, 2004 Germany Medium				
United Kingdom and Eire Bladder Tumouir Antigen Study Group, 1997 UK Medium	102/272 (38%) Tumor stage: NR Tumor grade: NR	BTA stat: Positive	NR	None reported
van Der Poel, 1998 the Netherlands Medium	58/103 (56%) Tumor stage: 40 Ta, 7 T1, 4 T2, 3 T3, 3 CIS Tumor grade: 7 G1, 27 G2, 20 G3	BTA stat: Positive	NR	None reported

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Toma, 2004 Germany Medium	FISH Overall: 0.69 (29/42) Ta: 0.62 (13/21) T1: 0.67 (10/15) T2-T4: 0.83 (5/6) CIS: 1.0 (2/2) G1: 0.57 (4/7) G2: 0.61 (14/23) G3: 0.83 (10/12) ImmunoCyt plus cytology Overall: 0.88 (37/42) Ta: 0.90 (19/21) T1: 0.87 (13/15) T2-T4: 0.83 (5/6) CIS: 1.0 (2/2) G1: 0.86 (6/7) G2: 0.91 (21/23) G3: 0.83 (10/12)			
United Kingdom and Eire Bladder Tumouir Antigen Study Group, 1997 UK Medium	0.58 (59/102)	0.85 (145/170)	3.7	0.53
van Der Poel, 1998 the Netherlands Medium	Overall: 0.34 (20/58) Ta: 0.25 (10/40) T1: 0.57 (4/7) T2: 0.75 (3/4) T3: 1.0 (3/3) CIS: 0 (0/3) G1: 0.43 (3/7) G2: 0.33 (9/27) G3: 0.40 (8/20)	Overall: 0.81 (65/80)	Overall: 1.8	Overall: 0.81

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Toma, 2004 Germany Medium					
United Kingdom and Eire Bladder Tumouir Antigen Study Group, 1997 UK Medium	0.70 (59/84)	0.77 (145/188)	NR	Bard UK Ltd.	Specificity reported as 86% but 85% based on 2 x 2 tables
van Der Poel, 1998 the Netherlands Medium	Overall: 0.57 (20/35)	Overall: 0.63 (65/103)	NR	Bard Diagnostic Sciences	

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Varella-Garcia, 2004 USA Medium	FISH (UroVysion)	Prospective	Cystoscopy with pathological confirmation	Patients undergoing surveillance for bladder cancer (n=19)	Mean age: 69 years Male: 84% Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: NR
Vriesema, 2001 the Netherlands Medium	ImmunoCyt	Prospective	Cystoscopy with pathological confirmation	Patients undergoing surveillance for bladder cancer	Mean age: 68 years Male: 83% Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: NR
Wiener, 1998 Austria Medium	NMP22 (quantitative) BTA stat	Prospective	Cystoscopy with pathological confirmation	Patients with symptoms suggestive of bladder tumors (n=190) or undergoing surveillance for bladder cancer (n=101)	Mean age: 65 years Male: 68% Race: NR Smoker: NR Signs or symptoms: 65% Prior bladder cancer stage/grade: NR

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Varella-Garcia, 2004 USA Medium	7/19 (37%) with bladder cancer Tumor stage: 3 Ta, 2 T1, 2 T2 Tumor grade: 2 G1, 3 G2, 2 G3	FISH: Positive (>16% cells with multiple chromosomes or >48% cells with 9p21 homozygous loss)	NR	None reported
Vriesema, 2001 the Netherlands Medium	22/86 (26%) with bladder cancer Tumor stage: 17 Ta, 3 T1, 1 T2-T4, 1 CIS Tumor grade: NR	ImmunoCyt: Positive (≥1 fluorescent cell)	18 excluded due to low cellularity specimens	None reported
Wiener, 1998 Austria Medium	91/291 (31%) with bladder cancer Tumor stage: 47 Ta, 25 T1, 19 T2-T4 Tumor grade: 23 G1, 38 G2, 30 G3	NMP: >10 U/mL BTA stat: Positive	NR	None reported

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Varella-Garcia, 2004 USA Medium	Overall: 0.86 (6/7) Ta: 1.0 (3/3) T1: 0.50 (1/2) T2: 1.0 (2/2) G1: 1.0 (2/2) G2: 1.0 (3/3) G3: 0.50 (1/2)	Overall: 1.0 (12/12)	Overall: Not calculable (specificity 1.0)	Overall: 0.14
Vriesema, 2001 the Netherlands Medium	ImmunoCyt: 0.32 (7/22) ImmunoCyt plus cytology: 0.52 (11/22)	ImmunoCyt: 0.87 (53/61) ImmunoCyt plus cytology: 0.64 (40/63)	ImmunoCyt: 2.5 ImmunoCyt plus cytology: 1.4	ImmunoCyt: 0.78 ImmunoCyt plus cytology: 0.75
Wiener, 1998 Austria Medium	NMP22 >10 U/mL Overall: 0.48 (44/91) Ta: 0.49 (23/47) T1: 0.44 (11/25) T2-T4: 0.53 (10/19) G1: 0.52 (12/23) G2: 0.45 (17/38) G3: 0.50 (15/30) Primary: 0.55 (42/77) Recurrent: 0.14 (2/14) BTA stat Overall: 0.57 (52/91) Ta: 0.55 (26/47) T1: 0.60 (15/25) T2-T4: 0.58 (11/19) G1: 0.48 (11/23) G2: 0.58 (22/38) G3: 0.63 (19/30) Primary: 0.62 (48/77) Recurrent: 0.29 (4/14)	NMP22 >10 U/mL Overall: 0.69 (138/200) Primary: 0.66 (75/113) Recurrent: 0.72 (63/87) Cystitis: 0.41 (9/22) Urolithiasis of upper tract: 0.73 (11/15) Benign lower tract lesion: 0.52 (13/25) Nonurological malignancy: 0.55 (6/11) Hematuria: 0.85 (34/40) BTA stat Overall: 0.68 (136/200) Primary: 0.65 (73/113) Recurrent: 0.72 (63/87) Cystitis: 0.59 (13/22) Urolithiasis of upper tract: 0.73 (11/15) Benign lower tract lesion: 0.60 (15/25) Nonurological malignancy: 0.82 (9/11) Hematuria: 0.65 (26/40)	NMP22 >10 U/mL Overall: 0.89 (58/65) Primary: Recurrent: BTA stat Overall: 0.87 (55/63) Primary: Recurrent:	NMP22 >10 U/mL Overall: 0.89 (58/65) Primary: Recurrent: BTA stat Overall: 0.87 (55/63) Primary: Recurrent:

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Varella-Garcia, 2004 USA Medium	Overall: 1.0 (6/6)	Overall: 0.92 (12/13)	NR	National Cancer Institute, Vysis Inc. provided UroVysion kit	
Vriesema, 2001 the Netherlands Medium	ImmunoCyt: 0.47 (7/15) ImmunoCyt plus cytology: 0.32 (11/34)	ImmunoCyt: 0.78 (53/68) ImmunoCyt plus cytology: 0.80 (40/50)	NR	NR	Used data for ImmunoCyt from 1 observer who evaluated 83 specimens (2 other observers evaluated 64 and 58 specimens, respectively)
Wiener, 1998 Austria Medium	NMP22 >10 U/mL Overall: 0.41 (44/106) Primary: 0.52 (42/80) Recurrent: 0.08 (2/26) BTA stat Overall: 0.45 (52/116) Primary: 0.55 (48/88) Recurrent: 0.14 (4/28)	NMP22 >10 U/mL Overall: 0.75 (138/185) Primary: 0.68 (75/110) Recurrent: 0.84 (63/75) BTA stat Overall: 0.78 (136/175) Primary: 0.72 (73/102) Recurrent: 0.86 (63/73)	NR	NR	

Author, Year Country Risk of Bias	Screening Test	Method of Data Collection	Reference Standard	Inclusion Criteria	Subjects
Witjes, 1998 the Netherlands Medium	NMP22 (quantitative)	Unclear	Cystoscopy with pathological confirmation	Patients undergoing surveillance for NMIBC (n=50)	Age: NR Sex: NR Race: NR Smoker: NR Signs or symptoms: NR Prior bladder cancer stage/grade: NMIBC, otherwise NR
Zippe, 1999 USA Medium	NMP22 (quantitative)	Unclear	Cystoscopy with pathological confirmation	Patients with microscopic or gross hematuria or other signs or symptoms suspicious for bladder cancer (n=146)	Mean age: 64 years Male: 77% Race: NR Smoker: NR Signs or symptoms: NR

Author, Year Country Risk of Bias	Proportion With Bladder Cancer, Bladder Cancer Stage and Grade	Definition of a Positive Screening Exam	Proportion Unexaminable by Screening Test	Proportion Who Did Not Undergo Reference Standard and Excluded From Analysis
Witjes, 1998 the Netherlands Medium	12/50 (24%) with bladder cancer Tumor stage: 2 Ta, 1 T1, 3 T2, 1 Tis, 5 not available Tumor grade: 1 G1, 3 G2, 2 G3, 5 not available	NMP: >10 U/mL	NR	None reported
Zippe, 1999 USA Medium	8/146 (5.5%) with bladder cancer Tumor stage: 3 Ta, 1 Ta/T1, 1 T1, 2 T2, 1 Tis Tumor grade: 2 G1, 1 G1/2, 2 G2, 1 G2/G3, 2 G3	NMP: >10 U/mL	NR	None reported

Author, Year Country Risk of Bias	Sensitivity- Report as n/N	Specificity-Report as n/N	Positive Likelihood Ratio	Negative Likelihood Ratio
Witjes, 1998 the Netherlands Medium	0.75 (9/12)	0.82 (31/38)	4.2	0.3
Zippe, 1999 USA Medium	1.0 (8/8)	0.90 (124/138)	10	0

Author, Year Country Risk of Bias	Positive Predictive Value	Negative Predictive Value	AUROC	Funding Source	Comments
Witjes, 1998 the Netherlands Medium	Overall: 0.56 (9/16)	Overall: 0.91 (31/34)	NR	NR	
Zippe, 1999 USA Medium	0.36 (8/22)	1.0 (124/124)	NR	NR	

Please see Appendix C. Included Studies for full study references.

Table E2. Key Question 3: Trials of intravesical compared with no intravesical therapy

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Abrams, 1981 RCT High	United Kingdom Single Center Study years: NR	Histologically confirmed superficial bladder tumor. Recurrent only, with presence of tumors at both of two previous endoscopies 12 months and 6 months before entry into trial. Stages Ta or T1; Included grades not specified, but "well" and "moderate" differentiation included.	None explicitly stated.	A: Doxorubicin, 50 mg (in 50 mL saline). Single installation, within 24 hours of TURBT. B: No adjuvant treatment. TURBT alone.	Duration: 6 months for all patients. Method: Cystoscopy

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Abrams, 1981 RCT High	Screened: NR Randomized: 60 Postrandomization exclusions: 2 Lost to followup: 1 Total Analyzed: 57 Per Group Analyzed (A vs. B): 29 vs. 28	A vs. B All characteristics reported for 60 randomized patients (30 per group), not the groups analyzed: Age (mean), years: 72 vs. 68 Male: 70% vs. 79% Race: NR Smoking status: NR Recurrent bladder cancer: 100% vs. 100% Stage: Ta: 73.3% vs. 76.7%; T1: 26.7% vs. 23.3%; Grade: Well Differentiated: 70.0% vs. 63.3%; Moderately Differentiated: 30.0% vs. 36.7% Functional Status: NR	Recurrence at 6 months: 79.3% (23/29) vs. 89.3% (25/28)

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Abrams, 1981 RCT High	No data reported. "The response to Adriamycin did not appear to be related to any recognised pre-treatment factors, such as number of bladder tumours, stage of tumour (pTa or pT1), or to the histological differentiation of the tumours."	NR	Group A (NR for group B): Severe bladder pain: n=1 Bladder discomfort for up to 24 hours after instillation: n=6 No change in "full blood count".	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Akaza, 1987 RCTs (2 studies) Study One (followup of Niijima, 1983) Medium	Japan Multicenter Study years: April 1980 - 1985	Histologically proven superficial bladder cancer (primary or recurrent). Stages Ta or T1; Grade not specified. Absence of tumor after TURBT.	Tis superficial cancer; other therapies, such as chemotherapy, immunotherapy, and/or radiotherapy within 3 or 4 weeks before initiation of study; severe cardiovascular, renal, hepatic or hematopoietic disturbances; simultaneous presence of another cancer.	A: Doxorubicin, 30 mg (in 30 mL saline). B: Doxorubicin, 20 mg (in 40 mL saline). C: Mitomycin C: 20 mg (in 40 mL saline). D: No adjuvant treatment. TURBT alone. For A, B, and C: First instillation within 1 week of TURBT. Twice weekly X 4 weeks (Total: 8 doses)	Duration: 5 years, maximum; NR as median/mean, nor for each group. Method: Cystoscopy and urinary cytology studies at 12-week intervals during the observation period.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Akaza, 1987 RCTs (2 studies) Study One (followup of Niijima, 1983) Medium	Screened: NR Randomized: 707 (192 vs. 176 vs. 185 vs. 154) Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 575* Per Group Analyzed: (149 vs. 148 vs. 139 vs. 139) * Nonevaluated patients due to protocol violations, cessation of instillation, adverse effects, or other reasons. Not quantified overall or by group.	A vs. B vs. C vs. D Age (years), average: 62.3 vs. 62.9 vs. 62.9 vs. 62.9 Sex (male): 82.6% (123/149) vs. 75.7% (112/148) vs. 74.8% (104/139) vs. 74.1% (103/139) Race: NR Smoking status: NR Recurrent bladder cancer: 29.5% (44/149) vs. 31.1% (46/148) vs. 33.8% (47/139) vs. 35.3% (49/139) Stage: NR* Grade: NR* Functional Status: NR Size: < 1 cm: 40.3% (60/149) vs. 37.2% (55/148) vs. 43.9% (61/139) vs. 46.0% (64/139); 1-3 cm: 43.0% (64/149) vs. 52.7% (78/148) vs. 38.8% (54/139) vs. 48.2% (67/139); 3-5 cm: 14.8% (22/149) vs. 74.3% (11/148) vs. 12.2% (17/139) vs. 5.0% (7/139) Number of tumors: 1: 64.4% (96/149) vs. 63.5% (94/148) vs. 48.2% (67/139) vs. 60.4% (84/139); 2-4: 26.2% (39/149) vs. 25.7% (38/148) vs. 39.6% (55/139) vs. 30.2% (42/139); 5+: 80.5% (12/149) vs. 10.8% (16/148) vs. 11.5% (16/139) vs. 9.4% (13/139) * No data provided on stage or grade, but reported "the number of patients were approximately the same in all four groups" and "no significant differences were found" (no statistical testing reported).	Recurrence-free survival at 1800 days, generalized Wilcoxon test: B > D, $p < 0.05$ C > D, $p < 0.05$ NR for other treatment group comparisons.

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Akaza, 1987 RCTs (2 studies) Study One (followup of Niijima, 1983) Medium	Primary tumor: Recurrence-free survival rate at 1 year (A vs. B vs. C vs. D): 73.1% vs. 76.6% vs. 84.0% vs. 70% Recurrence-free survival at 1800 days, generalized Wilcoxon test: B > D, p < 0.05 C > D, p < 0.01 Comparisons NR for other treatment group comparisons. Recurrent tumor: Recurrence-free survival at 1800 days, generalized Wilcoxon test: A > D; B > D; C > D; differences reported as nonsignificant, no p - values reported.	NR	A vs. B vs. C (NR for group D) Pollakiuria: 33.8% vs. 28.3% vs. 33.1% Dysuria: 36.9% vs. 27.5% vs. 27.4% Hematuria: 20.0% vs. 11.6% vs. 9.7% Pyuria: 23.8% vs. 19.6% vs. 8.9% "No significant systemic side effects"	Ministry of Health and Welfare of Japan	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Akaza, 1987 RCTs (2 studies) Study Two Medium Akaza, 1992 RCT Study Two (followup of sub-group of Akaza, 1987) High	Japan Number sites: Unclear Study years: July 1982 - 1985 Followup study: 1982-May 1990	Histologically proven superficial bladder cancer (primary only). Stages Ta or T1; Grade G1 or G2. Absence of tumor after TURBT.	Tis superficial cancer; other therapies, such as chemotherapy, immunotherapy, and/or radiotherapy within 3 or 4 weeks before initiation of study; severe cardiovascular, renal, hepatic or hematopoietic disturbances; simultaneous presence of another cancer.	A: Doxorubicin, 30 mg (in 30 mL saline). B: Doxorubicin, 20 mg (in 40 mL saline). C: Mitomycin C: 20 mg (in 40 mL saline). D: No adjuvant treatment. TURBT alone. For A, B, and C: First instillation within 1 week of TURBT. Once weekly X 2 weeks, then once every 2 weeks X 14 week, then once monthly X 8 months, then once every 3 month X 1 year (Total: 21 doses over 2 years)	Duration: 3.5 years, maximum Method: Cystoscopy and urinary cytology studies at 12-week intervals during the observation period. Followup study: Duration: median: 2,366 days (6.5 years); range: 480-2,817 days.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Akaza, 1987 RCTs (2 studies) Study Two Medium Akaza, 1992 RCT Study Two (followup of sub-group of Akaza, 1987) High	Screened: 671 Randomized: 665 (170 vs. 175 vs. 164 vs. 156) Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 607 Per Group Analyzed: (151 vs. 158 vs. 150 vs. 148) Followup study: Total Analyzed: 158 Per Group Analyzed: 44 vs. 42 vs. 41 vs. 31	A vs. B vs. C vs. D Age (years), average: 63.1 vs. 62.1 vs. 62.3 vs. 62.0 Sex (male): 80.1% (121/151) vs. 82.3% (130/158) vs. 82.0% (123/150) vs. 81.1% (120/148) Race: NR Smoking status: NR Recurrent bladder cancer: None (primary only) Stage: NR* Grade: NR* Functional Status: NR Size: < 1 cm: 31.8% (48/151) vs. 30.4% (48/158) vs. 36.0% (54/150) vs. 38.5% (57/148); 1-3 cm: 51.0% (77/151) vs. 53.2% (84/158) vs. 44.0% (66/150) vs. 49.3% (73/148); 3-5 cm: 14.6% (22/151) vs. 11.4% (18/158) vs. 11.3% (17/150) vs. 6.8% (10/148) Number of tumors: 1: 64.2% (97/151) vs. 55.7% (88/158) vs. 55.3% (83/150) vs. 66.9% (99/148); 2-4: 29.8% (45/151) vs. 30.4% (48/158) vs. 33.3% (50/150) vs. 23.6% (35/148); 5+: 6.0% (9/151) vs. 12.7% (20/158) vs. 10.7% (16/150) vs. 8.1% (12/148) * No data provided on stage or grade, but reported "absolutely no intergroup differences were found". Followup Study: Only reported overall; NR by treatment group Age ≤ 50 years: 13.3% (21/158) Age ≤ 60 years: 17.7% (28/158) Age < 70 years: 35.4% (56/158) Age ≥ 70 years: 33.5% (53/158) Sex (male): 84.8% (134/158) Stage: Tis: 1.3% (2/158); Ta: 44.3% (70/158); T1: 40.5% (64/158); Ta or T1: 13.9% (22/158) Grade: G1: 48.7% (77/158); G2: 45.6% (72/158); G1 or G2: 5.7% (9/158)	A vs. B vs. C vs. D Recurrence-free survival rate at 1 year: 74.8% vs. 75.0% vs. 76.3% vs. 66.7% Recurrence-free survival rate at 2 years: 62.3% vs. 59.1% vs. 62.3% vs. 51.8% Recurrence-free survival at 1260 days, generalized Wilcoxon test: A > D, p < 0.05 B > D, p < 0.05 C > D, p < 0.05 NR for other treatment group comparisons. Followup study: A vs. B vs. C vs. D Recurrence: Recurrence/year (number of recurrences/total observation period: 0.473 vs. 0.512 vs. 0.472 vs. 0.510 Progression (in stage, grade, or both): 43.2% (19/44) vs. 31.0% (13/42) vs. 26.8% (11/41) vs. 38.7% (12/31), "Statistics: no difference"

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Akaza, 1987 RCTs (2 studies) Study Two Medium Akaza, 1992 RCT Study Two (followup of sub-group of Akaza, 1987) High	NR	NR	A vs. B vs. C (NR for group D) Pollakiuria: 16% vs. 18.7% vs. 23.8% Dysuria: 25.6% vs. 25.2% vs. 27.0% Hematuria: 13.6% vs. 7.3% vs. 11.1% Pyuria: 10.4% vs. 10.6% vs. 19.8% "No significant systemic side effects"	Ministry of Health and Welfare of Japan	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Ali-El-Dein, 1997 (British J Urol) RCT Medium	Egypt Single center Study years: January 1992 - February 1996	Transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Stages pTa or pT1, confirmed histologically; Grade G1 - G3. Multiplicity; Patients with pTa were included if they had multiple, large (≥ 3 cm), recurrent and/or grade 2-3 tumors.	Prior pelvic radiotherapy or chemotherapy; Abnormal cardiac, hematologic, renal, or bladder function; CIS.	A: Epirubicin, 50 mg (in 50 mL normal saline); Single instillation immediately after TURBT. Retained intravesically for 2 hours. B: Epirubicin, 50 mg (in 50 mL normal saline); Initial instillation 1 - 2 weeks after TURBT. Retained intravesically for 2 hours; Then, instillations once a week X 7, then once monthly X 10 to complete 1 year of treatment. C: No adjuvant treatment. TURBT alone.	Duration, mean: 32.2 months Method: Cysto-urethroscopy, cytology, and DNA flow cytometry 8 weeks after resection, then every 3 months during first 2 years, and every 6 months thereafter during the next 2 years.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Ali-El-Dein, 1997 (British J Urol) RCT Medium	Screened: 181 Randomized: 179 Postrandomization exclusions: none Lost to followup: NR Total Analyzed: 168 Per Group Analyzed (A vs. B vs. C): 55 vs. 59 vs. 54	A vs. B vs. C Age, mean years (range): 52.1 (36-65) vs. 55 (30-68) vs. 53.4 (32-72) Race: NR Male: 67.3% (37/55) vs. 74.6% (44/59) vs. 70.4% (38/54) Smoking status: NR Recurrent bladder cancer: 47.2% (26/55) vs. 52.5% (31/59) vs. 44.4% (24/54), p=0.5 Stage: pTa: 16.3% (9/55) vs. 25.4% (15/59) vs. 18.5% (10/54); pT1: 83.7% (46/55) vs. 74.6% (44/59) vs. 81.5% (44/54), p=0.4. Grade: G1: 10.9% (6/55) vs. 18.6% (11/59) vs. 25.9% (14/54); G2: 54.5% (30/55) vs. 55.9% (33/59) vs. 53.7% (29/54); G3: 34.5% (19/55) vs. 25.4% (15/59) vs. 20.4% (11/54), p=0.2. Functional Status: NR Size: < 3 cm: 65% (36/55) vs. 71% (42/59) vs. 63% (34/54); $\geq$ 3 cm: 35% (19/55) vs. 29% (17/59) vs. 37% (20/54)	A vs. B vs. C Recurrence: 23.6% (13/55) vs. 25.4% (15/59) vs. 51.8% (28/54), A vs. B vs. C, p = 0.002, A and B vs. C, p < 0.001, A vs. B, p=0.8. Mean interval to first recurrence, months: 16 vs. 18 vs. 6.9, p < 0.05. Recurrence rate per 100 patient-months: 0.79 vs. 0.84 vs. 2.01 Progression: 5.5% (3/55) vs. 3.4% (2/59) vs. 9.3% (5/54), p=0.4.

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Ali-El-Dein, 1997 (British J Urol) RCT Medium	A vs. B (No data for group C) Simple recurrence rate according to stage: Ta: 0.0% (0/9) vs. 0.0% (0/15); T1: 28.3% (13/46) vs. 34.1% (15/44), p = 0.7. Simple recurrence rate according to grade: G1: 0.0% (0/6) vs. 27.3% (3/11); G2: 10.0% (3/30) vs. 27.3% (9/33), p=0.3; G3: 52.6% (10/19) vs. 20.0% (3/15), p = 0.05. Simple recurrence rate for large tumors (≥ 3 cm in greatest dimension): 21.1% (4/19) vs. 41.2% (7/17), p =0.5.	NR	A vs. B (No data for group C) Proportion of patients with an adverse event: 21.8% (12/55) vs. 25.4% (15/59), p=0.8. Mild toxicity: 75.0% (9/12) vs. 66.7% (10/15), p=0.8. Severe toxicity (i.e., requiring permanent or temporary discontinuation of treatment): 25.0% (3/12) vs. 33.3% (5/15) , p = 0.7. Contracted bladder: 0.0% (0/12) vs. 6.7% (1/15) Hematuria: 16.7% (2/12) vs. 20.0% (3/15) UTI: 8.3% (1/12) vs. 6.7% (1/15) No patients with systemic toxicity.	No financial support received	Note: Possible overlap of some study subjects (group B) with those in Ali-El-Dein, 1997 (J Urol)

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Ali-El-Dein, 1997 (J Urol) RCT Medium	Egypt Single center Study years: June 1991 - May 1995	Transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Stages Ta or T1; Associated CIS or other dysplastic mucosal changes; Grade G1 - G3. Rapid recurrence within 6 months of initial resection; Multicentricity; Positive posterior urethral biopsy and/or positive postoperative urinary cytology (only 2 patients with positive posterior urethral biopsy, who underwent resection of multiple tumors to provide bladder neck incompetence and sufficient contact of drug with prostatic urethra).	Prior pelvic radiotherapy or chemotherapy; Abnormal cardiac, hematologic, renal, or bladder function.	A: Epirubicin, 50 mg (in 50 mL normal saline). B: Epirubicin, 80 mg (in 50 mL normal saline). C: Doxorubicin, 50 mg (in 50 mL normal saline). D: No adjuvant treatment. TURBT alone. For Groups A - C: First instillation 7 to 14 days after TURBT. Retained intravesically for 2 hours; Instillations once a week X 8 weeks, then once monthly to complete 1 year of treatment.	Duration, mean: 30.1 months Method: Cystourethroscopy, urine cytology, and flow cytometry every 3 months during first 2 years, and every 6 months thereafter.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Ali-El-Dein, 1997 (J Urol) RCT Medium	Screened: NR Randomized: 253 Postrandomization exclusions: none Lost to followup: NR Total Analyzed: 253 Per Group Analyzed (A vs. B vs. C vs. D): 64 vs. 68 vs. 60 vs. 61	A vs. B vs. C vs. D Age: NR Race: NR Male: 81.4%, NR by treatment group Smoking status: NR Recurrent bladder cancer: 37.5% vs. 41.2% vs. 43.3% vs.45.9% Stage: pTa: 10.9% vs. 17.6% vs. 6.7% vs.9.8%; pT1: 89.1% vs. 82.4% vs. 93.3% vs.90.2%; Tis associated: 6.3% vs. 11.8% vs. 0.0% vs.0.0% Grade: G1: 9.4% vs. 16.2% vs. 16.7% vs.19.7%; G2: 78.1% vs. 69.1% vs. 70.0% vs.65.6%; G3: 12.5% vs. 14.7% vs. 13.3% vs.14.7% Functional Status: NR	A vs. B vs. C vs. D Recurrence: 25.0% (16/64) vs. 17.6% (12/68) vs. 36.7% (22/60) vs.65.6% (40/61), A, B, and C vs. D, p=0.0002, A and B vs. C, p=0.02, A vs. B, p > 0.05. Mean time to first recurrence, months (95% CI): 16 (12.2-19.8) vs. 15.4 (11.4-19.4) vs. 18.9 (14.4-23.4) vs. 6.3 (5.2-7.4); A, B, and C vs. D, p < 0.001; B vs. C, p = 0.05; A and B vs. C; p=0.05. Recurrence rate per 100 patient-months: 0.83 vs. 0.60 vs. 1.18 vs. 2.73, A, B, and C vs. D, p < 0.001, A and B vs. C; p < 0.05, A vs. B, p < 0.05. Progression (to muscle invasive): 10.9% (7/64) vs. 4.4% (3/68) vs. 10.0% (6/60) vs.8.2% (5/61). Mean interval to progression, months (95% CI): 31 (22-40) vs. 31 (18-44) vs. 33 (26-40) vs. 37 (30-44), p=0.6.

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Ali-El-Dein, 1997 (J Urol) RCT Medium	A vs. B vs. C vs. D Simple recurrence rate according to stage: Ta: 0.0% (0/16) vs. 0.0% (0/12) vs. 0.0% (0/22) vs. 2.5% (1/40), p > 0.05; T1: 93.8% (15/16) vs. 83.3% (10/12) vs. 100% (22/22) vs. 97.5% (39/40), A, B, and C vs. D, p < 0.0001, A and B vs. C, p=0.01, A vs. B, p=NS; pTis: 6.3% (1/16) vs. 16.7% (2/12) vs. NA vs. NA. Simple recurrence rate according to grade: G1: 0.0% (0/16) vs. 16.7% (2/12) vs. 13.6% (3/22) vs. 12.5% (5/40), p > 0.05; G2: 75.0% (12/16) vs. 58.3% (7/12) vs. 68.2% (15/22) vs. 67.5% (27/40), A, B, and C vs. D, p < 0.0001, A and B vs. C, p=0.04, A vs. B, p=NS; G3: 25.0% (4/16) vs. 25.0% (3/12) vs. 18.2% (4/22) vs. 20.0% (8/40), p > 0.05. Simple recurrence rate according to Grade 3-Stage pT1/Total: 66.7% (4/6) vs. 37.5% (3/8) vs. 57.1% (4/7) vs. 100% (8/8); A, B, and C vs. D, p < 0.05; A and B vs. C, p > 0.05.	NR	A vs. B vs. C (No data for group D) Proportion of patients with an adverse event: 15.6% (10/64) vs. 23.5% (16/68) vs. 41.7% (25/60), A and B vs. C, p=0.002, A vs. B, p=0.3, B vs. C, p < 0.04. Adverse events per # of instillations: 7.3% (88/1199) vs. 8.7% (111/1280) vs. 29.0% (324/1118), A and B vs. C, p < 0.0001, B vs. C, p < 0.05. Systemic toxicity: 0.0% (0/10) vs. 0.0% (0/16) vs. 12.0% (3/25), p < 0.05 Mild toxicity: 50.0% (5/10) vs. 68.8% (11/16) vs. 60.0% (15/25), A and B vs. C, p=0.02, A vs. B, p > 0.05, B vs. C, p=0.3. Severe toxicity (i.e., requiring permanent or temporary discontinuation of treatment): 20.0% (2/10) vs. 12.5% (2/16) vs. 12.0% (3/25), A and B vs. C, p > 0.05, A vs. B, p > 0.05, B vs. C, p > 0.05. Contracted bladder: 10.0% (1/10) vs. 6.3% (1/16) vs. 8.0% (2/25) Hematuria: 10.0% (1/10) vs. 12.5% (2/16) vs. 4.0% (1/25) UTI: 10.0% (1/10) vs. 0.0% (0/16) vs. 4.0% (1/25)	NR	Note: Possible overlap of some study subjects (group A) with those in Ali-El-Dein, 1997 (British J Urol)

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Berrum-Svennung, 2008 RCT Medium	Sweden Multicenter September 1998 - September 2004	Non-muscle invasive papillary bladder tumor (primary or recurrent). Stage Ta or T1; Grade G1 or G2. Maximal tumor diameter 30 mm.	Intravesical treatment with BCG or chemotherapy in previous year; History of muscle-invasive tumor or grade G3 tumor; Stage T2.	A: Epirubicin, 50 mg (in 50 mL saline). Single instillation within 6 hours after TURBT. Catheter clamped X 1 hour. B: Placebo. Saline, 50 mL. Single instillation within 6 hours after TURBT. Catheter clamped X 1 hour.	Duration: 2 years Method: Evaluated with cystoscopy according to the routine at each study center. Study plan recommended cystoscopy every 4 months X 1 year, then every 6 months X 1 year. Participants were free to follow their respective clinical routines after instillation.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Berrum-Svennung, 2008 RCT Medium	Screened: NR Randomized: 404 (203 vs. 201) Postrandomization exclusions: 14 Lost to followup: 11 Total Analyzed: 307 Per Group Analyzed: (A vs. B): 155 vs. 152	A vs. B Age, median: 74 years vs. 71 years Age, mean: 71 years vs. 69 years Sex (male): 69.7% (108/155) vs. 77.6% (118/152) Race: NR Smoking status: NR Recurrent bladder cancer: 49.7% (77/155) vs. 50.7% (77/152) Stage/Grade: Ta/G1-G2: 85.2% (132/155) vs. 82.2% (125/152); T1/G1-G2: 5.7% (8/155) vs. 8.0%(12/152); Unknown: 9.7% (15/155) vs. 9.9% (15/152) Functional Status: NR Size, median (mm): 10 vs. 10 Size, mean (mm): 13 vs. 13 Number of tumors: Single: 56.1% (87/155) vs. 61.2% (93/152); Multiple: 43.9% (68/155) vs. 38.8% (59/152)	A vs. B Recurrence, during 2 years: 51.0% (79/155) vs. 62.5% (95/152); Mann-Whitney U test, p=0.04, log-rank test, p = 0.022 Progression (stage to muscle invasion): 2.6% (4/155) vs. 1.3% (2/152), (difference "not significant").

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Berrum-Svennung, 2008 RCT Medium	NR	NR	NR	NR	Of the 307 patients, 48 (15.6%) were treated with a series of BCG or chemotherapy during the 2-year followup; including 14.8% (23/155) in Epirubicin group and 15.8% (24/152) in placebo group, p = 0.80.

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Böhle, 2009 RCT Medium	Germany and Turkey Multicenter Study years: January 2004 - June 2005	Papillary, non-muscle-invasive transitional cell carcinoma of the bladder (primary or recurrent). Stages Ta or T1; Grade G1 - G3. Karnofsky performance status $\geq$ 70%; WBC $\geq$ 4 X 10^9/L; platelets ≥ 140 X 10^9/L; Hgb $\geq$ 10g/dL; serum creatine < 2.0 mg/dL; bilirubin < 2.0 mg/dL; AST and ALT < 2.5 times upper limit of normal.	No concomitant CIS or history of CIS; weight loss > 15% during previous 6 months; prior chemotherapy within previous 6 months; more than 3 prior TURs.	A: Gemcitabine (GEM), 2000 mg (in 100 mL saline (0.9% NaCl)), instilled over 30 - 40 minutes immediately after TUR, followed by continuous irrigation with saline for $\geq$ 20 hours. B: Placebo (PBO), 100 mL saline (0.9% NaCl), instilled over 30 - 40 minutes immediately after TUR, followed by continuous irrigation with saline for ≥ 20 hours.	Duration: median: 23.6 months (range: 0 - 46). Method: Cystoscopy at least at month 3 and month 6, and every 6 months thereafter. A second TURBT (no instillation) and adjuvant BCG were allowed. If nonmalignancy, CIS, or ≥ pT2 disease detected during TURBT or histopathology, patients were discontinued but followed for safety for 3 months.
Burnand, 1976 RCT Medium	UK Single center Study years: NR	Superficial transitional cell carcinoma of the bladder suitable for endoscopic loop resection or fulguration	Not stated	A: Thiotepa, 90 mg (in 100 mL sterile water) immediately after TURBT B: No adjuvant treatment. TURBT alone	Duration: 2 to 5 years Method: Cystoscopy, interval NR

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Böhle, 2009 RCT Medium	Screened: NR Randomized: 355 Postrandomization exclusions (A vs. B): 13 (7.3%) vs. 14 (8.0%) Excluded after treatment (not eligible) (A vs. B): 42 (23.5%) vs. 38 (21.6%) Eligible for efficacy outcomes (A vs. B): 124 (69.3% of randomized) vs. 124 (70.5% of randomized) Lost to followup (A vs. B): 23 (18.5%) vs. 21 (16.9%) Total Analyzed: 248* Per Group Analyzed (A vs. B): 124 vs. 124	A vs. B Age, median (range): 65 years (24 - 89) vs. 67 years (39 - 87) Race: NR Sex (male): 76.6% (95/124) vs. 83.1% (103/124) Smoking status: NR Recurrent bladder cancer: 24.2% (30/124) vs. 21.0% (26/124) Stage: pTa: 75.0% (93/124) vs. 71.0% (88/124); pT1: 25.0% (31/124) vs. 29.0% (36/124) Grade: G1: 46.0% (57/124) vs. 53.2% (66/124); G2: 39.5% (49/124) vs. 34.7% (43/124); G3: 10.5% (13/124) vs. 11.3% (14/124); Unknown: 4.0% (5/124) vs. 0.8% (1/124) Multiple lesions: 47.6% vs. 38.7% Functional Status (Karnofsky score): score 90-100: 91.9% (114/124) vs. 94.4% (117/124); score 80-85: 7.3% (9/124) vs. 4.0% (5/124); score < 80: 0.8% (1/124) vs. 0.8% (1/124); missing: 0 vs. 0.8% (1/124)	A vs. B Recurrence: 35.5% (44/124) vs. 36.3% (45/124) Progression to muscle-invasive: 2.4% (3/124) vs. 0.8% (1/124) Median recurrence-free survival: 37.2 months vs. 40.2 months; HR (95% CI): 0.946 (0.64-1.39); log-rank test, p=0.78 12-month recurrence-free rate, % (95% CI): 77.7% (68.8-84.3) vs. 75.3% (66.3-82.3) 24-month recurrence-free rate, % (95% CI): 64.0% (54.1-72.3) vs. 60.7% (51.0-69.1) Mortality, disease-specific: 0.8% (1/124) vs. 0.8% (1/124) Mortality, overall: 2.4% (3/124) vs. 4.8% (6/124)
Burnand, 1976 RCT Medium	Screened: NR Randomized: 51 (19 vs. 32) Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 51	A vs. B Age, mean (years): 60 vs. 62 years Sex (male): 84% vs. 84% Race: NR Smoking status: NR Recurrent bladder cancer: NR Stage: NR Grade: NR Multifocal: Unclear	A vs. B Recurrence: 58% (11/19) vs. 97% (31/32) at 2 to 5 years, RR 0.60 (95% CI 0.41 to 0.88) Time to recurrence (months): 2.20 vs. 2.66

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Böhle, 2009 RCT Medium	A vs. B 12-month recurrence-free survival (RFS), %; HR (95% CI): G1/G2: 78.5% vs. 78.4%; 1.05 (0.69-1.59), p=0.82 G3: 66.7% vs. 42.4%; 0.48 (0.15-1.51), p=0.21 Single lesion: 84.1% vs. 81.0%; 0.87 (0.49-1.55), p =0.641 Multiple lesions: 71.5% vs. 66.5%; 0.996 (0.57-1.73), p =0.99 Primary tumor: 79.3% vs. 79.8%; 1.05 (0.67-1.63), p=0.85 Recurrent tumor: 72.2% vs. 58.9%; 0.70 (0.32-1.51), p=0.36	A vs. B 12-month recurrence-free survival (RFS), according to country: Germany: 77.5% vs. 78.7%: HR=1.14 (0.73-1.78), p =0.58 Turkey: 78.6% vs. 63.1%; HR=0.51 (0.23-1.13), p = 0.096	A vs. B All patients receiving instillation (GEM=166; PBO=162) followed for adverse effects until month 3. At least one adverse event: 29.5% vs. 26.5% Adverse events "possibly related to instillation treatment": 6.6% vs. 3.7% Adverse events reported more than once per group: Alopecia: 1.2% vs. 0% Pyrexia: 1.2% vs. 0.6% Procedural pain: 1.2% vs. 0%	Funded and sponsored by Eli Lilly and Company. The sponsor assisted in the design and conduct of the study; contributed to the management, analysis, interpretation, preparation, and review of the data; and approved the manuscript.	
Burnand, 1976 RCT Medium				NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Cheng, 2005 RCT Medium	Hong Kong Single center Study years: July 1986 - November 1991	Superficial transitional cell carcinoma of the bladder (primary or recurrent). Stages Ta or T1; Grade G1 - G3. Tumor > 1 cm. Multiple or recurrent tumors.	Carcinoma in situ; previous intravesical treatment	A: Doxorubicin, 50 mg (in 50 mL saline), administered intravesically and retained for 2 hours. First instillation 2 weeks after TURBT, followed by treatment weekly X 4 weeks, then monthly X 5 months, then 3-monthly X 6 months. B: No adjuvant treatment. TURBT alone. Patients with recurrences in either group were allowed treatment with doxorubicin or other intravesical therapy, such as epirubicin or BCG.	Duration: First recurrence, median: 45 months (range: 0 - 190). Progression, median: 128 months (range: 0 to 193) Duration of survival, median: 131.5 months (range: 1 to 193) Method: Cystoscopy every 3 months for 2 years, then urine cytology every 6 months. Cystoscopy at final examination, if none in previous 1 year.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Cheng, 2005 RCT Medium	Screened: 82 Randomized: 82 Postrandomization exclusions: None reported Lost to followup: 1 (NR which group) Total Analyzed: 82 Per Group Analyzed (A vs. B): 46 vs. 36	A vs. B Age, mean: 65.5 years (1.7) vs. 62.1 years (2.3), p=0.22 Race: NR Sex (male): 71.7% (33/46) vs. 86.1% (31/36), p=0.12 Smoking status: NR Recurrent bladder cancer: NR Stage: Ta: 67.4% (31/46) vs. 63.9% (23/36); T1: 21.7% (10/46) vs. 13.9% (5/36); NR: 10.9% (5/46) vs. 22.2% (8/36); p=0.52 (Ta and T1) Grade: G1: 34.8% (16/46) vs. 41.7% (15/36); G2: 32.6% (15/46) vs. 19.4% (7/36); G3: 23.9% (11/46) vs. 16.7% (6/36); NR: 8.7% (4/46) vs. 22.2% (8/36); p =0.43 (G1/G2/G3) Size (cm): 0.1 - 1.0: 21.7% (10/46) vs. 25.0% (9/36); 1.1 - 3.0: 43.5% (20/46) vs. 27.8% (10/36); 3.1 - 10.0: 23.9% (11/46) vs. 22.2% (8/36); NR: 10.9% (5/46) vs. 25.0% (9/36); p=0.60 (reported categories only) Multiplicity: Single: 50.0% (23/46) vs. 72.2% (26/36); Multiple: 43.5% (20/46) vs. 8.3% (3/36); NR: 6.5% (3/46) vs.19.4% (7/36); p=0.01 (single/multiple categories only) Functional Status: NR	A vs. B Recurrence (one or more): 37.0% (17/46) vs. 52.8% (19/36) Recurrence-free survival (RFS) curve, log rank test, p=0.12 Median RFS: 190 months vs. 89 months 10-year Kaplan-Meier estimate for RFS: 67% vs. 50% Median time to first recurrence: 13 months (range: 1 - 190) vs. 8 months (range: 1 - 175) Progression (≥ T2; positive lymph node; or distant metastasis): 13.0% (6/46) vs. 5.6% (2/36) Progression-free survival curve, log rank test, p=0.44 10-year Kaplan-Meier estimate for progression-free survival: 84% vs. 89% Median time to first progression: 34 months vs. 61 months Mortality (disease-specific): 6.5% (3/46) vs. 2.8% (1/36) 10-year Kaplan-Meier estimate for disease-specific survival: 95% vs. 97% Median time to death (disease-specific): 73 months vs. 55 months Mortality (other causes): 30.4% (14/46) vs. 16.7% (6/36) 10-year Kaplan-Meier estimate for overall survival: 68% vs. 83%

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Cheng, 2005 RCT Medium	In multivariate Cox proportional hazards models: Risk of recurrence increased with larger tumor size (p=0.013). Risk of progression increased with higher grade (p=0.004). Tumor stage or number not associated with recurrence or progression.	NR	NR	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
De Nunzio, 2011 RCT Medium	Italy Single center Study years: January 2000 - December 2009	Cystoscopy-verified primary low-risk bladder tumors. Stage Ta; Grade G1 - G2.	Multiple or large tumors (> 3 cm); Carcinoma in situ; Grade 3 or muscle-invasive on histological exam; History of intravesical therapy within previous year; Upper urinary tract tumor; age $\geq$ 80 years	A: Mitomycin C (MMC), 40 mg (in 50 mL saline) intravesical; infusion as soon as possible within 24 hours of TURBT; MMC retained in bladder for 1 hour, patient position changed every 15 minutes during instillation; bladder then irrigated for 12 hours with saline solution. B: No adjuvant therapy. After TURBT, irrigation with saline solution until clear.	Duration: median: 90 months (72-109) vs. 85 months (61-112), p=0.42 Method: Cystoscopy and urine cytology: every 3 months for year 1 and year 2, then every 4 months for year 3 and year 4, then every 6 months for year 5, then every year thereafter.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
De Nunzio, 2011 RCT Medium	Screened: NR Randomized: 210 Postrandomization exclusions: none reported Lost to followup: NR Total Analyzed: 102 Per Group Analyzed (A vs. B): 97 vs. 105	A vs. B Age, median: 60.8 years (52.5-69.2) vs. 61.5 years (53.4-69.5), p = 0.34 Race: NR Sex (male): 62.9% (61/97) vs. 68.6% (72/105), p=0.39 Smoking status: NR Recurrent bladder cancer: None Stage: Ta: 100% vs. 100% Grade: G1: 70.1% (68/97) vs. 77.1% (81/105), p=0.26; G2: 29.9% (29/97) vs. 22.9% (24/105), p=0.25 Size, median: 1.6 cm (0.6-2.1) vs. 1.8 (0.7-2.2), p=0.09 Functional Status: NR	A vs. B Overall Recurrence: 10.3% (10/97) vs. 43.8% (46/105), p=0.001; HR (95% CI): 0.20 (0.10-0.395), p=0.0001 Early recurrence (within 1 year of enrollment): 40.0% (4/10) vs. 34.8% (16/46), p=0.008 Early recurrence tumor size, median: 0.8 cm (0.5-1.0) vs. 0.8 (0.6-1.2), p=0.34 Early recurrence grade: G1: 75% (3/4) vs. 87.5% (14/16), p=0.53; G2: 25% (1/4) vs. 12.5% (2/16), p=0.53; G3: 0% vs. 0%, p = 0.53 Late recurrence (after 1 year of enrollment): 60.0% (6/10) vs. 60.9% (28/46), p=0.0001 Late recurrence tumor size, median: 1.2 cm (1.0-1.5) vs. 1.5 (1.0-1.7), p=0.001 Late recurrence grade: G1: 66.7% (4/6) vs. 71.4% (20/28), p=0.60; G2: 33.3% (2/6) vs. 21.4% (6/28), p=0.60; G3: 0% vs. 0% (0/6) vs. 7.1% (2/28), p=0.60 Progression (≥ T2): 0% (0/97) vs. 0.95% (1/105), p=0.33 All recurrences in treatment arm were Ta; 30.4% (14/46) of recurrences in control arm were T1. Absolute risk reduction (MMC vs. control): Overall=31%, Early recurrence=11%, Late recurrence=20% Number needed to treat to prevent one recurrence: Overall=3.26, Early recurrence=8.99; Late recurrence=5.12

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
De Nunzio, 2011 RCT Medium	NR	NR	NR	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Giannakopoulos, S, 1998 RCT Medium	Greece Number sites: unclear. Authors from 3 centers. Study years: NR	Superficial transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Stages Ta or T1; Grade G2.	Stage ≥ T2. Grade G1 or G3 (any stage). CIS; Other concomitant malignancy; Serious systemic disease; Previous intravesical chemotherapy or immunotherapy; TCC of upper urinary tract; Previous systemic chemo/immunotherapy or pelvic radiation therapy	A: No adjuvant treatment. TURBT alone. B: Interferon-α-2b (IFN-α-2b), 40 MU (in 50 mL normal saline). C: Interferon-α-2b (IFN-α-2b), 60 MU (in 50 mL normal saline). D: Interferon-α-2b (IFN-α-2b), 80 MU (in 50 mL normal saline). For Groups B - D: First instillation after histological verification of stage and grade; 48 - 72 hours after TURBT. Retained intravesically for 1 hour; patient position changed every 15 minutes. Instillations once a week X 2 months, then once every 15 days X 4 months, then once monthly X 6 months.	Duration: 36 months Method: Cystoscopy and urine cytology, every 3 months for 18 months, and every 6 months thereafter.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Giannakopoulos, S, 1998 RCT Medium	Screened: NR Randomized: 89 Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 89 Per Group Analyzed (A vs. B vs. C vs. D): 20 vs. 22 vs. 24 vs. 23	A vs. B vs. C vs. D Age, mean (SD): 61.6 years (9.62) vs. 62.1 years (9.49) vs. 60.9 years (9.43) vs. 61.9 years (9.98); p > 0.10 Race: NR Sex (male): 80.0% (16/20) vs. 81.8% (18/22) vs. 79.2% (19/24) vs. 82.6% (19/23); p > 0.10 Smoking status: NR Recurrent bladder cancer: NR Stage: Ta: 60.0% (12/20) vs. 59.1% (13/22) vs. 62.5% (15/24) vs. 56.5% (13/23); T1: 40.0% (8/20) vs. 40.9% (9/22) vs. 37.5% (9/24) vs. 43.5% (10/23); p > 0.10 Grade: All G2 Functional Status: NR	A vs. B vs. C vs. D Recurrence: 65.0% (13/20) vs. 36.4% (8/22) vs. 29.2% (7/24) vs. 21.7% (5/23); A vs. B, p=0.06; A vs. C, p < 0.05; A vs. D, p < 0.01; Differences between B, C, and D, p > 0.10. Recurrence-free survival time, months (mean): 15.0 vs. 21.4 vs. 26.1 vs. 30.0; A vs. B, p < 0.05; A vs. C, p < 0.001; A vs. D, p < 0.001; B vs. C, p=0.02, B vs. D, p < 0.01; C vs. D, p=NS. Recurrence rate per 100 patient-months: 2.91 vs. 1.19 vs. 0.88 vs. 0.63; A vs. B, p < 0.001; A vs. C, p < 0.001; A vs. D, p < 0.001; B vs. C, p="significant", B vs. D, p = "significant"; C vs. D, p=0.026. Progression: 30.0% (6/20) vs. 13.6% (3/22) vs. 4.2% (1/24) vs. 4.3% (1/23); A vs. B, p=NS; A vs. C, p < 0.05; A vs. D, p < 0.05; B vs. C, p=NS, B vs. D, p=NS; C vs. D, p=NS. Progression details: A: Ta to T1 (n=3), T1 to MIBC (n=3); B: Ta to T1 (n=1), T1 to MIBC (n=2); C: T1 to MIBC (n=1); D: T1 to MIBC (n=1).

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Giannakopoulos, S, 1998 RCT Medium	A vs. B vs. C vs. D Simple recurrence rate according to stage: Ta: 53.8% (7/13) vs. 50.0% (4/8) vs. 57.1% (4/7) vs. 40.0% (2/5); For all comparisons between groups, p > 0.10. T1: 46.2% (6/13) vs. 50.0% (4/8) vs. 42.9% (3/7) vs. 60.0% (3/5); For all comparisons between groups, p > 0.10. Recurrence-free survival time according to stage, Mean months (SD): Ta: 15.4 (5.86) vs. 23.3 (6.65) vs. 28.5 (7.55) vs. 31.5 (6.36); A vs. B, p < 0.01; A vs. C, p < 0.001; A vs. D, p < 0.001; B vs. C, p=0.05, B vs. D, p < 0.001; C vs. D, p=NS. T1: 14.5 (6.95) vs. 19.5 (9.33) vs. 23.0 (9.17) vs. 29.0 (7.55); A vs. B, p < 0.05; A vs. C, p < 0.001; A vs. D, p < 0.001; B vs. C, p=0.048, B vs. D, p < 0.001; C vs. D, p < 0.01. Recurrence rate per 100 patient-months according to stage: Ta: 2.43 vs. 0.96 vs. 0.78 vs. 0.44; A vs. B, p < 0.001; A vs. C, p < 0.001; A vs. D, p < 0.001; Differences between B, C, and D, p=NS. T1: 3.77 vs. 1.55 vs. 1.05 vs. 0.8; Results "similar" to stage Ta, no p=values reported.	NR	No side effects of the drugs were noted. No adverse reactions noted. Five patients (groups NR) developed fevers and were found to have urinary tract infections.	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Gudjónsson, 2009 RCT Medium	Sweden Multicenter Study years: 1997 - 2004	Low to intermediate risk bladder tumors (primary or recurrent). Stages Ta or T1; Grade G1 or G2. Single or multiple tumors. No upper limit on size.	CIS; Grade 3 cancer; Muscle-invasive tumor. History of high-risk tumor (G3 or CIS) and intravesical therapy within previous year; upper urinary tract tumor; age > 85 years. Patients with muscle invasion on re-TURBT. Histopathology report could not confirm malignancy.	A: Epirubicin, 80 mg (in 30 mL saline) intravesically as soon as possible within 24 hours of TURBT. A single instillation, retained intravesically for 1 hour; fluid restriction and patient position changed every 15 minutes. B: No adjuvant treatment. TURBT alone.	Duration: median 3.9 years. Median (patients without recurrence): 3.6 years (range: 0.4 - 7.4 years) Method: Cystoscopy and urine cytology, every 3 months during year 1, and every 4 months during year 2. Thereafter, surveillance performed according to local routines at each center.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Gudjónsson, 2009 RCT Medium	Screened: NR Randomized: 305 Postrandomization exclusions: 9 Lost to followup: 6 Total Analyzed: 219 Per Group Analyzed: 102 vs. 117	A vs. B Age, median (years)/mean (years): 71/70 vs.72/70 Race: NR Sex (male): 72.5% (74/102) vs. 69.3% (81/117) Smoking status: NR Recurrent bladder cancer: 46.1% (47/102) vs. 48.7% (57/117) Stage: Ta: 81.4% (83/102) vs. 86.3% (101/117) ; T1: 9.8% (10/102) vs. 6.8% (8/117) ; Unknown: 7.8% (8/102) vs. 6.0% (7/117) ; "Low malignant potential": 1.0% (1/102) vs. 0.9% (1/117) Grade: G1: 53.9% (55/102) vs. 48.7% (57/117) ; G2: 39.2% (40/102) vs. 44.4% (52/117) ; Unknown: 6.9% (7/102) vs. 6.8% (8/117) Functional Status: NR Number of tumors: 1: 44% (45/102) vs. 46% (54/117); 2-3: 21% (21/102) vs. 27% (32/117); ≥ 4: 33% (34/102) vs. 26% (30/117) All comparisons between the two groups statistically non significant (p-values between 1.0 and 0.34)	A vs. B Recurrence: 62% (63/102) vs. 77% (90/117) Difference in Recurrence-free survival, p = 0.016 Univariate HR (95% CI): 0.67 (0.49-0.93), p=0.017 Multivariate HR (95% CI), adjusting for tumor multiplicity, number of recurrences/year, sex, age, and tumor grade: 0.56 (0.39-0.80), p=0.002

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Gudjónsson, 2009 RCT Medium	A vs. B Recurrence rate according to primary or recurrent tumor: Primary: 40% (22/55) vs. 67% (40/60), p=0.008 Recurrent: 87% (41/47) vs. 88% (50/57), p=0.49 Recurrence rate according to solitary or multiple tumors: Solitary: 36% (16/45) vs. 67% (36/54), p=0.004 Multiple: 84% (46/55) vs. 85% (53/62), p=0.26	NR	NR	FoU Kronoberg; Swedish Cancer Society; Skane County Council Research and Development Foundation	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Gustafson, 1991 RCT Medium	Sweden Number of sites: unclear. Authors from 4 centers. Study years: NR	Superficial bladder cancer. Recurrent included, unclear if primary included. Stages Ta or T1; Grade G1, G2, or G3. Single or multiple tumors.	None explicitly stated. However, no patient had previously been treated with radiotherapy, systemic or topical chemotherapy.	A: Mitomycin C. Dosages "varied according to individual patient's bladder capacity". Range: "5 mg in 20 mL" to "40 mg in 250 mL". First instillation approximately 2 weeks after TURBT. Instillations weekly X 4 weeks, then monthly X 11 months. B: Doxorubicin. Dosages "varied according to individual patient's bladder capacity". Range: "10 mg in 20 mL" to "80 mg in 250 mL". First instillation approximately 2 weeks after TURBT. Instillations weekly X 4 weeks, then monthly X 11 months. C: No adjuvant treatment. TURBT alone.	Duration: mean, months (range): 47 (12-65) vs. 45 (14-69) vs. 35 (10-68) Method: Cystoscopy every 3 months during year 1; thereafter, every 6 months unless recurrence, in which case every 3 months. Micturition frequency, pain on micturition, other subjective symptoms recorded before and after each instillation. Blood tests (including CBC and creatinine) after 2nd and 4th instillation and every month, thereafter.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Gustafson, 1991 RCT Medium	Screened: NR Randomized: 62 Postrandomization exclusions: NR Lost to followup: 2 Total Analyzed: 60 Per Group Analyzed: 19 vs. 20 vs. 21	A vs. B vs. C Age, mean (Overall; NR by group): 67 years Race: NR Sex (Overall male: female; NR by group): "Four to one" Smoking status: NR Recurrent bladder cancer: NR Stage: Ta: 89.5% (17/19) vs. 90.0% (18/20) vs. 95.2% (20/21); T1: 10.5% (2/19) vs. 10.0% (2/20) vs. 4.8% (1/21) Grade: G1: 36.8% (7/19) vs. 35.0% (7/20) vs. 33.3% (7/21); G2: 63.2% (12/19) vs. 65.0% (13/20) vs. 61.9% (13/21); G3: 0% (0/19) vs. 0% (0/20) vs. 4.8% (1/21) Functional Status: NR	A vs. B vs. C Recurrence: Tumor-free survival during treatment year: 52.6% (10/19) vs. 15% (3/20) vs. 14.3% (3/21) Tumor-free survival for duration of followup: 26.3% (5/19) vs. 10% (2/20) vs. 4.8% (1/21) Mean disease-free interval, months (A vs. B): 14 vs. 6, p=0.02 Recurrence rate/100 patient-months: 7.7 vs. 18.3 vs. 18.6, p=0.02 Progression: Increased stage: 0% (0/19) vs. 5% (1/20) vs. 4.8% (1/21) Increased grade: 0% (0/19) vs. 15% (3/20) vs. 9.5% (2/21) Increased stage and grade: 10.5% (2/19) vs. 10% (2/20) vs. 0% (0/21)

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Gustafson, 1991 RCT Medium	NR	NR	No significant changes in frequency of micturition. No serious side-effects detected by blood samples. Mild pain on micturition (A vs. B): 60 % vs. 45%	King Gustaf V Jubilee Foundation	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Herr, 1988 RCT Medium Herr, 1995 (10 year followup) Cookson, 1997 (15 year followup) Herr, 1997 (15 year followup Subgroup analysis) Pinsky, 1985	USA Number of sites: unclear. 1978-1981	Recurrent, superficial transitional-cell carcinoma of the bladder (Ta, T1, Tis) <u>Subgroup analysis:</u> T1 tumors Grade 2-3		3-5 weeks after TURBT began weekly treatments for 6 weeks: A. TURBT B. TURBT plus BCG 120 mg (Armand Frappier strain) in 50 mL saline	Duration: Median followup 72 months (14-108 months) 10 year followup: Median followup: 108 vs. 140 months 15 year followup: median 184 months 15 year Subgroup analysis: 15 years Method: Cytology and cystoscopy every 3-6 months

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Herr, 1988 RCT Medium Herr, 1995 (10 year followup) Cookson, 1997 (15 year followup) Herr, 1997 (15 year followup Subgroup analysis) Pinsky, 1985	Screened: NR Randomized: 88 Post-randomization exclusions: 2 (withdrew after randomization) Loss to followup: Last followup are tick marks on graph Analyzed: 86 (43 vs. 43) 10 year followup: Analyzed: 43 vs. 43 15 year followup: Loss to followup: 2 TURBT patients Analyzed: 84 (41 vs. 43) 15 year Subgroup analysis: Randomized: 48 (39 patients received one or more courses of BCG Analyzed: 48 (23 vs. 25)	Age (median) 60 vs. 61 Male: 77% vs. 74% Race: NR Smoking: NR Stage: Ta: 31 (72%) vs. 30 (70%) T1: 12 (28%) vs. (30%) +TIS: 26 (60%) vs. 23 (53%) 15 year Subgroup analysis: Age (median): 59 Male: 32/48 (67%) Stage: T1: 5 (10%) T1 + Tis: 43 (90%)	Progression based on T stage: 41 (95%) vs. 23 (53%) Median progression-free interval: 12 months vs. 60 months Died due to bladder cancer: 14 vs. 6 <u>10 year followup:</u> Progression based on invasion of bladder muscle or metastases: 26 (60%) vs. 16 (37%) Died of bladder cancer: 17 vs. 10 <u>15 year followup:</u> Progression based on muscle invasion, node positive disease, metastases: 23 (53%) vs. 23 (53%) <u>15 year Subgroup analysis:</u> Progression-free survival: 15 (65%) vs. 10 (40%)

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Herr, 1988 RCT Medium Herr, 1995 (10 year followup) Cookson, 1997 (15 year followup) Herr, 1997 (15 year followup Subgroup analysis) Pinsky, 1985			NR	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Hirao, 1992 RCT Medium	Japan Single center Study years: November 1, 1986 - March 30, 1990	Superficial bladder cancer. Primary only. Stages $\leq$ pT1b; Grade $\leq$ G2. Single or multiple tumors.	Muscle invasion or grade G3 detected by postoperative pathological exam.	A: Thiotepa, 30 mg (in 30 mL physiological saline), for a total of 32 instillations over a 2-year period. Initial treatment was maintained until 3rd recurrence or disease progression. B: No adjuvant therapy. TURBT only.	Duration, mean: months (range): 19.6 ± 10.8 (1-38) vs. 14.9 ± 10.7 (1-42) Method: Cystoscopy and urinary cytology every 3 months for 3 years, every 6 months thereafter "until at least 5 years".

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Hirao, 1992 RCT Medium	Screened: NR Randomized: 103 (2 groups: 52 vs. 51) Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 93 (2 groups) Per Group Analyzed: 45 vs. 48	A vs. B Age, mean (years): 59.1 (± 12.9) vs. 64.2 (± 12.2) Race: NR Sex (male): 73.1% (38/45) vs. 76.5% (39/48) Smoking status: NR Recurrent bladder cancer: NR Stage: Ta: 31.1% (14/45) vs. 41.7% (20/48); T1: 68.9% (31/45) vs. 58.3% (28/48) Grade: G1: 8.9% (4/45) vs. 22.9% (11/48); G2: 91.1% (41/45) vs. 77.1% (37/48) Multiplicity: Solitary: 35.6% (16/45) vs. 31.3% (15/48); Multiple: 64.4% (29/45) vs. 68.8% (33/48) Functional Status: NR No significant differences in any characteristic, except lower mean age of group A.	A vs. B Recurrence at 3 years: 15% vs. 46%, $p < 0.05$ Cumulative recurrence rate (CRR)*, all cases: 0.70 vs. 3.07 * CRR is 100 X total # recurrences/total followup period in months.

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Hirao, 1992 RCT Medium	Nonrecurrence rates at 3 years, according to stage: G1, no significant difference between groups; G2, A > B significant. Nonrecurrence rates at 3 years, according to grade: Ta, no significant difference between groups; T1, A > B significant. Nonrecurrence rates at 3 years, according to tumor multiplicity: single tumor, no significant difference between groups; Multiple tumors, A > B significant. Cumulative recurrence rate (CRR): Ta: 0.97 vs. 2.03 T1: 0.55 vs. 3.80 G1: 1.33 vs. 1.92 G2: 0.64 vs. 3.99 Solitary: 0.77 vs. 2.44 Multiple: 0.48 vs. 4.86	NR	Group A: Irritable bladder: n=1 (8.9%) Contracted bladder: n=1 (2.2%) Leukopenia: n=1 (2.2%) Dermatitis: n=1 (2.2%) Group B: NR	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Igawa, 1996 RCT Medium	Japan Number sites: unclear. Authors from 3 centers. Study years: NR	Superficial bladder cancer (primary or recurrent). Stages Ta or T1; Grade G1 - G3.	None reported	A: Epirubicin, 20 mg (in 40 mL saline). First instillation within 2 weeks of TURBT, retained in bladder X 2 hours; Once a month X 24 months (Total 24 instillations). B: No adjuvant treatment. TURBT alone.	Duration: Median 20 months (range 3-42). Method: Cystoscopy every 3 months X 2 years, then every 6 months thereafter.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Igawa, 1996 RCT Medium	Screened: NR Randomized: 82 Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 75 Per Group Analyzed: 43 vs. 32	Population characteristics NR according to treatment status (see comment).	A vs. B Recurrence: 60.5% (26/43) vs. 68.8% (22/32), p-value NR. Progression: 20.9% (9/43) vs. 3.1% (1/32), p=0.024

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Igawa, 1996 RCT Medium	A vs. B [reported for Biopsy (+) (concomitant dysplasia/CIS) and Biopsy (-) status] Recurrence: Biopsy (+): 100% (10/10) vs. 75.0% (6/8), p=0.36; Biopsy (-): 48.5% (16/33) vs. 66.7% (16/24), p = 0.27. Recurrence-free survival: Biopsy (+): B > A, log-rank test=NS, p-value NR; Biopsy (-): A > B, log-rank test=NS, p-value NR. Mean time (months) to recurrence: Biopsy (+):9.0 vs. 10.9, p=0.72; Biopsy (-): 9.6 vs. 7.3, p=0.37. Progression (stage): Biopsy (+): 10.0% (1/10) vs. 0.0% (0/8), p > 0.95; Biopsy (-): 3.0% (1/33) vs. 0.0% (0/24), p > 0.95. Progression (grade): Biopsy (+): 40.0% (4/10) vs. 0.0% (0/8), p=0.23; Biopsy (-): 9.1% (3/33) vs. 4.2% (1/24), p > 0.09.	NR	NR	NR	Principal focus of the study was comparison of patients with and without concomitant urothelial dysplasia or CIS, as determined by biopsy of apparently normal urothelium after TURBT. These two groups (biopsy + / biopsy -) were each randomized to receive epirubicin or not. Baseline patient characteristics were only reported according to dysplasia/CIS status.

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Kim, 1989 RCT Medium	Korea, Single center Study years: 1983-1986	Superficial bladder tumor (primary or recurrent). High risk of recurrence, based on multiplicity (> 3), large size (> 3 cm), or previous recurrences (> 3). Stages Ta or T1; Grades G1, G2, or G3.	None explicitly stated, but none of the patients had been treated with intravesical chemotherapy or radiotherapy.	A: MMC, 40 mg (in 50 mL saline). Weekly for 8 weeks. B: TURBT alone.	Duration: 32 months vs. 31 months (mean). Method: Cystoscopy, cytology every 3 to 4 months
Koontz, 1981 (prophylaxis) RCT Medium	USA Multicenter 1974-1977	Multifocal NMIBC or bladder cancer on ≥3 occasions in last 18 months; clinical assessment that prophylaxis warranted (2 tumors within 6 months); or complete response to thiotepa (30 responders from Koontz 1981 thiotepa treatment trial enrolled)	WBC <3000, platelet count <100,000, hemoglobin <10, low bladder capacity, urinary extravasation or severe vesicoureteral reflux, pregnant, chemotherapy within 1 month	A: Thiotepa 30 mg/30 mL distilled water (once every 4 weeks for maximum 2 years) B: Thiotepa 60 mg/60 mL distilled water (once every 4 weeks for maximum 2 years) C: No thiotepa	Duration, median: 15 months Method: Cystoscopy every 3 months

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Kim, 1989 RCT Medium	Screened: 167 Randomized: 43 Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 43 Per Group Analyzed (A vs. B): 21 vs. 22	A vs. B Age (years), mean (range): 51.6 (36-64) vs. 57.0 (39-71) Male: 90.5% vs. 86.4% Race: NR Smoking status: NR Recurrent bladder cancer: 71.4% vs. 55.5% Stage: Ta: 23.8% vs. 27.3%; T1: 76.2% vs. 72.7% Grade: G1: 9.5% vs. 4.5%; G2: 76.2% vs. 86.4%; G3: 14.3% vs. 9.1% Functional Status: NR Size: < 3 cm: 38.1% vs. 27.3%; ≥ 3 cm: 61.9% vs. 72.7% Number of tumors: < 3: 14.3% vs. 18.2%; ≥ 3: 85.7% vs. 81.8%	Recurrence rate: 42.9% vs. 40.9% (3 months); 81.0% vs. 77.3% (24 months); 81.0% vs. 81.0% (3 years; log-rank test p > 0.05). Mean tumor free interval: 7.24 months vs. 7.24 months. Recurrence per 100 patient-months: 8.7 vs. 8.9 Progression to muscle invasive or metastases: 9.5% (2/21) vs. 18.2% (4/22).
Koontz, 1981 (prophylaxis) RCT Medium	Screened: NR Randomized: 95 Postrandomization exclusions: 2 Loss to followup: NR Analyzed: 93 (23 vs. 23. vs. 47)	Age (median): 65 years Male: 88% Race: NR Smoking status: NR Primary: Unclear Stage: NR Grade: NR Multifocal: Unclear Tumor size: NR	% recurrence-free at 12 months: 63% vs. 69% vs. 40% (p=0.02 for A or B vs. C)

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Kim, 1989 RCT Medium	A vs. B Progression: Stage: T1: 100% (2/2) vs. 100% (4/4) Grade: G2: 50% (1/2) vs. 50% (2/4); G3: 50% (1/2) vs. 50% (2/4) Recurrent: 50% (1/2) vs. 75% (3/4) Size: < 3 cm: 50% (1/2) vs. 25% (1/4); ≥ 3 cm: 50% (1/2) vs. 75% (3/4) Number of tumors: < 3: 0.0% (0/2) vs. 25% (1/4); > 3: 100% (2/2) vs. 75% (3/4)	NR	Only reported for group A (MMC): "Most patients tolerated mitomycin C without systemic side effects. Approximately half of the patients experienced various degrees of bladder irritative symptoms. Overall, the side effect was minimal."	NR	
Koontz, 1981 (prophylaxis) RCT Medium	A or B vs. C % recurrence-free at 12 months Cytology positive: 56% vs. 40% Cytology negative: 69% vs. 40%		Leukopenia (WBC <3000): 0% (0/23) vs. 4.3% (1/23) vs. 0% (0/47) Thrombocytopenia (platelets <100,000): 0% (0/23) vs. 4.3% (1/23) vs. 0% (0/47) UTI: 0% (0/23) vs. 17% (4/23) vs. 0% (0/47)	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Krege, 1996 RCT Medium	Germany, Multicenter 1985-1992	histological evidence of superficial bladder cancer (stage pTa/1 grades 1 to 3), no intravesical chemotherapy during last 6 months or previous radiation	Primary stage pTa grade 1 tumor	A. TURBT only B. TURBT + MMC 20 mg in 50 mL saline every 2 weeks during year 1 and monthly during year 2 C. TURBT + BCG 120 mg (Connaught strain) in 50 mL saline and subcutaneous BCG 0.5 mg in the forearm weekly for 6 weeks and then monthly for 4 months	Duration: mean 20 months Method: Evaluated after 3, 6, 9, 12, 18, 24, 30, and 36 months

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Krege, 1996 RCT Medium	Number screened: NR Randomized: 337 Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 336 (122 vs. 112 vs. 102)	Age (mean): 65 (not specified by group) Male: 75% vs. 84% vs. 80% Race: NR Smoking: NR Stage: Ta: 95 (78%) vs. 84 (74%) vs. 78 (77%) T1: 27 (22%) vs. 29 (26%) vs. 24 (24%) Grade: Grade 1: 47 (39%) vs. 40 (39%) vs. 36 (41%) Grade 2: 69 (57%) vs. 57 (51%) vs. 57 (56%) Grade 3: 6 (5%) vs. 12 (11%) vs. 4 (4%)	Recurrence: 56 46%) vs. 30 (25%) vs. 26 (25%)

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Krege, 1996 RCT Medium			Cystitis: NR vs. 16% vs. 34% Hematuria: NR vs. 3% vs. 6% Fever: NR vs. 0 vs. 18	Ministry of Science and Technology, Germany	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Kurth, 1997 RCT (followup of Kurth, 1984) Medium	Europe (multinational) Multicenter Study years: December 1979 - December 1983	Histologically proved, transurethrally resectable transitional cell carcinoma of the bladder or carcinoma in situ (primary or recurrent). Stages Ta or T1; Grade G0, G1, G2 or G3.	None reported	A: Doxorubicin, 50 mg (in 50 mL normal saline). First instillation 3 to 14 days after TURBT and retained for 1 hour. Then, weekly for 1 month, then monthly for 11 months. Nitrofurantoin, 100 mg, was given after each instillation 3 times/day X 3 days. WBC, platelets, and urinalysis before each instillation. Chemotherapy delayed until WBC ≥ 4 X 109/L and platelets ≥ 1.5 X 109/L; or until any bacterial cystitis was controlled. B: No adjuvant treatment. TURBT alone.	Duration, median: For recurrence: 3.4 years For Invasion: 5 years For Time to death from malignancy: 7.2 years For Survival: 10.7 (maximum followup 14 years). Method: Cystoscopy every 12 weeks during year 1, every 16 weeks during year 2, and every 24 weeks thereafter.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Kurth, 1997 RCT (followup of Kurth, 1984) Medium	A vs. B Screened: NR Randomized: 264 (2 groups: 191 vs. 73) Postrandomization exclusions: NR Analyzed for Recurrence: 236 (166 vs. 70) Total Analyzed for Progression and Survival: 252 (181 vs. 72)	A vs. B Age: < 50 years: 8% vs. 7% 50-59 years: 21% vs. 28% 60-69 years: 28% vs. 35% 70-79 years: 39% vs. 24% ≥ 80: 4% vs. 7% Unknown: 1% vs. 0% Race: NR Sex (male): 80% (145/182) vs. 90% (65/72); Unknown: 1% (1/182) vs. 0% (0/72) Smoking status: NR Recurrent bladder cancer: 30.2% (55/182) vs. 34.7% (25/72); Unknown: 1% (1/182) vs. 0% (0/72) Stage: T0: 0% (0/182) vs. 0% (0/72); Ta: 50% (91/182) vs. 58% (42/72); T1: 45% (82/182) vs. 40% (29/72); Tis: 4% (7/182) vs. 1% (1/72); Unknown: 1% (1/182) vs. 0% (0/72) Grade: G0: 8% (15/182) vs. 15% (11/72); G1: 43% (78/182) vs. 40% (29/72); G2: 33% (59/182) vs. 36% (26/72); G3: 12% (22/182) vs. 1% (1/72); Unknown: 4% (7/182) vs. 5% (4/72) Functional Status: NR	A vs. B Recurrence: 50% (83/166) vs. 67% (47/70) Recurrence rate per year: 0.30 vs. 0.68; p-value significant. Recurrence-free at 3 years: 48% (95% CI: 40-56) vs. 29% (95% CI: 17-41) Time to first recurrence: A > B, p < 0.001. Progression to ≥ stage T2: 13.8% (25/181) vs. 18.1% (13/72) Progression-free (≥ stage T2) at 5 years: 86% (95% CI: 80-92) vs. 87% (95% CI: 77-96) Free of distant metastases at 5 years: 97% (95% CI: 94-100) vs. 98% (95% CI: 95-100) Survival (all cause) at 5 years: 74% (95% CI: 67-81) vs. 73% (95% CI: 61-84) Survival (all cause) at 10 years: 46% (95% CI: 37-54) vs. 42% (95% CI: 29-56) Survival (death from malignancy) at 5 years: 92% (95% CI: 88-96) vs. 97% (95% CI: 92-100) Survival (death from malignancy) at 10 years: 82% (95% CI: 75-89) vs. 82% (95% CI: 70-95)

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Kurth, 1997 RCT (followup of Kurth, 1984) Medium	A (n=86) vs. B (n=69) [preliminary results reported for a subset of patients; average followup approximately 1 year]* Recurrence rate/100 patient-months: Primary tumor (n=48 vs. n=43): 3.10 vs. 4.81, p=NS Recurrent tumor (n=38 vs. n=26): 5.41 vs. 11.45, p=0.026 * from Kurth, 1984	NR	Group A only (data for n=176); NR for group B Bacterial cystitis: 14.2% (25/176) Chemical cystitis: 2.8% (5/176) Systemic side effects: 5.1% (9/176) [allergic reaction, mild nausea, diarrhea, and vomiting]	National Cancer Institute	Patients themselves performed the documentation. Patients "received from a central coordinator a form with data on the instillations and cystoscopic controls".

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Matsumura, 1992 RCT Medium	Japan Multicenter 1987-1989	Ta, T1, or Tis transitional cell carcinoma of the bladder; primary with multiple lesions or recurrent with one or more lesions	NR	A: Doxorubicin, 20 mg (in 40 mL physiological saline). Total 21 instillations over 2 years, after TURBT: Timing of first dose not specified; instillations once a week X 2, then every 2 weeks X 7, then once a month X 8, then once every 3 months X 4. B: Doxorubicin, 20 mg (in 40 mL physiological saline). Total 6 instillations over 2 weeks before TURBT; specific schedule NR. C: No adjuvant treatment. TURBT alone.	Duration, median: 240 days Method: NR

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Matsumura, 1992 RCT Medium	Screened: NR Randomized: 443 (182 vs. 126 vs. 135) Postrandomization exclusions: 42 (16 vs. 13 vs. 13) Lost to followup: 26 (NR by group) Total Analyzed: 284 (126 vs. 75 vs. 83)	A vs. B vs. C Age: ≤ 49 years: 7.1% (9/126) vs. 4.0% (3/75) vs. 12.1% (10/83); 50-59 years: 15.1% (19/126) vs. 20.0% (15/75) vs. 13.3% (11/83); 60-69 years: 34.1% (43/126) vs. 32.0% (24/75) vs. 31.3% (26/83); ≥ 70 years: 42.9% (54/126) vs. 44.0% (33/75) vs. 42.2% (35/83); age overall, p=NS Race: NR Sex (male): 81.7% (103/126) vs. 78.7% (59/75) vs. 84.3% (70/83), p=NS Smoking status: NR Recurrent bladder cancer: 59.5% (75/126) vs. 61.3% (46/75) vs. 50.6% (42/83), p=NS Stage: Ta: 32.5% (41/126) vs. 20.6% (26/75) vs. 32.5% (27/83); T1: 42.9% (54/126) vs. 20.6% (26/75) vs. 36.1% (30/83); Tis: 0.8% (1/126) vs. 2.7% (2/75) vs. 3.6% (3/83); Unknown: 23.8% (30/126) vs. 28.0% (21/75) vs. 26.5% (22/83); p=NS Grade: G0: 2.4% (3/126) vs. 8.0% (6/75) vs. 2.4% (2/83); G1: 33.3% (42/126) vs. 34.7% (26/75) vs. 32.5% (27/83); G2: 36.5% (46/126) vs. 30.7% (23/75) vs. 36.1% (30/83); G3: 4.0% (5/126) vs. 4.0% (3/75) vs. 0.0% (0/83); Unknown: 23.8% (30/126) vs. 22.7% (17/75) vs. 28.9% (24/83); p=NS Functional Status: NR Size: ≈ 1 cm: 52.4% (66/126) vs. 49.3% (37/75) vs. 55.4% (46/83); ≈ 3 cm: 34.1% (43/126) vs. 42.7% (32/75) vs. 33.7% (28/83); ≈ 5 cm: 7.1% (9/126) vs. 6.7% (5/75) vs. 7.2% (6/83); > 5 cm: 0.8% (1/126) vs. 1.3% (1/75) vs. 1.2% (1/83); Unknown: 5.6% (7/126) vs. 0.0% (0/75) vs. 2.4% (2/83); p=NS Multiplicity: Single: 26.2% (33/126) vs. 22.7% (17/75) vs. 24.1% (20/83); 2-4: 58.7% (74/126) vs. 46.7% (35/75) vs. 54.2% (45/83); ≥ 5: 11.9% (15/126) vs. 25.3% (19/75) vs. 18.1% (15/83); Unknown: 2.4% (3/126) vs. 2.7% (2/75) vs. 2.4% (2/83); p=NS	A vs. B vs. C Recurrence-free survival rate at 240 days: 73.8% vs. 57.8% vs. 61.2%; A vs. B, p < 0.05; other comparisons, p=NS Recurrence-free survival rate at 480 days: 52.0% vs. 37.0% vs. 32.0%; A vs. C, p < 0.01; other comparisons, p=NS Recurrence-free survival rate at 720 days: 38.2% vs. 18.8% vs. 17.8%; A vs. B, p < 0.05; A vs. C, p < 0.01; other comparisons, p=NS

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Matsumura, 1992 RCT Medium	NR	NR	A vs. B (NR for group C) Pollakiuria: 10.3% (13/126) vs. 17.3% (13/75) Pain on urination: 10.3% (13/126) vs. 12.0% (9/75) Dysuria: 3.2% (4/126) vs. 4.0% (3/75) Hematuria: 4.0% (5/126) vs. 8.0% (6/75) Pyuria: 4.0% (5/126) vs. 9.3% (7/75) Contracted bladder: 0.0% (0/126) vs. 1.3% (1/75)	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Melekos, 1990 RCT Medium	Greece Number of sites: unclear. Study years NR	Superficial bladder carcinoma (Ta and T1)		A. TURBT B. TURBT plus BCG 150 mg (Pasteur F) in 50 mL saline 2-3 weeks after last TURBT and then weekly for 8 weeks and then maintenance BCG every 3-5 days after each followup evaluation when there was no evidence of tumor	Duration: Mean followup: 30 vs. 29 months Method: Cytology and cystoscopy every 3 months for 24 months

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Melekos, 1990 RCT Medium	Screened: NR Randomized: 100 Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 100 (33 vs. 67)	Age (mean): 68 vs. 68 Male: 85% vs. 85% Race: NR Smoking: NR Stage: Ta: 16 (48%) vs. 27 (40%) T1: 17 (52%) vs. 40 (60%) Grade: Grade 1: 11 (33%) vs. 24 (36%) Grade 2: 19 (58%) vs. 34 (51%) Grade 3: 3 (9%) vs. 9 (13%)	Patients with recurrences: 19 (58%) vs. 22 (33%), p<0.05 Mean interval to tumor recurrences, months: 10 vs. 13, p<0.05 Tumor progression in stage: 8 (24%) vs. 4 (6%), p<0.01 Tumor progression in grade: 5 (15%0 vs. 3 (4%), p<0.01

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Melekos, 1990 RCT Medium			Irritative vesical symptoms: 84% Fever: 27% Macroscopic hematuria: 21% Influenza-like syndrome: 10%	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Melekos, 1992 RCT Medium	Greece Number of sites: unclear. Authors from two centers. Study years: NR	Histologically proved superficial carcinoma of the bladder (primary or recurrent). Stage Ta or T1; Grade G1, G2, or G3.	CIS; Existence of another cancer; History of another cancer outside the bladder; Previous local or systemic chemotherapy or radiotherapy.	A: Epirubicin, 50 mg (in 5 mL sterile saline), retained in bladder for 1.5 hours. First instillation within 2 weeks after TURBT; One dose weekly X 6 weeks (Total 6 instillations for all patients). Then, single dose given at each followup exam for patients who were recurrence-free during following 2 years (maximum 7 additional instillations). Antimicrobial agents given orally for 2-3 days after each instillation. B: No adjuvant treatment. TURBT alone.	Duration: NR. Method: Cystoscopy and urinary cytology every 3 months X 1 year, then every 4 months X 1 year, then every 6 months thereafter.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Melekos, 1992 RCT Medium	Screened: NR Randomized: 80 (2:1, but numbers NR) Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 65 (43 vs. 22)	A vs. B Age, mean (SD): 66.2 years (17) vs. 67.4 years (14.3), p > 0.50 Race: NR Sex (male): 83.7% (36/43) vs. 86.4% (31/22), p > 0.80 Smoking status: NR Recurrent bladder cancer: 32.6% (14/43) vs. 31.8% (7/22), p > 0.75 Stage: Ta: 60.5% (26/43) vs. 59.1% (13/22); T1: 39.5% (17/43) vs. 40.1% (9/22); Associated Tis: 4.7% (2/43) vs. 4.5% (1/22); p > 0.75 Grade: G1: 44.2% (19/43) vs. 45.5% (10/22); G2: 44.2% (19/43) vs. 41.0% (9/22); G3: 11.6% (5/43) vs. 13.6% (3/22); p > 0.90 Functional Status: NR Multiplicity: Single: 69.8% (30/43) vs. 72.7% (16/22); Multiple: 30.2% (13/43) vs. 27.3% (6/22); p > 0.90	A vs. B Recurrence: 37.2% (16/43) vs. 54,5% (12/22), p > 0.50 Recurrence-free survival (40 months), A > B, Mantel-Haenszel test, p=0.11 Relative recurrence rate: 0.81 vs. 1.46, p > 0.05 Recurrence rate/100 patient-months: 1.4 vs. 2.6, p > 0.10 Mean time to recurrence: 18.7 month vs. 12.2 months, p < 0.02 Progression (stage and/or grade): 9.3% (4/43) vs. 22.7% (5/22), p > 0.30

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Melekos, 1992 RCT Medium	A vs. B Relative risk of recurrence: Primary: 0.84 vs. 1.33, p > 0.50; Recurrent: 0.70 vs. 2.33, p < 0.05 Solitary: 0.87 vs. 1.29, p > 0.50; Multiple: 0.68 vs. 2.32, p ≈ 0.05 Stage: Ta: 0.77 vs. 1.52, p > 0.25; T1: 0.83 vs. 1.45, p > 0.25 Grade: G1: 0.79 vs. 1.49, p > 0.50; G2: 0.81 vs. 1.51, p > 0.25; G3: 0.84 vs. 1.32, p > 0.80 Recurrence rate/100 patient-months: Primary: 0.93 vs. 1.48, p > 0.30; Recurrent: 2.89 vs. 10.53, p < 0.01 Solitary: 1.16 vs. 1.77, p > 0.30; Multiple: 2.18 vs. 7.46, p < 0.03 Stage: Ta: 0.86 vs. 1.78, p > 0.10; T1: 2.82 vs. 4.80, p > 0.20 Grade: G1: 0.80 vs. 1.54, p > 0.30; G2: 1.61 vs. 2.87, p > 0.30; G3: 5.41 vs. 10.34, p > 0.30 Recurrence-free survival: Recurrent tumor, A (n=14) vs. B (n = 7): A > B, Mantel-Haenszel test, p = 0.018 Multiple tumors, A (n=13) vs. B (n = 6): A > B, Mantel-Haenszel test, p = 0.05	NR	Only reported for group A (% patients; % instillations) Chemical cystitis, mild: 20.9 %; 8.9% Chemical cystitis, moderate-severe, requiring delay: 7%; 1.2% Macroscopic hematuria: 14%; 3.6% Fever: 2.3%; 0.8% Nausea and vomiting: 2.3%; 0.4% Generalized skin rash: 2.3%; 0.4% No hematological side effects were observed.	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Melekos, 1993 RCT Medium	Greece Number of sites: unclear. Study years NR	Histologically proven superficial transitional cell carcinoma of the bladder; primary or recurrent neoplasms	Multifocal carcinoma in situ and another cancer or history of another cancer outside the bladder and who had had previous local or systemic chemotherapy or radiotherapy	2 weeks after last resection began 6 weekly instillations of: A. BCG 150 mg (Pasteur F strain) in 50 mL saline maintenance therapy every 3 months for first 2 years then every 6 months; if at high risk for recurrence and initially responsive to treatment then received a separate 4-week course at month 6 of followup B. Epirubicin: 50 mg in 50 mL saline maintenance therapy every 3 months for first 2 years then every 6 months if at high risk for recurrence and initially responsive to treatment then received a separate 4-week course at month 6 of followup C. TURBT alone	Duration: Total months of followup: 1784 vs. 1745 vs. 603 Method: Cystoscopy and urinary cytology every 3 months for first 2 years than every 6 months thereafter

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Melekos, 1993 RCT Medium	Screened: NR Randomized: 190 (2:2:1) Post-randomization exclusions: 29 patients ineligible due to protocol violation, loss to followup, or other reason Analyzed: 161 (62 vs. 67 vs. 32)	Age (mean): 67 vs. 66 vs. 68 years Male: 82% vs. 84% vs. 84% Race: NR Smoking: NR Stage: Ta: 66% vs. 63% vs. 66% T1: 34% vs. 37% vs. 34% Grade: Grade 1: 44% vs. 46% vs. 41% Grade 2: 44% vs. 37% vs. 44% Grade 3: 13% vs. 16% vs. 16% Tis: 6% vs. 4% vs. 6%	Recurrence: 32% vs. 40% vs. 59% Interval before recurrence: 18 months vs. 16 months vs. 11 months Progression: 6% vs. 9% vs. 22% Muscle invasion: 3% vs. 4% vs. 13%

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Melekos, 1993 RCT Medium			Withdrawals due to AE: NR Cystitis:79% vs. 34% vs. NR Fever: 27% vs. 3% vs. NR Flu-like illness:13% vs. 0% vs. NR Macroscopic hematuria: 23% vs. 15% vs. NR Reduced bladder volume: 0% vs. 1% vs. NR Treatment delay: 5% vs. Epirubicin 8% vs. NR	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Medical Research Council Working Party on Urological Cancer, 1994 Medium Also: Medical Research Council Working Party on Urological Cancer, 1985 RCT	UK Multicenter Study years: December 1981 - February 1984	Primary Ta or T1 bladder cancer, WHO performance status 0-2	Urinary tract infection, WBC <3 x 109/l, platelets <100 x 109/l	A: Thiotepa, 30 mg (in 50 mL saline) immediately following TURBT, then once every 3 months for 1 year (5 instillations) B: Thiotepa , 30 mg (in 50 mL saline) immediately following TURBT C: No adjuvant treatment. TURBT alone.	Duration: median 8 years and 9 months Method: Cystoscopy every 3 months for one year, at least every 6 months for 2 years, then annually

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Medical Research Council Working Party on Urological Cancer, 1994 Medium Also: Medical Research Council Working Party on Urological Cancer, 1985 RCT	Screened: NR Randomized: 417 Post-randomization exclusions: 38 Lost to followup: 12 had no follow-up, other lost to followup NR Total Analyzed: 379; 122 vs. 126 vs. 131	A vs. B vs. C Age: 51-59 years: 24% vs. 17% vs. 26%; 60-69 years: 37% vs. 43% vs. 31%; 70-79 years: 23% vs. 25% vs. 24% Sex: NR Race: NR Smoking status: NR Recurrent bladder cancer: All primary Ta: 76% vs. 72% vs. 78% T1: 15% vs. 18% vs. 14% G1: 56% vs. 65% vs. 62% G2: 31% vs. 23% vs. 30% G3: 13% vs. 11% vs. 6.9% Multifocal: 72% Vs. 70% vs. 69%	Recurrence-free time at median 8.75 years: HR 1.09 (95% CI 0.96 to 1.56) for A vs. C, HR 1.11 (95% CI 0.78 to 1.5) for B vs. C Recurrence: 51% (62/122) vs. 46% (58/126) vs. 40% (50/124) at 1 year, HR 1.15 (95% CI 0.76 to 1.79) for A vs. C, HR 1.27 (95% CI 0.81 to 1.89) for B vs. C Failure-free (no progression or death from bladder cancer) at median 8.75 years: HR 1.75 (95% CI 0.79 to 3.85) for A vs. C, HR 1.59 (95% CI 0.68 to 3.70) for B vs. C Mortality: 31% (38/122) vs. 29% (36/1216) vs. 31% (40/131) at median 8.75 years, HR 0.99 (95% CI 0.56 to 1.82) for A or B vs. C Bladder cancer mortality: 7.4% (9/122) vs. 7.9% (10/126) vs. 4.6% (6/131)

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Medical Research Council Working Party on Urological Cancer, 1994 Medium Also: Medical Research Council Working Party on Urological Cancer, 1985 RCT			1 patient had fluid retention and edema after each thiotepa instillation and 3 patients had urinary frequency and one of these had a rash (NR by thiotepa regimen)	Medical Research Council	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Niijima, 1983 [see also Akaza, 1987] RCT Medium	Japan Multicenter Study years: April 1980 - 1985	Histologically proven superficial bladder cancer (primary or recurrent). Stages Ta or T1; Grade not specified. Absence of tumor after TURBT.	Tis superficial cancer; other therapies, such as chemotherapy, immunotherapy, and/or radiotherapy within 3 or 4 weeks before initiation of study; severe cardiovascular, renal, hepatic or hematopoietic disturbances; simultaneous presence of another cancer.	A: Doxorubicin, 30 mg (in 30 mL saline). B: Doxorubicin, 20 mg (in 40 mL saline). C: Mitomycin C: 20 mg (in 40 mL saline). D: No adjuvant treatment. TURBT alone. For A, B, and C: First instillation within 1 week of TURBT. Twice weekly X 4 weeks (Total: 8 doses)	Duration: 5 years, maximum; Mean/Median NR Method: Cystoscopy and urinary cytology studies at 12-week intervals during the observation period.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Niijima, 1983 [see also Akaza, 1987] RCT Medium	Screened: NR Randomized: 707 (192 vs. 176 vs. 185 vs. 154) Post-randomization exclusions: NR Lost to followup: NR Total Analyzed: 575* Per Group Analyzed: (149 vs. 148 vs. 139 vs. 139) * Nonevaluated patients due to protocol violations, cessation of instillation, adverse effects, or other reasons. Not quantified overall or by group.	A vs. B vs. C vs. D Age (years), average: 62.3 vs. 62.9 vs. 62.9 vs. 62.9 Sex (male): 82.6% (123/149) vs. 75.7% (112/148) vs. 74.8% (104/139) vs. 74.1% (103/139) Race: NR Smoking status: NR Recurrent bladder cancer: 29.5% (44/149) vs. 31.1% (46/148) vs. 33.8% (47/139) vs. 35.3% (49/139) Stage: NR Grade: NR Functional Status: NR Size: < 1 cm: 40.3% (60/149) vs. 37.2% (55/148) vs. 43.9% (61/139) vs. 46.0% (64/139); 1-3 cm: 43.0% (64/149) vs. 52.7% (78/148) vs. 38.8% (54/139) vs. 48.2% (67/139); 3-5 cm: 14.8% (22/149) vs. 74.3% (11/148) vs. 12.2% (17/139) vs. 5.0% (7/139) Number of tumors: 1: 64.4% (96/149) vs. 63.5% (94/148) vs. 48.2% (67/139) vs. 60.4% (84/139); 2-4: 26.2% (39/149) vs. 25.7% (38/148) vs. 39.6% (55/139) vs. 30.2% (42/139); 5+: 80.5% (12/149) vs. 10.8% (16/148) vs. 11.5% (16/139) vs. 9.4% (13/139) * From Akaza, 1987. No data provided on stage or grade, but reported "the number of patients were approximately the same in all four groups" and "no significant differences were found" (no statistical testing reported).	A vs. B vs. C vs. D Recurrence-free survival rate at 540 days*: 56.6% vs. 52.0% vs. 42.4% vs. 38.5%, generalized Wilcoxon test: A vs. D, $p < 0.05$ B vs. D, $p < 0.05$ C vs. D, $p < 0.10$ NR for other treatment group comparisons.

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Niijima, 1983 [see also Akaza, 1987] RCT Medium		NR	A vs. B vs. C (NR for group D) Pollakiuria: 33.8% vs. 28.3% vs. 33.1% Dysuria: 36.9% vs. 27.5% vs. 27.4% Hematuria: 20.0% vs. 11.6% vs. 9.7% Pyuria: 23.8% vs. 19.6% vs. 8.9%	Ministry of Health and Welfare of Japan	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Obata, 1994 RCT Medium	Japan Multicenter Study years: July 1985 - June 1987	Superficial bladder cancer (primary or recurrent). Stages Ta or T1; Grade G1 - G2. Only multiple primary tumors (i.e., solitary primary tumors not included).	Primary and solitary tumor; Residual tumor; Grade G3; Stage T2; Tis; Double cancers; Benign tumor; "Prior treatment within the past 3 weeks".	A: Doxorubicin, 20 mg (in 40 mL physiological saline). Total 19 instillations over 1 year, after TURBT: Timing of first dose not specified; instillations twice a week X 4 weeks, then once a month X 11 months. B: No adjuvant treatment. TURBT alone.	Duration: until January, 1991. NR as mean/median. Method: NR

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Obata, 1994 RCT Medium	Screened: NR Randomized: 544 Postrandomization exclusions: 58 Lost to followup: NR Total Analyzed: 331 Per Group Analyzed (2 groups, A vs. B): 90 vs. 76	A vs. B Age: ≤ 49 years: 11.1% (9/90) vs. 8.0% (3/76); 50-59 years: 15.6% (14/90) vs. 25.0% (19/76); 60-69 years: 40.0% (36/90) vs. 32.9% (25/76); ≥ 70 years: 33.3% (30/90) vs. 34.2% (26/76) Race: NR Sex (male): 77.8% (70/90) vs. 81.6% (62/76) Smoking status: NR Recurrent bladder cancer: 54.4% (49/90) vs. 48.7% (37/76) Stage: Ta: 33.3% (30/90) vs. 43.4% (33/76); T1: 52.2% (47/90) vs. 42.1% (32/76); Tx: 12.2% (11/90) vs. 11.8% (9/76) Grade: G0: 0.0% (0/90) vs. 0.0% (0/76); G1: 31.1% (28/90) vs. 48.7% (37/76); G2: 64.4% (58/90) vs. 46.1% (35/76); Gx: 3.3% (3/90) vs. 3.9% (3/76) Functional Status: NR Size: < 1 cm: 51.1% (46/90) vs. 57.9% (44/76); 1-3 cm: 36.7% (33/90) vs. 32.9% (25/76); > 3 cm: 8.9% (8/90) vs. 5.7% (4/76); Unknown: 3.3% (3/90) vs. 3.9% (3/76) Multiplicity: Single: 16.7% (15/90) vs. 11.8% (9/76); 2-4: 56.7% (51/90) vs. 68.4% (52/76); ≥ 5: 24.4% (22/90) vs. 18.4% (14/76); Unknown: 1.1% (1/90) vs. 1.3% (1/76) (Statistical testing only reported for all 4 groups combined, not for A vs. B)	A vs. B Recurrence-free survival rate at 3 years: 44% vs. 30% (Statistical testing only reported for all 4 groups combined, not for A vs. B)

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Obata, 1994 RCT Medium	A vs. B Recurrence-free survival rate at 3 years: Primary tumor: 47% vs. 37% Recurrent tumor: 41% vs. 23% Risk ratio (B as reference): Primary-multiple: 0.81 Recurrent-solitary: 1.09 Recurrent-multiple: 0.40 (Statistical testing only reported for all 4 groups combined, not for A vs. B)	NR	Reported for A only Pollakiuria: 18.9% (17/90) Pain on urination: 22.2% (20/90) Dysuria: 4.4% (4/90) Hematuria: 12.2% (11/90) Contracted bladder: 1.1% (1/90)	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Okamura, 2002 RCT Medium	Japan Number of sites: unclear. Authors from multiple centers. Study years: May 1994 - July 1998	Superficial bladder carcinoma that could be resected transurethrally (primary or recurrent). Solitary; smaller than 30 mm. Stages Ta or T1; Grade G1 or G2.	No recurrence within 1 year prior to enrollment. Eastern Cooperative Oncology Group performance status > 2; age > 85 years; history of another cancer; tumor in upper urinary tract; uncontrollable UTIs.	A: Doxorubicin [(2' ' R)-4'-0-Tetrahydropyranyl-Doxorubicin)], 30 mg (in 30 mL normal saline). Single intravesical instillation within 6 hours of TURBT; retained in bladder for 1 hour. B: No adjuvant treatment. TURBT alone.	Duration: median 40.8 months. Method: Cystoscopy and urinary cytology every 3 months X 2 years. Then, cystoscopy every 6 months X 3, and "1 year after that". Patients were monitored for local and systemic side toxicities.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Okamura, 2002 RCT Medium	Screened: NR Randomized: 170 (84 vs. 86) Postrandomization exclusions: none Lost to followup: None Total Analyzed: 160 (81 vs. 79)	A vs. B Age, mean: 59.7 ± 11.7 (range, 23-82) vs. 61.9 ± 11.6 (range, 28-82) Race: NR Sex (male): NR Smoking status: NR Recurrent bladder cancer: 7.4% (6/81) vs. 2.5% (2/79) Stage: pTa: 95.1% (77/81) vs. 93.7% (74/79); pT1: 4.9% (4/81) vs. 6.3% (5/79) Grade: G1: 50.6% (41/81) vs. 45.6% (36/79); G2: 46.9% (38/81) vs. 49.4% (39/79); G3: 2.5% (2/81) vs. 5.1% (4/79) Functional Status: All patients had Eastern Cooperative Oncology Group performance status ≤ 2 "There was no significant difference in patient characteristics between the 2 groups".	A vs. B Recurrence-free survival: A > B, p = 0.0026 Mean interval to initial recurrence, months: 41.9 vs. 18.0 Net benefit for recurrence at 1 year: 25.4% Net benefit for recurrence at 2 years: 27.0% Net benefit for recurrence at 3 years: 21.5% Recurrence rate per year: 0.11 ± 0.22 vs. 0.24 ± 0.36, p=0.007 HR (adjust; covariates not specified) for recurrence for A (B as reference): 0.31 (95% CI: 0.17-0.56, p=0.0001)

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Okamura, 2002 RCT Medium	NR	NR	Only local toxicities observed; No severe local toxicities encountered. Adverse events only reported for Group A: Dysuria : 10.7% (9/84) Urinary frequency/urgency: 6.0% (5/84) Macroscopic hematuria: 8.3% (7/84)	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Oosterlinck, 1993 RCT Medium	Europe (multinational) Multicenter Study years: October 1986 - October 1989	Biopsy-proved, papillary transitional cell carcinoma of the bladder (primary or recurrent). Stage Ta or T1; Grade G1, G2, or G3. Single tumor.	Stage Tis; WHO performance status > 2; Age > 85 years; Uncontrollable UTI; Previously treated with chemotherapy within previous 12 months.	A: Epirubicin, 80 mg (in 50 mL physiological solution). Single instillation within 6 hours after TURBT. Catheter clamped X 1 hour, then irrigated with normal saline X 24 hours. For recurrence, repeat TURBT and repeat instillation for each recurrence until maximum of 3. B: Placebo. Sterile water, 50 mL. Single instillation within 6 hours after TURBT. Catheter clamped X 1 hour, then irrigated with normal saline X 24 hours. For recurrence, repeat TURBT and repeat instillation for each recurrence until maximum of 3.	Duration: 2 years (average); 4.5 years (maximum). Method: Cystoscopy, urine cytology, urinalysis; first followup cystoscopy 4 weeks after TURBT, then every 3 months for year 1, then every 4 months for year 2, then every 6 months thereafter. For recurrence on followup cystoscopy, patients had repeat TURBT and repeat of original instillation for each recurrence until maximum of 3. Patients excluded after 3 recurrences, multiple recurrent tumors, stage Tis, increase in stage greater than T1, or distant metastases.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Oosterlinck, 1993 RCT Medium	Screened: NR Randomized: 512 (257 vs. 255) Postrandomization exclusions: 11 Lost to followup: 21 Total Analyzed: Baseline: 420 (205 vs. 215); followup: 399 (194 vs. 205)	A vs. B (205 vs. 215) Age: NR ("comparable in the 2 treatment groups", no p-value) Race: NR % Male: NR ("comparable in the 2 treatment groups", no p-value) Smoking status: NR Recurrent bladder cancer: 21.0% (43/205) vs. 23.0% (49/215) Stage: pTa: 70.7% (145/205) vs. 76.7% (165/215); pT1: 29.3% (60/205) vs. 23.0% (49/215); Unknown: 0.0% (0/205) vs. 0.5% (1/215) Grade: G1: 38.0% (78/205) vs. 50.7% (109/215); G2: 47.8% (98/205) vs. 40.9% (88/215); G3: 11.7% (24/205) vs. 7.0% (15/215); Gx: 2.4% (5/205) vs. 1.4% (3/215) Functional Status: NR Size: < 1 cm: 26.3% (54/205) vs. 30.2% (65/215); < 3 cm: 58.5% (120/205) vs. 54.0% (116/215); > 3 cm: 11.7% (24/205) vs. 13.9% (29/215); Unknown: 3.4% (7/205) vs. 2.3% (5/215)	A vs. B Recurrence: 29% (56/194) vs. 41% (84/205), log-rank test, p=0.02 Recurrence rate/year: 0.17 vs. 0.32, p < 0.0001 Progression: 8.8% (17/194) vs. 7.3% (15/205), "no evidence of difference", p-value NR.

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Oosterlinck, 1993 RCT Medium	A vs. B Recurrence rate: Primary tumor: 0.15 vs. 0.31, p < 0.0001; Recurrent tumor: 0.26 vs. 0.35, p=0.38.	NR	A vs. B (205 vs. 215), followup duration not clear. Chemical cystitis: 11.7% (24/205) vs. 1.9% (4/215) Skin allergy: 1.0% (2/205) vs. 0.0% (0/215) Other: 3.4% (7/205) vs. 0.9% (2/215) No hematological toxicity noted at 8 days after TURBT. No serious or long-lasting side effects were noted.	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Pagano, 1991 RCT High Preliminary results Pagano, 1990 RCT High	Italy Single center 1986-1988	Patients followed for one year after the study or until recurrence or progression were included in the report. Multiple (>3 tumors at entry), superficial papillary and nonpapillary tumors	NR	A. TURBT+BCG 75 mg (Pasteur strain) in 50 mL saline, 6 weekly instillations, if recurrence without progression then additional 6 week course of BCG, maintenance monthly instillations for 1 year and then quarterly for one year B. TURBT alone	Duration: mean 21 months Method: NR
Portillo, 1997 RCT Medium	Spain Number of sites: unclear. Authors from single center. Study years: July 1990 - January 1994	Completely resected transitional cell carcinoma of the bladder (primary and recurrent). Stage pT1; Grades G1, G2 or G3. (G1 recurrent only). Life expectancy > 1 year.	Stage Ta tumor; G1 primary tumor; History of any other tumors (except nonmelanoma cutaneous tumors); Refractory urinary infection; Urethral stenosis.	A: Interferon-α-2b, 60 million units. B: Placebo (double distilled water). A and B: First instillation 2-3 weeks after TURBT; Once weekly X 12 weeks, then once monthly X 9 months (Total: 21 instillations over 1 year).	Duration: mean 43months (range 9 to 67 months). Method: Cystoscopy, urinary cytology, laboratory blood tests (hemogram and biochemical analysis), urine test, urine culture, every 3 months X 1 year, then every 4 months X 1 year, then every 6 months thereafter. Also, occasional ultrasound or urography. After first relapse, patients were switched to intracavitary BCG, 81 mg weekly X 6.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Pagano, 1991 RCT High Preliminary results Pagano, 1990 RCT High	Screened: NR Randomized: 189 Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 133 (70 vs. 63)	Age (mean): 57 years Male: 91% Race: NR Smoking: NR	Complete responses Complete response: 52(74%) vs. 11 (17%) Progression: 3 (4%) vs. 11 (17%) Recurrence rate: 4% vs. 12%
Portillo, 1997 RCT Medium	Screened: NR Randomized: 90 Postrandomization exclusions: NR Lost to followup: 12 Total Analyzed: 78 (39 vs. 39)	A vs. B Age, mean: 64.9 years, overall (NR by group) Race: NR Sex (male): 87.2% (68/78), overall (NR by group) Smoking status: NR Recurrent bladder cancer: 19.1%, overall (NR by group, p=NS) Stage and Grade: T1G1: 2.6% (1/39) vs. 12.8% (5/39); T1G2: 82.1% (32/39) vs. 61.5% (24/39); T1G3: 15.4% (6/39) vs. 25.6% (10/39); p=NS Functional Status: NR Multiplicity: Single tumor: 60.0% (23/39) vs. 69.2% (27/39); 2-3 tumors: 10.3% (4/39) vs. 20.5% (8/39); > 3 tumors: 30.8% (12/39) vs. 10.3% (4/39); p=NS.	A vs. B Recurrence at 12 months: 28.2% (11/39) vs. 35.9% (14/39) Recurrence at mean followup of 43 months: 53.8% (21/39) vs. 51.3% (20/39), p=NS. Recurrence-free interval: 17 months vs. 9.6 months, p=NS Progression (stage, grade, diffuse CIS, and/or metastasis): 7.7% (3/39) vs. 17.9% (7/39), p=NS Mortality due to bladder cancer: 5.1% (2/39) vs. 5.1% (2/39), p=NS

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Pagano, 1991 RCT High Preliminary results Pagano, 1990 RCT High			NR	NR	
Portillo, 1997 RCT Medium	"A comparison of relapses according to histologic grades and treatment groups revealed no statistically significant difference between the groups (p=NS)"	NR	A vs. B UTI: 23.3% vs. 16.7%, p=NS "Analytical changes" (hypercholesterolemia, hyperuricemia): 6.7% vs. 13.3%, p=NS "There were no reports of flu-like syndrome."	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Rajala, 1999 [see also Rajala, 2002] RCT Medium	Finland Multicenter Study years: December 1991 - September 1994	Superficial bladder cancer; Primary only. Stages pTa or pT1; Grade G1, G2 or G3.	Recurrent bladder cancer; invasive disease (stage ≥ pT2); CIS.	A: Interferon-α-2b, 50 million units (in 100 mL physiological saline). Single intravesical instillation immediately after TURBT, retained in bladder X 2 hours. B: Epirubicin, 100 mg (in 100 mL physiological saline). Single intravesical instillation immediately after TURBT, retained in bladder X 2 hours. C: No adjuvant treatment. TURBT alone.	Duration: Overall duration of study was 2 years. Mean/median followup durations NR. Method: Cystoscopy and urinary cytology every 3 months X 2 years.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Rajala, 1999 [see also Rajala, 2002] RCT Medium	Screened: 283 Randomized: 283 Postrandomization exclusions: 40 Lost to followup: NR Total Analyzed: 200 (66 vs. 68 vs. 66)	A vs. B vs. C Age: NR Race: NR Sex (male): 81.8% (54/66) vs. 70.6% (48/68) vs. 65.2 (43/66) Smoking status: NR Recurrent bladder cancer: None; All primary. Stage: pTa: 80.3% (53/66) vs. 79.4% (54/68) vs. 83.3% (55/66); pT1: 19.7% (13/66) vs. 20.6% (14/68) vs. 16.7% (11/66) Grade: G1: 43.9% (29/66) vs. 50.0% (34/68) vs. 57.6% (38/66); G2: 43.9% (29/66) vs. 26.8% (25/68) vs. 31.8% (21/66); G3: 12.1% (8/66) vs. 13.2% (9/68) vs. 10.6% (7/66) Functional Status: NR Multiplicity: Single tumor: 77.3% (51/66) vs. 76.5% (52/68) vs. 71.2% (47/66); Multiple tumors: 22.7% (15/66) vs. 23.5% (16/68) vs. 28.8% (19/66)	A vs. B vs. C Recurrence: 63.7% (42/66) vs. 33.8% (23/68) vs. 60.6 (40/66)

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Rajala, 1999 [see also Rajala, 2002] RCT Medium	A vs. B vs. C Recurrence by stage: Ta: 64.2% (34/53) vs. 35.2% (19/54) vs. 56.4% (31/55), p < 0.05 T1: 61.5% (8/13) vs. 28.6% (4/14) vs. 81.8% (9/11), p < 0.01 Recurrence by grade: G1: 51.7% (15/29) vs. 20.6% (7/34) vs. 52.6% (20/38), p < 0.01 G2: 70.0% (20/29) vs. 44.0% (11/25) vs. 66.7% (14/21), p=0.09 G3: 87.5% (7/8) vs. 55.6% (5/9) vs. 85.7% (6/7), p=NS Recurrence by tumor multiplicity: Single: 62.7% (32/51) vs. 26.9% (14/52) vs. 55.3% (26/47), p < 0.01 Multiple: 66.7% (10/15) vs. 56.3% (9/16) vs. 73.7% (14/19), p=NS	NR	A vs. B vs. C Fever: 6% (4/66) vs. 0% (0/68) vs. 1.5% (1/66) Dysuria: 1.5% (1/66) vs. 5.9% (4/68) vs. 0% (0/66)	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Rajala, 2002 [see also Rajala, 1999] RCT Medium	Finland Multicenter Study years: December 1991 - September 1994	Superficial bladder cancer; Primary only. Stages pTa or pT1; Grade G1, G2 or G3.	Recurrent bladder cancer; invasive disease (stage ≥ pT2); CIS.	A: Interferon-α-2b, 50 milliunits (in 100 mL physiological saline). Single intravesical instillation immediately after TURBT, retained in bladder X 2 hours. B: Epirubicin, 100 mg (in 100 mL physiological saline). Single intravesical instillation immediately after TURBT, retained in bladder X 2 hours. C: No adjuvant treatment. TURBT alone.	Duration: Median 72 months (range 6-102). Method: Cystoscopy and urinary cytology every 3 months X 1 year. Thereafter, followup cystoscopy according to the practice at each center.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Rajala, 2002 [see also Rajala, 1999] RCT Medium	Screened: 283 Randomized: 283 [see comment] Postrandomization exclusions: 40 [see comment] Lost to followup: NR Total Analyzed: 200 (66 vs. 68 vs. 66)	A vs. B vs. C Age, mean: 66.3 vs. 65.1 vs. 64.6 Race: NR Sex (male): 81.8% (54/66) vs. 70.6% (48/68) vs. 65.2 (43/66) Smoking status: NR Recurrent bladder cancer: None; All primary. Stage: pTa: 80.3% (53/66) vs. 79.4% (54/68) vs. 83.3% (55/66); pT1: 19.7% (13/66) vs. 20.6% (14/68) vs. 16.7% (11/66) Grade: G1: 43.9% (29/66) vs. 50.0% (34/68) vs. 57.6% (38/66); G2: 43.9% (29/66) vs. 26.8% (25/68) vs. 31.8% (21/66); G3: 12.1% (8/66) vs. 13.2% (9/68) vs. 10.6% (7/66) Functional Status: NR Multiplicity: Single tumor: 77.3% (51/66) vs. 76.5% (52/68) vs. 71.2% (47/66); Multiple tumors: 22.7% (15/66) vs. 23.5% (16/68) vs. 28.8% (19/66)	A vs. B vs. C Recurrence: 68.2% (45/66) vs. 45.6% (31/68) vs. 72.7 (48/66), p=0.002 Recurrence-free at 72 months: 31.4% vs. 50.8% vs. 23.7% Recurrence-free survival: B > A or C, p = 0.002 Median time to first recurrence, months (95% CI): 12 (9-15) vs. [not attained] vs. 9 (5-13)

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Rajala, 2002 [see also Rajala, 1999] RCT Medium	A vs. B vs. C Recurrence by stage: Ta: 67.9% (36/53) vs. 46.3% (25/54) vs. 70.9% (39/55) T1: 69.2% (9/13) vs. 42.9% (6/14) vs. 81.8% (9/11) Recurrence by grade: G1: 58.6% (17/29) vs. 38.2% (13/34) vs. 65.8% (25/38) G2: 72.4% (21/29) vs. 52.0% (13/25) vs. 81.0% (17/21) G3: 87.5% (7/8) vs. 55.6% (5/9) vs. 85.7% (6/7) Recurrence by tumor multiplicity: Single: 64.7% (33/51) vs. 42.3% (22/52) vs. 70.2% (33/47) 2 tumors: 70.0% (7/10) vs. 33.3% (3/9) vs. 83.3% (10/12) 3 tumors: 100% (3/3) vs. 80.0% (4/5) vs. 33.3% (1/3) $\geq$ 4 tumors: 100% (2/2) vs. 100% (2/2) vs. 100% (4/4)	NR	NR	Finnish Cancer Foundation; Pharmacia; Roche and Schering-Plough	Study is followup of Rajala, 1999. Description of followup cystoscopy internal after year 1 is not consistent with Rajala, 1999. Number randomized and postrandomization exclusion taken from Rajala, 1999.

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Saika, 2010 RCT Medium	Japan Multicenter Study years: April 1995 - January 2001	Transitional cell carcinoma of the bladder (primary or recurrent). Stages Ta or T1; Grade G1, G2, or G3. Age ≥ 20 years.	Concurrent or previous CIS; Concurrent or previous urinary tract cancer; Concurrent or previous muscle invasive disease; Lethal disease.	A. Epirubicin, 20 mg (in 40 mL physiological saline). Two intravesical infusions, one immediately after (< 1 hour) TURBT and one in the early morning of the following day, retained in bladder for 1 hour. B. Epirubicin, 50 mg (in 100 mL physiological saline). Same procedure as A. C. No adjuvant therapy. TURBT only.	Duration, median: Overall: 44 months; A vs. B vs. C: 44 vs. 46 vs. 42 Method: Cystoscopy every 3 months for 2 years and every 6 months thereafter.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Saika, 2010 RCT Medium	Screened: NR Randomized: 303 Postrandomization exclusions: 21 Eligible: 257 (83 vs. 90 vs. 84) Lost to followup: 17 Total analyzed: 240 (79 vs. 84 vs. 77)	A vs. B vs. C (based on eligible patents, n=257) Median age, years: 69 vs. 69 vs. 71 Sex (male): 81% (67/83) vs. 89% (80/90) vs. 88% (74/84) Race: NR Recurrent bladder cancer: 40% (33/83) vs. 43% (39/90) vs. 40% (34/84) Stage Ta: 54% (45/83) vs. 60% (54/90) vs. 64% (54/84) Stage T1: 46% (36/83) vs. 40% (36/90) vs. 36% (30/84) Grade G1: 25% (21/83) vs. 33% (30/90) vs. 31% (26/84) Grade G2: 59% (49/83) vs. 47% (42/90) vs. 52% (44/84) Grade G3: 14% (12/83) vs. 20% (18/90) vs. 17% (14/84) Functional status: NR	A vs. B vs. C Median recurrence-free survival, months: 24 vs. 38 vs. 13; A vs. B, p=0.48; A vs. C, p=0.25; B vs. C, p=0.05 Progression: 0.0% (0/83) vs. 1.1% (1/90) vs. 0.0% (0/84)

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Saika, 2010 RCT Medium	NR	NR	A vs. B (NR for group C) Local: Bladder Grade 1 irritabilities (e.g., micturition pain and/or frequency): 22.9% vs. 35.6%; p = 0.106 Systemic: Grade 1 anemia: 2.4% (2/83) vs.2.2% (2/90) Grade 1 serum transaminases elevation: 1.2% (1/83) vs. 3.3% (3/90) Grade 1 leukopenia: 0.0% (0/83) vs.1.1% (1/90)	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Schulman, 1978 RCT Medium	Europe Multicenter Study years: 1975-1978	Biopsy proven papillary carcinoma of the bladder (primary or recurrent). Stage T1. Neither induration nor a mass could be palpated on bimanual exam after TURBT. In case of UTI, trial was delayed until control of infection.	Presence of another cancer or previous local or systemic cancer chemotherapy; Bladder lesions other than papillary lesions; General condition such that expected survival for duration of the study was unlikely; Expected difficulties with followup related to overt psychosis, marked senility; too large distance between patient home and investigation center; WBC < 4500/mm^3 and/or platelet count < 150,000 mm^3; Bladder papillomatosis not resectable by TUR.	A. Thiotepa 30 mg (in 30 mL sterile water). Total 15 installations over 1 year. First instillation 1 month after TURBT, then every week X 4 weeks, then once every 4 weeks X 11 months. B. No adjuvant therapy. TURBT alone.	Duration: Approximately 10 months, some patients with followup as long as 2 years. Method: Followup with cystoscopy every 12 weeks for 1st year, then every 12 weeks for second year. Urinalysis, WBC and platelet counts before each instillation.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Schulman, 1978 RCT Medium	Screened: NR Randomized: 224 (115 vs. 109) Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 144 Per Group Analyzed (A vs. B): 75 vs. 69	Age: NR Sex: NR Race: NR Smoking status: NR Recurrent bladder cancer: 38.7% vs. 43.5% Stage: T1: 100% Grade: G1: NR Multifocal: NR	Recurrence: 49.3% (37/75) vs. 52.2% (36/69) Recurrence rate/100 patient months: 6.93 vs. 9.97; p=0.04 Progression of stage: 4.0% (3/75) vs. 5.8% (4/69) Progression of grade: 6.7% (5/75) vs. 7.2% (5/69) Progression of stage and grade: 2.7% (2/75) vs. 2.9% (2/69)

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Schulman, 1978 RCT Medium	A vs. B Recurrence: Primary: 37.0% (17/46) vs. 41.0% (16/39) Recurrent: 69.0% (20/29) vs. 66.7% (20/30) Recurrence rate/100 patient months: Primary: 4.98 vs. 6.74 Recurrent: 9.33 vs. 14.19 Progression of stage: Primary: 0.0% (0/46) vs. 0.0% (0/39) Recurrent: 10.3% (3/29) vs. 13.3% (4/30) Progression of grade: Primary: 4.4% (2/46) vs. 0.0% (0/39) Recurrent: 10.3% (3/29) vs. 16.7% (5/30) Progression of stage and grade: Primary: 0.0% (0/46) vs. 0.0% (0/39) Recurrent: 6.9% (2/29) vs. 6.7% (2/30)	NR	NR	National Cancer Institute	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Solsona, 1999 RCT Medium	Spain Number of sites: unclear. Authors from single center. Study years: January 1988 - August 1992	Low risk superficial bladder cancer. Primary or recurrent (disease-free for more than 1 year); Stages Ta or T1; Grade G1 or G2; Single tumor $\leq$ 3 cm; Papillary; Upper urinary tract normal on excretory urography.	Muscle -invasive; Grade G3; CIS; WHO performance status > 2; Age > 80 years; Uncontrolled UTIs; Psychological disturbances.	A: Mitomycin C, 30 mg (in 50 mL saline). Single intravesical dose; installed when hematuria ceased, usually within 6 hours of TURBT; Retained in bladder for 1 hour with catheter clamping; bladder then irrigated with saline. B: No adjuvant therapy. TURBT only.	Duration: median 94 vs. 93 months Method: Urinary cytology and cystoscopy at 3, 6, 9, 12, 18, and 24 months; and then once per year. At 15 and 21 months, urinary cytology and bladder ultrasound, intercalated with annual endoscopic evaluations.
Stavropoulos, 2002 RCT Medium	Greece Number of sites: unclear. Authors from 3 centers. Study years: NR	Superficial transitional cell carcinoma of the bladder (primary or recurrent). Stages Ta or T1; Grade G2 or G3. Of patients with TaG2 tumors, only those with recurrent and/or multiple tumors were included.	Concomitant carcinoma in situ; History of another neoplasia elsewhere in the body; Previously treated with any form of intravesical instillations.	A. Interferon-γ, 21 MU (in 50 mL physiological saline) per week for 8 weeks, retained in the bladder for 2 hours. B. No adjuvant treatment. TURBT alone.	Duration: Mean: 12.1 months; Median: 9 months; Range: 3-40 months. (NR for each group separately). Method: Cystoscopy every 3 months for 15 months and every 6 months thereafter. Freedom of recurrence established cystoscopically and cytologically.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Solsona, 1999 RCT Medium	Screened: NR Randomized: 131 Postrandomization exclusions: none Lost to followup: 3 Total analyzed: 121 (57 vs. 64)	A vs. B Age, mean (years): 62.2 vs. 59.9 Race: NR Sex (male): 91.2% (52/57) vs. 92.2% (59/64) Smoking status: NR Recurrent bladder cancer: 10.5% (6/57) vs. 12.5% (8/64) Stage Ta: 49.1% (28/57) vs. 48.4% (31/64) Stage T1: 50.9% (29/57) vs. 51.6% (33/64) Grade G1: 52.6% (30/57) vs. 51.6% (33/64) Grade G2: 47.4% (27/57) vs. 48.4% (31/64) All patients with WHO performance status $\leq$ 2.	A vs. B Recurrence: Early (during first 2 years followup): 15.8% (9/57) vs. 34.4% (22/64), p=0.019 Late (after 2 years followup): 22.8% (13/57) vs. 21.9% (14/64), p=0.575 Early + Late: 10.5% (6/57) vs. 12.5% (8/64), p=0.734 Overall: 40.4% (23/57) vs. 54.7% (35/64), p=0.115 Recurrence free at 24 months: 84.2% vs. 65.6%; log-rank test for early recurrence-free, p=0.013 Recurrence free at 108 months: 57.0% vs. 42.2%; log-rank test for overall recurrence-free, p=0.057 Progression: 1.8% (1/57) vs. 1.6% (1/64)
Stavropoulos, 2002 RCT Medium	Screened; NR Randomized: 60 Postrandomization exclusions: none Lost to followup: 6 (4 vs. 2) Total analyzed: 54 (26 vs. 28)	A vs. B Mean age: 66 vs. 64 years Male sex: 88% (23/26) vs. 71% (20/28) Race: NR Smoking status: NR Recurrent bladder cancer: 27% (7/26) vs. 29% (8/28) Stage Ta: 42% (11/26) vs. 64% (18/28) Stage T1: 58% (15/26) vs. 36% (10/28) Grade G2: 58% (15/26) vs. 57% (16/28) Grade G3: 42% (11/26) vs. 43% (12/28) Functional status: NR	A vs. B Recurrence: 61.5% (16/26) vs. 85.7% (24/28); p=0.043 Median time to first recurrence:12.0 months vs. 7.5 months Disease-free survival, median months (95% CI): 12.0 (8.3-15.7) vs. 7.0 (4.4-9.6); log-rank test, p=0.024. Progression to muscle-invasive disease: 3.8% (1/26) vs. 3.6% (1/28).

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Solsona, 1999 RCT Medium	NR	NR	Group A: Two patients (3.5%) had chemical cystitis and slight allergic skin reactions. Group B: One patient (1.6%) had cystitis with negative urine culture. No hematological changes were noted.	NR	
Stavropoulos, 2002 RCT Medium	NR	NR	"Apart from transient and mild irritative voiding symptoms, no significant side effects were noted"	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Tolley, 1996 RCT Medium (followup of Tolley, 1988)	United Kingdom Multicenter Study years: March 1984 - December 1986	Patients with newly diagnosed stage Ta or T1 transitional cell carcinoma of the bladder; Grades 1 -3.	CIS alone	A: Mitomycin C 40 mg (in 40 mL water), single instillation within 24 hours of TURBT; retained for 60 minutes. B: Mitomycin C 40 mg (in 40 mL water), instillation within 24 hours of TURBT; retained for 60 minutes. Additional instillations (same dose) every 3 months x 1 year (total 5 instillations). C: No adjuvant treatment. TURBT alone.	Duration, median: (A and B, NR for C): 7 years Method: Cystoscopy every 3 months for a year, then every 6 months for a year, annually thereafter.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Tolley, 1996 RCT Medium (followup of Tolley, 1988)	Screened: 502 Randomized: 452 Postrandomization exclusions: NR Lost to followup: 5* (2 vs. 1 vs. 2) Total analyzed: 452 (149 vs. 146 vs. 157) * reportedly with no followup data, but included in ITT analyses	A vs. B vs. C Age 24-50: 13% (19/149) vs. 9% (13/146) vs. 9% (14/157) Age 51-60: 24% (36/149) vs. 23% (33/146) vs. 29% (46/157) Age 61-70: 36% (54/149) vs. 37% (54/146) vs. 34% (53/157) Age 71-80: 23% (34/149) vs. 30% (44/146) vs. 25% (40/157) Age 81-100: 4% (6/149) vs. 1% (2/146) vs. 3% (2/157) Male sex: NR Race: NR Smoking status: NR Stage Ta: 50% (75/149) vs. 52% (76/146) vs. 56% (88/157) Stage T1: 48% (72/149) vs. 50% (73/146) vs. 43% (67/157) Grade 1: 37% (55/149) vs. 34% (50/146) vs. 45% (71/157) Grade 2: 52% (77/149) vs. 55% (81/146) vs. 46% (73/157) Grade 3: 10% (15/149) vs. 10% (15/146) vs. 8% (13/157) Functional status: NR	A vs. B vs. C Annual recurrence rate (positive cystoscopies) during first 2 years: 0.42 vs. 0.31 vs. 0.82; A vs. C, p=0.001; B vs. C, p<0.001; A vs. B, p=0.14 Recurrence, relative risk, HR (95% CI): A vs. C (ref): 0.66 (0.48 to 0.91), log-rank test, p=0.01; B vs. C (ref): 0.50 (0.36 to 0.70), log-rank test, p=0.0001; A vs. B (ref): 0.74 (0.51 to 1.06), log-rank test, p = 0.10 Progression, relative risk, HR (95% CI): A vs. C: 0.84 (0.42 to 1.52), log-rank test, p = 0.64; B vs. C: 0.82 (0.40 to 1.68), log-rank test, p=0.59; A vs. B: 0.97 (0.46 to 2.06), log-rank test, p=0.94 All-cause mortality: 33.6% (50/149) vs. 42.5% (62/146) vs. 32.5% (51/157); A+B vs. C, HR 1.1 (95% CI 0.80 to 1.53) Bladder cancer mortality: 5.4% (8/149) vs. 5.5% (8/146) vs. 7.6% (12/157)

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Tolley, 1996 RCT Medium (followup of Tolley, 1988)	NR	NR	A vs. B (none reported for C) Dysuria and frequency: 0% (0/149) vs. 6.2% (9/146) Delayed healing of biopsy site: 0.7% (1/149) vs. 4.1% (6/146) Chemical cystitis was NR as a side effect by any patient in either group.	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Tsushima, 1987 RCT Medium	Japan Number sites: Unclear (multicenter) Study years: 1981-end date NR	Superficial bladder tumors (primary or recurrent). Stage: Ta or T1;	Grade 3 tumor; Receipt of preoperative intravesical chemotherapy.	A: Doxorubicin, 50 mg (in 100 mL physiological saline). B: MMC, 30 mg (in 100 mL physiological saline). C: No adjuvant treatment. TURBT or transurethral coagulation (TUC) alone. For A and B: Total 58 installations: Six times in first 2 weeks after TURBT, then on 2 consecutive days every 4 weeks X 2 years. If recurrence, repeat TURBT or TUC and resume 2 consecutive days every 4 weeks until 2 years after initial treatment. For C: If recurrence, repeat TURBT or TUC x 2 recurrences, then removed from protocol.	Duration: 15 months vs. 21 months vs. 13 months (median). Method: Followup with cystoscopy every 3 months.

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)	Results: Primarily recurrence, progression, survival
Tsushima, 1987 RCT Medium	Screened: NR Randomized: 134 Postrandomization exclusions: 2 Lost to followup: 20 Total Analyzed: 103 Per Group Analyzed (A vs. B vs. C): 33 vs. 37 vs. 33	A vs. B vs. C Age (average), years: 66.1 (not specified by group); age range (years): 28-89 Male: 84.8% vs. 81.1% vs. 81.8% Race: NR Smoking: NR Recurrent bladder cancer: 39.4% vs. 16.2% vs. 33.3% Stage: All Ta or T1, NR by group. Grade: G1: 27.3% vs. 35.1% vs. 27.3%; G2: 63.6% vs. 64.9% 66.7%; Other: 9.1% vs. 0.0% vs. 6.1% Functional Status: NR Number: Solitary: 51.5% vs. 54.1% vs. 45.5%; Multiple: 48.5% vs. 45.9% vs. 54.5% Papillary: 84.9% vs. 94.6% vs. 84.9% Nonpapillary: 9.1% vs. 5.4% vs. 9.1%	A vs. B vs. C Recurrence: 18.2% (6/33) vs. 35.1% (13/37) vs. 63.6% (21/33) Recurrence rate:19.7% vs. 23.9% vs. 70.0% (1 year); 26.4% vs. 36.6% vs. 77.5% (2 years); A vs. C, generalized Wilcoxon test, $p < 0.001$; B vs. C, generalized Wilcoxon test, $p < 0.01$

Author, Year Study Design Risk of Bias	Results: According to Tumor Characteristics	Results: According to Patient Characteristics	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Tsushima, 1987 RCT Medium	A vs. B vs. C Solitary tumor: Recurrence: 11.8% (2/17) vs. 25.0% (5/20) vs. 40.0% (6/15) Recurrence rate:18.0% vs. 5.0% vs. 41.7% (1 year); 18.0% vs. 31.0% vs. 61.2% (2 years); A vs. C, generalized Wilcoxon test, p=NS; B vs. C, generalized Wilcoxon test, p=NS Multiple tumors: Recurrence: 25.0% (4/16) vs. 47.1% (8/17) vs. 83.3% (15/18) Recurrence rate: 21.7% vs. 43.7% vs. 92.6% (1 year); 31.5% vs. 43.7% vs. 92.6% (2 years); A vs. C, generalized Wilcoxon test, p < 0.001; B vs. C, generalized Wilcoxon test, p < 0.05	NR	A vs. B (NR for group C) Bladder irritability: 7.1% (3/42) vs. 8.3% (4/48) Renal dysfunction: 2.4% (1/42) vs. 0.0% (0/48) Itching: 2.4% (1/42) vs. 2.1% (1/48) Macrohematuria: 0.0% (0/42) vs. 2.1% (1/48) Total: 11.9% (5/42) vs. 10.4% (5/48)	NR	

Please see Appendix C. Included Studies for full study references.

Table E3. Key Question 3: Trials of intravesical therapy versus intravesical therapy

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Addeo, 2010 RCT Medium	Italy Number sites: Unclear (authors from 4 centers) Study years (enrollment): March 2003 - November 2005	Recurrent transitional cell carcinoma. Stages Ta or T1; any grade (1, 2, or 3). Progression or relapse after intravesical BCG; Ineligible for BCG	Prior pelvic irradiation; intractable UTIs	A: Mitomycin (MMC), 40 mg (in 50 mL normal saline) intravesical; first infusion within 2 days after TURBT, then 4 weekly treatments. B: Gemcitabine (GEM), 2,000 mg (in 50 mL normal saline) intravesical; "6-week induction course of infusion", dosing not otherwise specified. A and B: Maintenance therapy of 10 monthly treatments for initial responders who remained free of recurrence. Oral antibiotics for 2 days after each infusion.

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Addeo, 2010 RCT Medium	Duration, median: 36 months for each group Method: NR	Screened: NR Randomized: 120 Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 109 Per Group Analyzed: A: 55; B: 54	A vs. B Age (years), mean (SD): 67.9 (10.2) vs. 64.9 (SD 10.55) Age (years), median: 70 vs. 66.5 Sex (male): 85.5% (47/55) vs. 85.2% (46/54) Race: NR Smoking status: NR Recurrent bladder cancer: 100% (34/55, single; 21/55, multiple) vs.100% (29/54, single; 25/54, multiple) Stage: Ta: 63.6% (35/55) vs.68.5% (37/54); T1: 36.4% (20/55) vs. 31.5% (17/54) Grade: G1: 25.5% (14/55) vs. 20.4% (11/54); G2: 49.1% (27/55) vs. 51.9% (28/54); G3: 25.5% (14/55) vs. 27.8% (15/54) Functional Status: NR Previous treatment: A: BCG: 45/55, Epirubicin: 10/55; B: BCG: 46/54, Epirubicin: 8/54

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Addeo, 2010 RCT Medium	Median time to recurrence: A: 15.0 months; B: "Not reached" Relative risk of recurrence: A: 0.94; B: 0.72; p=0.291 Recurrence rate/100 patient-months: A: 1.72; B: 1.26; p =0.31 Patients with tumor progression by stage: A: 10; B: 6; p =0.14 Probability of disease-free survival over time (Kaplan-Meier curve): GEM > MMC; p=0.0021	Probability of disease-free survival over time for grade 3 neoplasms (Kaplan-Meier curve): GEM > MMC; p=0.049 No differences in G1, G2, T1 or number of tumors between the two treatment arms.

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Addeo, 2010 RCT Medium	NR	Withdrawals due to AE: NR precisely, though between 1 and 4 Dysuria, n (%): A: 11 (20%); B: 5 (9.2%); p=0.023 Suprapubic pain, n (%): A: 4 (7.2%); B: 6 (11%); p = 0.949 Hematuria, n (%): A: 4 (7.2%); B: 2 (3.7%); p = 0.601 Chemical cystitis, n (%): A: 12 (21.1%); B: 3 (5.5%); p=0.013 Local reactions, n (%): A: 5 (9%); B: 2 (3.7%); p = 0.465 Skin reaction, n (%): A: 6 (10.9%); B: 3 (5.5%); p = 0.505 Total, n (%): A: 40 (72.2%); B: 21 (38.8%); p=0.021	Lega Italiana per la Lotta contro I Tumori; Financial support by two of the authors	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Akaza, 1987 RCTs (2 studies) Study One (followup of Niijima, 1983) Medium	Japan Multicenter Study years: April 1980 - 1985	Histologically proven superficial bladder cancer (primary or recurrent). Stages Ta or T1; Grade not specified. Absence of tumor after TURBT.	Tis superficial cancer; other therapies, such as chemotherapy, immunotherapy, and/or radiotherapy within 3 or 4 weeks before initiation of study; severe cardiovascular, renal, hepatic or hematopoietic disturbances; simultaneous presence of another cancer.	A: Doxorubicin, 30 mg (in 30 mL saline). B: Doxorubicin, 20 mg (in 40 mL saline). C: Mitomycin C: 20 mg (in 40 mL saline). D: No adjuvant treatment. TURBT alone. For A, B, and C: First instillation within 1 week of TURBT. Twice weekly X 4 weeks (Total: 8 doses)

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Akaza, 1987 RCTs (2 studies) Study One (followup of Niijima, 1983) Medium	Duration: 5 years, maximum; NR as median/mean, nor for each group. Method: Cystoscopy and urinary cytology studies at 12-week intervals during the observation period.	Screened: NR Randomized: 707 (192 vs. 176 vs. 185 vs. 154) Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 575* Per Group Analyzed: (149 vs. 148 vs. 139 vs. 139) * Nonevaluated patients due to protocol violations, cessation of instillation, adverse effects, or other reasons. Not quantified overall or by group.	A vs. B vs. C vs. D Age (years), average: 62.3 vs. 62.9 vs. 62.9 vs. 62.9 Sex (male): 82.6% (123/149) vs. 75.7% (112/148) vs. 74.8% (104/139) vs. 74.1% (103/139) Race: NR Smoking status: NR Recurrent bladder cancer: 29.5% (44/149) vs. 31.1% (46/148) vs. 33.8% (47/139) vs. 35.3% (49/139) Stage: NR* Grade: NR* Functional Status: NR Size: < 1 cm: 40.3% (60/149) vs. 37.2% (55/148) vs. 43.9% (61/139) vs. 46.0% (64/139); 1-3 cm: 43.0% (64/149) vs. 52.7% (78/148) vs. 38.8% (54/139) vs. 48.2% (67/139); 3-5 cm: 14.8% (22/149) vs. 74.3% (11/148) vs. 12.2% (17/139) vs. 5.0% (7/139) Number of tumors: 1: 64.4% (96/149) vs. 63.5% (94/148) vs. 48.2% (67/139) vs. 60.4% (84/139); 2-4: 26.2% (39/149) vs. 25.7% (38/148) vs. 39.6% (55/139) vs. 30.2% (42/139); 5+: 80.5% (12/149) vs. 10.8% (16/148) vs. 11.5% (16/139) vs. 9.4% (13/139) * No data provided on stage or grade, but reported "the number of patients were approximately the same in all four groups" and "no significant differences were found" (no statistical testing reported).

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Akaza, 1987 RCTs (2 studies) Study One (followup of Niijima, 1983) Medium	Recurrence-free survival at 1800 days, generalized Wilcoxon test: B > D, p < 0.05 C > D, p < 0.05 NR for other treatment group comparisons.	Primary tumor: Recurrence-free survival rate at 1 year (A vs. B vs. C vs. D): 73.1% vs. 76.6% vs. 84.0% vs. 70% Recurrence-free survival at 1800 days, generalized Wilcoxon test: B > D, p < 0.05 C > D, p < 0.01 Comparisons NR for other treatment group comparisons. Recurrent tumor: Recurrence-free survival at 1800 days, generalized Wilcoxon test: A > D; B > D; C > D; differences reported as nonsignificant, no p - values reported.

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Akaza, 1987 RCTs (2 studies) Study One (followup of Niijima, 1983) Medium	NR	A vs. B vs. C (NR for group D) Pollakiuria: 33.8% vs. 28.3% vs. 33.1% Dysuria: 36.9% vs. 27.5% vs. 27.4% Hematuria: 20.0% vs. 11.6% vs. 9.7% Pyuria: 23.8% vs. 19.6% vs. 8.9% "No significant systemic side effects"	Ministry of Health and Welfare of Japan	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Akaza, 1987 RCTs (2 studies) Study Two Medium Akaza, 1992 RCT Study Two (followup of sub-group of Akaza, 1987) High	Japan Number sites: Unclear Study years: July 1982 - 1985 Followup study: 1982-May 1990	Histologically proven superficial bladder cancer (primary only). Stages Ta or T1; Grade G1 or G2. Absence of tumor after TURBT.	Tis superficial cancer; other therapies, such as chemotherapy, immunotherapy, and/or radiotherapy within 3 or 4 weeks before initiation of study; severe cardiovascular, renal, hepatic or hematopoietic disturbances; simultaneous presence of another cancer.	A: Doxorubicin, 30 mg (in 30 mL saline). B: Doxorubicin, 20 mg (in 40 mL saline). C: Mitomycin C: 20 mg (in 40 mL saline). D: No adjuvant treatment. TURBT alone. For A, B, and C: First instillation within 1 week of TURBT. Once weekly X 2 weeks, then once every 2 weeks X 14 week, then once monthly X 8 months, then once every 3 month X 1 year (Total: 21 doses over 2 years)

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Akaza, 1987 RCTs (2 studies) Study Two Medium Akaza, 1992 RCT Study Two (followup of sub-group of Akaza, 1987) High	Duration: 3.5 years, maximum; NR as median/mean, nor for each group. Method: Cystoscopy and urinary cytology studies at 12-week intervals during the observation period. Followup study: Median, overall: 2,366 days (6.5 years); range: 480-2,817 days. NR for each group.	Screened: 671 Randomized: 665 (170 vs. 175 vs. 164 vs. 156) Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 607 Per Group Analyzed: (151 vs. 158 vs. 150 vs. 148) Followup study: Total Analyzed: 158 Per Group Analyzed: 44 vs. 42 vs. 41 vs. 31	A vs. B vs. C vs. D Age (years), average: 63.1 vs. 62.1 vs. 62.3 vs. 62.0 Sex (male): 80.1% (121/151) vs. 82.3% (130/158) vs. 82.0% (123/150) vs. 81.1% (120/148) Race: NR Smoking status: NR Recurrent bladder cancer: None (primary only) Stage: NR* Grade: NR* Functional Status: NR Size: < 1 cm: 31.8% (48/151) vs. 30.4% (48/158) vs. 36.0% (54/150) vs. 38.5% (57/148); 1-3 cm: 51.0% (77/151) vs. 53.2% (84/158) vs. 44.0% (66/150) vs. 49.3% (73/148); 3-5 cm: 14.6% (22/151) vs. 11.4% (18/158) vs. 11.3% (17/150) vs. 6.8% (10/148) Number of tumors: 1: 64.2% (97/151) vs. 55.7% (88/158) vs. 55.3% (83/150) vs. 66.9% (99/148); 2-4: 29.8% (45/151) vs. 30.4% (48/158) vs. 33.3% (50/150) vs. 23.6% (35/148); 5+: 6.0% (9/151) vs. 12.7% (20/158) vs. 10.7% (16/150) vs. 8.1% (12/148) * No data provided on stage or grade, but reported "absolutely no intergroup differences were found". Followup Study: Only reported overall; NR by treatment group Age ≤ 50 years: 13.3% (21/158) Age ≤ 60 years: 17.7% (28/158) Age < 70 years: 35.4% (56/158) Age ≥ 70 years: 33.5% (53/158) Sex (male): 84.8% (134/158) Stage: Tis: 1.3% (2/158); Ta: 44.3% (70/158); T1: 40.5% (64/158); Ta or T1: 13.9% (22/158) Grade: G1: 48.7% (77/158); G2: 45.6% (72/158); G1 or G2: 5.7% (9/158)

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Akaza, 1987 RCTs (2 studies) Study Two Medium Akaza, 1992 RCT Study Two (followup of sub-group of Akaza, 1987) High	A vs. B vs. C vs. D Recurrence-free survival rate at 1 year: 74.8% vs. 75.0% vs. 76.3% vs. 66.7% Recurrence-free survival rate at 2 years: 62.3% vs. 59.1% vs. 62.3% vs. 51.8% Recurrence-free survival at 1260 days, generalized Wilcoxon test: A > D, $p < 0.05$ B > D, $p < 0.05$ C > D, $p < 0.05$ NR for other treatment group comparisons. Followup study: A vs. B vs. C vs. D Recurrence: Recurrence/year (number of recurrences/total observation period: 0.473 vs. 0.512 vs. 0.472 vs. 0.510 Progression (in stage, grade, or both): 43.2% (19/44) vs. 31.0% (13/42) vs. 26.8% (11/41) vs. 38.7% (12/31), "Statistics: no difference"	NR

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Akaza, 1987 RCTs (2 studies) Study Two Medium Akaza, 1992 RCT Study Two (followup of sub-group of Akaza, 1987) High	NR	A vs. B vs. C (NR for group D) Pollakiuria: 16% vs. 18.7% vs. 23.8% Dysuria: 25.6% vs. 25.2% vs. 27.0% Hematuria: 13.6% vs. 7.3% vs. 11.1% Pyuria: 10.4% vs. 10.6% vs. 19.8% "No significant systemic side effects"	Ministry of Health and Welfare of Japan	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Ali-El-Dein, 1997 (J Urol) RCT Medium	Egypt Single center Study years: June 1991 - May 1995	Transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Stages Ta or T1; Associated CIS or other dysplastic mucosal changes; Grade G1 - G3. Rapid recurrence within 6 months of initial resection; Multicentricity; Positive posterior urethral biopsy and/or positive postoperative urinary cytology (only 2 patients with positive posterior urethral biopsy, who underwent resection of multiple tumors to provide bladder neck incompetence and sufficient contact of drug with prostatic urethra).	Prior pelvic radiotherapy or chemotherapy; Abnormal cardiac, hematologic, renal, or bladder function.	A: Epirubicin, 50 mg (in 50 mL normal saline). B: Epirubicin, 80 mg (in 50 mL normal saline). C: Doxorubicin, 50 mg (in 50 mL normal saline). D: No adjuvant treatment. TURBT alone. For Groups A - C: First instillation 7 to 14 days after TURBT. Retained intravesically for 2 hours; instillations once a week X 8 weeks, then once monthly to complete 1 year of treatment.

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Ali-El-Dein, 1997 (J Urol) RCT Medium	Duration, mean: 30.1 months Method: Cystourethroscopy, urine cytology, and flow cytometry every 3 months during first 2 years, and every 6 months thereafter.	Screened: NR Randomized: 253 Postrandomization exclusions: none Lost to followup: NR Total Analyzed: 253 Per Group Analyzed (A vs. B vs. C vs. D): 64 vs. 68 vs. 60 vs. 61	A vs. B vs. C vs. D Age: NR Race: NR Male: 81.4%, NR by treatment group Smoking status: NR Recurrent bladder cancer: 37.5% vs. 41.2% vs. 43.3% vs.45.9% Stage: pTa: 10.9% vs. 17.6% vs. 6.7% vs.9.8%; pT1: 89.1% vs. 82.4% vs. 93.3% vs.90.2%; Tis associated: 6.3% vs. 11.8% vs. 0.0% vs.0.0% Grade: G1: 9.4% vs. 16.2% vs. 16.7% vs.19.7%; G2: 78.1% vs. 69.1% vs. 70.0% vs.65.6%; G3: 12.5% vs. 14.7% vs. 13.3% vs.14.7% Functional Status: NR

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Ali-El-Dein, 1997 (J Urol) RCT Medium	A vs. B vs. C vs. D Recurrence: 25.0% (16/64) vs. 17.6% (12/68) vs. 36.7% (22/60) vs.65.6% (40/61), A, B, and C vs. D, p=0.0002, A and B vs. C, p = 0.02, A vs. B, p > 0.05. Mean time to first recurrence, months (95% CI): 16 (12.2-19.8) vs. 15.4 (11.4-19.4) vs. 18.9 (14.4-23.4) vs. 6.3 (5.2-7.4); A, B, and C vs. D, p < 0.001; B vs. C, p=0.05; A and B vs. C; p=0.05. Recurrence rate per 100 patient-months: 0.83 vs. 0.60 vs. 1.18 vs. 2.73, A, B, and C vs. D, p < 0.001, A and B vs. C; p < 0.05, A vs. B, p < 0.05. Progression (to muscle invasive): 10.9% (7/64) vs. 4.4% (3/68) vs. 10.0% (6/60) vs.8.2% (5/61). Mean interval to progression, months (95% CI): 31 (22-40) vs. 31 (18-44) vs. 33 (26-40) vs. 37 (30-44), p=0.6.	A vs. B vs. C vs. D Simple recurrence rate according to stage: Ta: 0.0% (0/16) vs. 0.0% (0/12) vs. 0.0% (0/22) vs. 2.5% (1/40), p > 0.05; T1: 93.8% (15/16) vs. 83.3% (10/12) vs. 100% (22/22) vs. 97.5% (39/40), A, B, and C vs. D, p < 0.0001, A and B vs. C, p=0.01, A vs. B, p=NS; pTis: 6.3% (1/16) vs. 16.7% (2/12) vs. NA vs. NA. Simple recurrence rate according to grade: G1: 0.0% (0/16) vs. 16.7% (2/12) vs. 13.6% (3/22) vs. 12.5% (5/40), p > 0.05; G2: 75.0% (12/16) vs. 58.3% (7/12) vs. 68.2% (15/22) vs. 67.5% (27/40), A, B, and C vs. D, p < 0.0001, A and B vs. C, p=0.04, A vs. B, p = NS; G3: 25.0% (4/16) vs. 25.0% (3/12) vs. 18.2% (4/22) vs. 20.0% (8/40), p > 0.05. Simple recurrence rate according to Grade 3-Stage pT1/Total: 66.7% (4/6) vs. 37.5% (3/8) vs. 57.1% (4/7) vs. 100% (8/8); A, B, and C vs. D, p < 0.05; A and B vs. C, p > 0.05.

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Ali-El-Dein, 1997 (J Urol) RCT Medium	NR	A vs. B vs. C (No data for group D) Proportion of patients with an adverse event: 15.6% (10/64) vs. 23.5% (16/68) vs. 41.7% (25/60), A and B vs. C, p=0.002, A vs. B, p=0.3, B vs. C, p < 0.04. Adverse events per # of instillations: 7.3% (88/1199) vs. 8.7% (111/1280) vs. 29.0% (324/1118), A and B vs. C, p < 0.0001, B vs. C, p < 0.05. Systemic toxicity: 0.0% (0/10) vs. 0.0% (0/16) vs. 12.0% (3/25), p < 0.05 Mild toxicity: 50.0% (5/10) vs. 68.8% (11/16) vs. 60.0% (15/25), A and B vs. C, p=0.02, A vs. B, p > 0.05, B vs. C, p=0.3. Severe toxicity (i.e., requiring permanent or temporary discontinuation of treatment): 20.0% (2/10) vs. 12.5% (2/16) vs. 12.0% (3/25), A and B vs. C, p > 0.05, A vs. B, p > 0.05, B vs. C, p > 0.05. Contracted bladder: 10.0% (1/10) vs. 6.3% (1/16) vs. 8.0% (2/25) Hematuria: 10.0% (1/10) vs. 12.5% (2/16) vs. 4.0% (1/25) UTI: 10.0% (1/10) vs. 0.0% (0/16) vs. 4.0% (1/25)	NR	Note: Possible overlap of some study subjects (group A) with those in Ali-El-Dein, 1997 (British J Urol)

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Ali-El-Dein, 1999 RCT Medium	Egypt Single center 1993-1997	Grade 2 or 3, stage pT1 disease, rapid disease recurrence within 6 months of initial resection, multicentricity, aneuploid DNA pattern, tumor size equal to or not more than 3 cm, assoc carcinoma in situ or other dysplastic mucosal changes and/or positive postoperative urinary cytology	Prior pelvic radiotherapy or systemic chenotherapy	1-3 weeks after transurethral resection of bladder tumor: A. BCG/epirubicin: alternating weekly 150 mg Pasteur strain 5x10^8 to 5x1069 CFU BCG with 50 mg epirubicin in 50 mL saline for 2 hours B. BCG only: 150 mg in 50 mL saline for 2 hours Treatment was weekly for 6 weeks then monthly for 10 months
Bilen, 2000 RCT Medium	Turkey Single center 1994-1995	Superficial transitional-cell carcinoma of the bladder; patients with pT1 who had an additional one of four prognostic factors (grade 3 tumors, multiple tumors, tumors greater than 40 mm, recurrent tumors) were included	Patients with Ta tumors, previous treatment with any kind of intravesical therapy, radiotherapy, systemic chemotherapy were excluded	A. BCG 81 mg (Connaught strain) weekly for 6 weeks B. Sequential BCG 81 mg (Connaught) and epirubicin 50 mg with epirubicin given weeks 1, 2, 3, 4, and 12 and BCG given weeks 5, 6, 7, 9, 10, and 11
Boccardo, 1994 RCT Medium	Italy Number sites: unclear (authors from 5 centers) Study years (enrollment): March 1987 - December 1989	Primary superficial bladder cancer (no prior history of bladder tumors). Stages and Grade: pTa G2; pT1 G1; pT1 G2. Negative urine cytology after TURBT; No previous local or systemic treatment for the disease; No evidence of concurrent conditions that might alter compliance with protocol; geographic ineligibility.	Primary or secondary CIS; Tumors involving prostatic urethra; urethral stenosis; active urinary infection.	A: Mitomycin (MMC), 40 mg (in 50 mL saline) intravesical, with retention "suggested" for 120 minutes; weekly dose X 8 weeks. Drug retained in bladder for approx. 120 minutes: yes, 124 (87.9%); no, 10 (7.1%); unknown, 7 (5.0%). B: Interferon alfa-2b (IFN), 50 X 106 IU (in 50 mL saline) intravesical, with retention "suggested" for 120 minutes; weekly dose X 8 weeks. Drug retained in bladder for approx. 120 minutes: yes, 135 (92.4%); no, 8 (5.5%); unknown, 3 (2.1%).

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Ali-El-Dein, 1999 RCT Medium	Duration: mean followup: 30 months Method: Patients evaluated every 3 months for 2 years then every 6 months thereafter with: cystourethroscopy, urine cytology and flow cytometry	Screened: NR Randomized: 139 Post-randomization exclusions: 15 (11%) due to severe side effects (3 vs. 12) Loss to followup: NR Analyzed: 124 (66 vs. 58)	Age (mean): 57 vs. 59 Male: 81% vs. 72% Race: NR Smoking: NR Stage: Ta: 8% vs. 7% T1: 92% vs. 93% CIS: 11% vs. 2% Grade: Grade 1: 12% vs. 10% Grade 2: 55% vs. 57% Grade 3: 33% vs. 33%
Bilen, 2000 RCT Medium	Duration: median followup: 18 months Method: 3-monthly cystoscopies for first year and biannually thereafter	Screened: NR Randomized: 41 (21 vs. 20) Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 41 (21 vs. 20)	Age (mean): 53 vs. 57 Male: 95% vs. 95% Race: NR Smoking: NR Grade: Grade 1: 3 (14%) vs. 2 (10%) Grade 2: 14 (67%) vs. 13 (65%) Grade 3: 4 (19%) vs. 5 (25%)
Boccardo, 1994 RCT Medium	Duration: 42 months, maximum; NR as median/mean, nor for each group. Method: Cystoscopy: 1 month after treatment; then every 3 months during first year; every 4 months during second year; then every 6 months Urine cytology on 3 samples before each cystoscopy; if persistent positive cytology with negative cystoscopy, bladder mapping performed.	Screened: NR Randomized: 287 Postrandomization exclusions: none Lost to followup: none Total Analyzed: 287 Per Group Analyzed: A: 141; B: 146	A vs. B Age, median (range): 64 years (33 - 82) vs. 63 years (20 - 79). Sex (male): 87.9% (124/141) vs. 84.9% (124/146) Race: NR Smoking status: NR Recurrent bladder cancer: None Stage/Grade: pTa/G2: 55.3% (78/141) vs. 53.4% (78/146), pT1/G1-G2: 45.7% (63/141) vs. 45.6%(68/146) Functional Status: NR Size: < 3 cm: 75.2% (106/141) vs. 78.1% (114/146); ≥ 3 cm: 24.1% (34/141) vs. 21.9% (32/146) Number of tumors: 1: 63.2% (89/141) vs. 61.7% (90/146); 2: 14.9% (21/141) vs. 17.1% (25/146); 3+: 20.5% (29/141) vs. 21.2% (31/146)

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Ali-El-Dein, 1999 RCT Medium	Recurrence: 11% (7/66) vs. 21% (12/58) Progression: 5% (3/66) vs. 9% (5/58)	
Bilen, 2000 RCT Medium	Recurrence: 4 (19%) vs. 3 (15%) Progression: 2 (10%) vs. 1 (5%) Median time to first recurrence: 16 months vs. 11 months, p>0.05	
Boccardo, 1994 RCT Medium	A vs. B Patients with recurrence, % (n/N): 36.9% (52/141) vs. 47.9% (70/146) Relative recurrence rate: 0.82 vs. 1.2; p=0.04 Recurrence risk ratio: 0.68 Median time to recurrence (months): 36.0 vs. 21.0; p=0.048 Recurrence rate/100 patient/month: 2.4 vs. 3.4; p =0.04 Patients developing muscle-invasive cancer or advance in stage: 5.7% (8/141) vs. 3.4% (5/146)	Median time to recurrence (months): A vs. B: Stage pTa: "Not reached" vs. 20.0; p=0.004 Stage pT1: 19.0 vs. 27.0; p=0.84 Grade G1: Median times NR; p=0.43 Grade G2: 36.0 vs. 20.0; p=0.014 Relative risk of recurring (RR (95% CI)), A; B: Stage (pT1 vs. pTa): 2.41 (1.21-4.77), p=0.013; 0.93 (0.55-1.58), p = 0.81 Grade (G2 vs. G1):1.73 (0.81-3.7), p=0.15; 2.3 (1.01-5.2), p=0.035 Tumor size (≥ 3cm vs. < 3 cm): 1.03 (0.52-2.00), p=0.93; 1.26 (0.71-2.21), p=0.43 Number of tumors (multiple vs. single): 1.49 (0.85-2.6), p=0.16; 2.4 (1.47-3.86), p < 0.001

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Ali-El-Dein, 1999 RCT Medium		Withdrawals due to AE: 15 post-randomization exclusions due to severe side effects Overall toxicity: 27% vs. 71% (p=0.001) Systemic toxicity: 6% vs. 36% (p=0.001) Cystitis: 27% vs. 62% Hematuria: 0% vs. 7% Postponed treatment: 6% vs. 17% (p=0.03) Discontinued treatment 4% vs. 17% (p=0.02)	NR	
Bilen, 2000 RCT Medium		Irritative bladder symptoms: 9 (43%) vs. 7 (35%) Hematuria: 8 (38%) vs. 4 (20%) Fever: 3 (14%) vs. 2 (10%) Contracted bladder 0 vs. 1 (5%)	NR	
Boccardo, 1994 RCT Medium	Relative risk of recurring (RR (95% CI)) A; B: Age (> 60 years vs. ≤ 60 years): 1.12 (0.61-2.05), p=0.70; 1.01 (0.62-1.68), p = 0.93 Sex (female vs. male): 1.42 (0.58-3.45), p = 0.45; 1.02 (0.53-1.94), p=0.96	Withdrawals due to AE: none reported A vs. B (%) Local: Dysuria: 46.3 vs. 42.7; p=NS Pollakiuria: 47.0 vs. 40.6; p=NS Strangury: 45.5 vs. 30.8; p=0.01 Hematuria: 19.4 vs. 9.8; p=0.02 Systemic: Hematologic: 0.7 vs. 2.5; p=NS Gastrointestinal: 1.7 vs. 2.4; p=NS Muscular: 1.5 vs. 0.7; p=NS Neurologic: 1.7 vs. 3.1; p=NS Fever: 1.4 vs. 11.2; p=0.003	Schering-Plough, Milan, Italy (in part)	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Brosman, 1982 RCT Medium	USA Single center Study years not reported	At least one NMIBC tumor recurrence within the preceding four months	Not reported	A: BCG: 6 x 10^9 TICE BCG in 60mL saline B: Thiotepa: 60mg in 60mL saline Both treatment groups were treated with weekly x 6 instillations, every 2 weeks for 3 months, then monthly until a total treatment period of 24 months.
Cai, 2008 RCT Medium	Italy Single center 2005-2007	High risk NMIBC patients with recurrent urothelial cancer and with tumor recurrence at same stage and grade of the initial tumor at diagnosis	Locally infiltrative or metastatic tumors (T2 or greater), upper urinary tract tumors, lesions which could not be completely removed transurethrally, other neoplastic diseases, lower urinary tract diseases or major concomitant disease	After TURBT: A. Epirubicin/BCG: 80 mg Epirubicin in 50 mL normal saline within 6 hours of surgery; weekly x 6 instillations with 5 x 10^8 CFU OncoTICE BCG in 50 mL saline with boosters of BCG given at 3, 6, 12, 18, 24, 30, and 36 months B. BCG: weekly x 6 instillations with 5 x 10^8 CFU OncoTICE BCG in 50 mL saline with boosters of BCG given at 3, 6, 12, 18, 24, 30, and 36 months
Cheng, 2005 RCT Medium	China Single center 1991-1999	Superficial bladder cancer (Ta or T1) with one or more of the following: stage>a, grade>1size>1cm or multiple or recurrent tumors	Carcinoma in situ or previous intravesical treatment	A. BCG 81 mg (Connaught strain) 6 weeks, maintenance course 10 months B. Epirubicin 50mg weekly for 4 weeks, monthly for 5 months and then 3 monthly for 6 months

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Brosman, 1982 RCT Medium	Duration: Minimum of 24 months Method: Cystoscopy at regular intervals (exact timing not reported)	Screened: Not Reported Randomized: 49, plus additional 12 non randomized patients who previously failed thiotepa, 27 + 12 nonrandomized vs. 22 Postrandomization exclusions: not reported Lost to followup: not reported Analyzed: 25+10 non randomized vs. 19	Age (mean): 63.4 Race: Not reported Male: 74% Smoking: Not reported Recurrent bladder cancer: 100% Stage: All ≤ T1 Functional status: Not reported
Cai, 2008 RCT Medium	Duration: Median Followup: 15 months vs. 15 months Method: Urine cytology, ultrasound and cystoscopy with biopsies of suspicious lesions every 3 months; selected patients with previous CIS also underwent multiple bladder cold cup biopsies at first cystoscopy	Screened: NR Randomized: 163 Post-randomization exclusions: none reported Loss to followup: 2 who were then excluded from the study Analyzed: 161 (80 vs. 81)	Age (mean): 74 vs. 70 Male: 85% vs. 86% Race: NR Smoking: NR Stage: Ta: 74% vs. 78% T1: 26% vs. 22% Grade: Grade 2: 39% vs. 33% Grade 3: 61% vs. 67% CIS: 20% vs. 22%
Cheng, 2005 RCT Medium	Duration: Median followup: 23 months (range 0-125 months) for recurrence, 47 months (0-127 months) for progression, 61 months (3-127 months) for survival Method: Cystoscopy every 3 months for 2 years, urine cytology every 6 months	Screened: NR Randomized: 209 Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 209 (102 vs. 107)	Age (mean): 70 vs. 70 Male: 72% vs. 71% Race: NR Smoking: NR Stage: Ta: 63 (62%) vs. 77 (72%) T1: 39 (38%) vs. 29 (27%) Grade: Grade 1: 19 (19%) vs. 30 (28%) Grade 2: 47 (46%) vs. 55 (51%) Grade 3: 33 (32%) vs. 20 (19%)

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Brosman, 1982 RCT Medium	Recurrence: 0/39 (includes 12 nonrandomized patients) vs. 9/19 (47%)	Not reported
Cai, 2008 RCT Medium	Recurrence: 43% (34/80) vs. 49% (40/81), p=0.82 Progression to invasive disease: 3% (2/80) vs. 5% (4/81), p=0.32 No evidence of disease at followup: 58% (46/80) vs. 51% (41/81), p=0.82	
Cheng, 2005 RCT Medium	Patients with recurrences: 30 (29%) vs. 59 (55%) Median time to first recurrence 7 months vs. 8 months Progression 16 (16%) vs. 16 (15%) Median time to progression: 17.5 months vs. 22 months Died of bladder cancer: 13 (13%) vs. 7 (7%) Overall mortality: 41 (40%) vs. 41 (38%)	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Brosman, 1982 RCT Medium	Not reported	Required hospitalization: 4 Bladder irritability: 100% vs. 7/19 (37%)	National Bladder Cancer Project Grant	
Cai, 2008 RCT Medium		Withdrawals due to AE: NR Painful urination: 3% (2/80) vs. 1% (1/81)	NR	
Cheng, 2005 RCT Medium		NR	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Cho, 2009 RCT Medium	Korea Single center 2005-2006	Patients with intermediate-risk (i.e., Ta, T1, G1-G2 multifocal, recurrent lesions > 3 cm, or high-risk (T1, G3 lesions or CIS) were included	Low risk (i.e., single Ta, G1 lesion < 3 cm)	A. BCG 12.5 mg 6 weekly instillations B. GEM 1000 mg perioperatively then 2000 mg at week 1, then BCG weekly for 6 weeks
De Reijke, 2005 RCT Medium	Europe Multicenter 1993-1999	Patients with biopsy proven primary, secondary or concurrent carcinoma in-situ (CIS) of the bladder with or without primary urinary cytology.	CIS in the prostrate stroma, previous pelvic irradiation, concurrent or previous muscle invasive disease	A. Epirubicin 50mg intravesical 8 weekly instillations followed by maintenance instillations at months 3, 6, 12, 18, 24, 30, 36 B. BCG 81 mg (Connaught strain) 6 weekly instillations, followed by maintenance instillations at months 3, 6, 12, 18, 24, 30, 36
DeBruyne, 1992 RCT Medium Debruyne, 1988 RCT Medium Witjes, 1998 RCT Medium	The Netherlands, the UK, Belgium Multicenter 1985-1986	Primary or recurrent superficial bladder cancer, including CIS, Ta, T1	Patients treated previously with intravesical or systemic cytotoxic agents or with radiotherapy	A. MMC 30 mg in 50 mL saline weekly for 4 weeks then monthly for 6 months B. BCG-RIVM (5 x 10^8 CFU) in 50 mL saline weekly for 6 weeks

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Cho, 2009 RCT Medium	Duration: Mean followup 32 and 34 months Method: Cystoscopy and cytology every 3 months	Screened: NR Randomized: 87 Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 87 (51 vs. 36)	Age: 63 vs. 64 Male: 94% vs. 89% Race: NR Smoking: NR Stage: Ta: 18 (35%) vs. 14 (39%) T1: 33 (65%) vs. 22 (61%) CIS: 7 (14%) vs. 5 (14%) Grade: Grade 1: 2 (4%) vs. 2 (6%) Grade 2: 26 (51%) vs. 21 (58%) Grade 3: 23 (45%) vs. 13 (36%)
De Reijke, 2005 RCT Medium	Duration: Median followup: 67 months Method: Cystoscopy at 10 weeks, 6 months and every 3 months thereafter for 2 years and every 6 months thereafter if patient remained in complete response	Screened: NR Randomized:168 (84 vs. 84) Post-randomization exclusions: 7 (ineligible: 4 vs. 3) Loss to followup: None reported Analyzed: 169 (84 vs. 84)	Age: <60 years: 19 (23%) vs. 22 (26%) 60-69 years: 28 (33%) vs. 27 (32%) 70-79 years: 32 (38%) vs. 30 (36%) 80 or older: 4 (5%) vs. 4 (5%) Male: 89% vs. 94% Race: NR Smoking: NR Primary CIS: 19 (23%) vs. 20 (24%) Secondary CIS: 22 (26%) vs. 19 (23%) Concurrent CIS: 43 (51%) vs. 44 (52%)
DeBruyne, 1992 RCT Medium Debruyne, 1988 RCT Medium Witjes, 1998 RCT Medium	Duration: Median followup: 21 months Method: Cystoscopies every 3 months	Screened: NR Randomized: 361 Post-randomization exclusions: 17 Loss to followup: 9 (3 vs. 6) Analyzed: 325 (167 vs. 158)	Age <50: 20 (12%) vs. 8 (14%) Age 50-59: 25 (14%) vs. 36 (21%) Age 60-69: 63 (36%) vs. 54 (32%) Age 70-79: 48 (28%) vs. 57(33%) Age >79: 17 (10%) vs. 10 (8%) Male: 80% vs. 83% Race: NR Smoking: NR Stage: pTa: 110 (64%) vs. 107 (63%) pT1: 58 (33%) vs. 59 (34%) pTis only: 5 (3%) vs. 5 (3%) CIS: 16 (9%) vs. 24 (14%)

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Cho, 2009 RCT Medium	Patients with recurrences: 17 (33%) vs. 14 (39%) Progression: 5 (10%) vs. 3 (8%)	
De Reijke, 2005 RCT Medium	Complete response: 47 (56%) vs. 55 (65%), p=0.21 Complete response for primary CIS: 63% vs. 60% Complete response for secondary CIS: 59% vs. 63% Complete response for concurrent CIS: 51% vs. 69% Progression: 4 (5%) vs. 4 (5%) Time to first recurrence (median): 1.4 years vs. 5.1 years, p=0.0004 Progression: 23 (27%) vs. 15 (18%) Mortality: 34 (40%) vs. 26 (31%) Died due to bladder cancer: 13 (15%) vs. 9 (11%)	
DeBruyne, 1992 RCT Medium Debruyne, 1988 RCT Medium Witjes, 1998 RCT Medium	Recurrence: 60 (36%) vs. 66 (42%) 7 year followup: Recurrence 72 (43%) vs. 76 (48%) Progression 12 (7%) vs. 21 (12%) Mortality: 51 vs. 46 Malignant disease: 18 vs. 15	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Cho, 2009 RCT Medium		Dysuria: 17 (33%) vs. 13 (36%) Hematuria: 3 (6%) vs. 7 (19%)	NR	
De Reijke, 2005 RCT Medium		Withdrawals due to AE 8 (10%) vs. 26 (31%) Hematuria: 23 (28%) vs. 33 (41%) Severe dysuria: 8 (10%) vs. 19 (24%) Chemical cystitis: 2 (2%) vs. 14 (18%) Local symptoms: 5 (6%) vs. 6 (20%)	NR	
DeBruyne, 1992 RCT Medium Debruyne, 1988 RCT Medium Witjes, 1998 RCT Medium		Drug-induced cystitis: 37 (21%) vs. 30 (18%) Stopped treatment due to AE: 5 (3%) vs. 3 (2%)	National Cancer Institute	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Di Lorenzo, 2010 RCT Low	Italy Multicenter 2006-2008	Patients with high risk NMIBC based on the European Organization for Research and Treatment of Cancer Scoring System failing BCG therapy for which radical cystectomy was indicated but not conducted because of refusal or ineligibility because of age or comorbidities and high anesthesiological risk.	Concurrent or previous MIBC or tumor in the upper urinary tract or prostatic urethra, chronic urinary tract infection, previous pelvic irradiation	A. Gemcitabine twice weekly (Day 1 and 4) at a dose of 2000mg/50mL for 6 consecutive weeks, and then weekly for 3 consecutive weeks at 3, 6 and 12 months B. BCG 81mg/50 mL (Connaught strain) over 6 weeks and then each week for 3 weeks at 3, 6 and 12 months
Di Stasi, 2003 Prospective Randomized Study Low	Italy Number of sites: unclear 1994-2001	Adequate bone marrow reserve; normal renal function; normal liver function; a Karnofsky performance score of 50 to 100; reliable for long-term followup	Prior carcinoma of the bladder and/or upper urinary tract; other malignancies within 5 years of registration; pregnancy	A. BCG 81 mg wet weight (Pasteur) lyophilized and suspended in 50 mL bacteriostatic-free NaCl 0.9% solution retained for 120 minutes B. Passive MMC 40 mg with 960 mg incipient NaCl dissolved in 100 mL water, held for 60 minutes C. Electromotive MMC 40 mg with 960 mg incipient NaCl dissolved in 100 mL water, with 20 mA pulsed electronic current for 30 minutes All groups received 6 weekly treatments, with 10 monthly treatments for patients with a complete response and 6 more weekly treatments for those with persisting disease. A crossover in treatment for those with persisting disease after 6 months.

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Di Lorenzo, 2010 RCT Low	Duration: Median followup 15 months Method: Cystoscopy and cytology at 3-month intervals	Screened: 92 Randomized: 40 vs. 40 Post-randomization exclusion: None reported Loss to followup: None reported Analyzed: 80 (40 vs. 40)	Age (mean): 69 vs. 71 Male: 68% vs. 55% Race: NR Smoking: NR Stage: Ta: 10 (25%) vs. 8 (20%) T1: 30 (75%) vs. 32 (80%) Grade: Grade low: 11 (28%) vs. 13 (33%) Grade high: 29 (73%) vs. 27 (68%)
Di Stasi, 2003 Prospective Randomized Study Low	Duration: Median followup: 43 vs. 42 vs. 45 months Method: Cystoscopy, biopsy and urinary cytology. Biopsies at 3 and 6 months, thereafter only if indicated by suspicious cytological findings or cystoscopy. In tumor-free cases cystoscopy and urinary cytology were repeated at 3 month intervals fir 2 years, 6 month intervals for 3 years and yearly thereafter	Screened: 117 Randomized: 108 (36 vs. 36 vs. 36) Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 108 (36 vs. 36 vs. 36)	Age (median): 66.5 vs. 68.5 vs. 64.5 Male: 75% vs. 72% vs. 72% Race: NR Smoking: NR Stage: Cis only: 3 (8.3%) vs. 3 (8.3%) vs. 4 (11.1%) Cis + pTa: 33 (91.7%) vs. 33 (91.7%) vs. 32 (88.9%) Grade: Grade 2: 19 (57.6%) vs. 19 (57.6%) vs. 18 (56.3%) Grade 3: 14 (42.4%) vs. 14 (42.4%) vs. 14 (43.7%)

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Di Lorenzo, 2010 RCT Low	Patients with recurrences: 53% (21/40) vs. 88% (35/40), p=0.002 Time to first recurrence: 3.9 months vs. 3.1 months; p=0.9 2 year recurrence-free survival: 19% vs. 3%, p<0.008 Progression: 7 (33%) vs. 13 (38%) Deaths: 0 vs. 1	
Di Stasi, 2003 Prospective Randomized Study Low	Recurrence: 52.8% vs. 75% vs. 52.8% Progression: 16.7% vs. 22.2% vs. 16.7% Mortality: 11/36 vs. 12/36 vs. 9/36	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Di Lorenzo, 2010 RCT Low		Dysuria: 6 (15%) vs. 8 (20%) Hematuria: 2 (5%) vs. 5 (13%) Fever: 1 (3%) vs. 3 (8%)	NR	
Di Stasi, 2003 Prospective Randomized Study Low		Withdrawals due to adverse events: 4 (11.1%) vs. 5 (5.6%) vs. 3 (8.3%) Drug induced cystitis: 24 (66.7%) vs. 9 (25.0%) vs. 13 (36.1%) Visible hematuria: 26 (72.2%) vs. 6 (16.7%) vs. 8 (22.2%) Fever: 7 (19.4%) vs. 0 vs. 0	Progetti di Ricerca di Ateneo; Tor Vergata University of Rome; Physion Srl, Medolla, Italy.	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Duchek, 2010 RCT Low Hemdan, 2014	Sweden, Norway, Finland Multicenter 1999-2006	Patients with newly detected T1 G2-G3 urinary bladder cancer.	Recurrent bladder tumor of any stage, MIBC at a second look resection, involvement of the urethra, prostate or upper urinary tract, a history of radiotherapy or systemic chemotherapy, previous endovesical treatment, with the investigational drugs other than a single instillation of chemotherapy including epirubicin after TURBT	A. BCG 2mL in 100mL saline (OncoTICE) B. Epirubicin 50mg dry substance+10 million units of IFN-2b (dissolved in 100 mL saline) Both regimens induction treatment: 6 weeks, maintenance treatment 2 years
Eto, 1994 RCT Medium	Japan Multicenter Study years: January 1990 - December 1992	Superficial bladder cancer (primary or recurrent). Stages Ta or T1; Grade G1 - G3.	Presence of another cancer, residual tumor, CIS; previous treatment with doxorubicin or derivatives; severe dysfunction of heart, liver, kidney or bone marrow; severe complications; poor general condition suggesting that survival for duration of study was unlikely.	A: Epirubicin, 30 mg (in 30 mL physiological saline). B: Doxorubicin, 30 mg (in 30 mL physiological saline). Each group received 19 intravesical instillations over 1 year. instillations performed 2 times/week for 4 weeks, then 1 time/month for 11 months.

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Duchek, 2010 RCT Low Hemdan, 2014	Duration: Followup: 24 months; Median followup: 6.9 years Method:Cystoscopy and cytology every 3 months for the first 2 years, and every 6 months thereafter until 5 years from start of treatment	Screened: NR Randomized: 256 (128 vs. 128) Post randomization exclusions: 2 vs. 4 Loss to followup: None reported Analyzed: 250 (126 vs. 124)	Age (mean): 66 vs. 67 Male: 80% vs. 78% Race: NR Smoking status: NR Grade: Grade 2: 35 (28%) vs. 32 (26%) Grade 3: 91 (72%) vs. 92 (74%)
Eto, 1994 RCT Medium	Duration: A vs. B Mean (± SD): 674 days (± 315) vs. 606 (± 318) Method: Cystoscopy every 3 months for 3 years. Urinary cytology monthly for 1 year, then every 3 months for 3 years.	Screened: NR Randomized: 150 Postrandomization exclusions: 22 ("data not collected"=20; protocol violation=2) (NR by group) Other excluded (not eligible): 6 (NR by group) Lost to followup: 8 (NR by group) Total Analyzed: 114 Per Group Analyzed (A vs. B): 60 vs. 54	A vs. B Age, median (range): 65 years (24 - 89) vs. 67 years (39 - 87); $p < 0.01$ Race: NR Sex (male): 85.0% (51/60) vs. 87.0% (47/54) Smoking status: NR Recurrent bladder cancer: 14.8% (8/54) vs. 16.3% (8/49); Unknown: 10% (6/60) vs. 9.3% (5/54); p=NS Stage: Ta: 35.0% (21/60) vs. 31.5% (17/54); T1: 48.3% (29/60) vs. 57.4% (31/54); Unknown: 16.7% (10/60) vs. 11.1% (6/54); p=NS Grade: G1: 33.3% (20/60) vs. 20.4% (11/54); G2: 48.3% (29/60) vs. 66.7% (36/54); G3: 11.7% (7/60) vs. 7.4% (4/54); Unknown: 6.7% (4/60) vs. 5.6% (3/54): p=NS Functional Status: NR Size: < 1 cm: 45% (27/60) vs. 50% (27/54); 1- 3 cm: 40% (24/60) vs. 46% (25/54); 3-5 cm: 13% (8/60) vs. 4% (2/54); > 5 cm: 17% (1/60) vs. 0% (0/54) Number of tumors: 1: 47% (28/60) vs. 63% (34/54); 2-4: 38% (23/60) vs. 22% (12/54); ≥ 5: 12% (7/60) vs. 11% (6/54)

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Duchek, 2010 RCT Low Hemdan, 2014	Recurrence or progression at 6 months: 34 (27%) vs. 47 (38%), p=0.065 Disease-free survival: favors BCG, p=0.012 Progression-free survival: no difference between groups	
Eto, 1994 RCT Medium	A vs. B Recurrence (at 1 year): 6.7% (4/60) vs. 13.0% (7/54) Recurrence free at 1 year, generalized Wilcoxon test, p=non significant. Recurrence (at 2 years): 11.6% (7/60) vs. 18.5% (10/54) Recurrence free at 2 years, generalized Wilcoxon test, p=non significant.	A vs. B Recurrence free at 1 year and 2 years according to: Stage Ta: 1 year: 100.0% vs. 87.5%; 2 years: 100.0% vs. 87.5%; p = 0.201 Stage T1: 1 year: 88.3% vs. 86.8%; 2 years: 83.6% vs. 82.9%; p=0.554 Grade G1: 1 year: 94.7% vs. 80.0%; 2 years: 94.7% vs. 80.0%; p=0.509 Grade G2: 1 year: 96.0% vs. 94.2%; 2 years: 96.0% vs. 87.5%; p=0.225 Primary: 1 year: 90.5% vs. 92.4%; 2 years: 87.6% vs. 86.6%; p=0.966 Recurrent: 1 year: 100.0% vs. 62.5%; 2 years: 87.5% vs. 62.5%; p = 0.091 Size < 1 cm: 1 year: 100.0% vs. 91.8%; 2 years: 95.2% vs. 87.5%; p = 0.342 Size ≥1 cm:1 year: 87.4% vs. 81.1%; 2 years: 83.6% vs.76.1%; p=0.325 Single tumor: 1 year: 92.4% vs. 85.1%; 2 years: 92.4% vs. 81.2%; p = 0.193 Multiple tumor: 1 year: 92.9% vs. 88.5%; 2 years: 84.6% vs. 82.6%; p = 0.744

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Duchek, 2010 RCT Low Hemdan, 2014		Withdrawals due to adverse events: 11 (8%) vs. 2 (2%), p=0.06	Cancerforkningsfonden, Pharmacia and Upjohn, Schering-Plough Nordic Biotech, and Organon Teknika AB	
Eto, 1994 RCT Medium	NR	A vs. B Micturitional pain: 10.0% (6/60) vs. 14.8% (8/54); p = NS Pollakisuria: 15.0% (9/60) vs. 14.8% (8/54); p=NS Hematuria: 5.0% (3/60) vs. 0.0% (0/54)	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Flanigan, 1986 RCT Medium	USA Single center 1981-1984	Recurrent or multiple transitional cell cancers, stage Ta or T1, two or more tumors on initial presentation or documented recurrent tumor within the previous 12 months	Stage Tis	A: MMC 40 mg in 40 cc sterile water, 8 weekly instillations, then monthly for 2 years B: Thiotepa 60 mg in 60 cc sterile water, 8 weekly instillations, then monthly for 2 years
Friedrich, 2007 RCT Medium	Germany, Multicenter 1995-2002	Patients with primary transitional cell carcinoma of the bladder or patients with tumor recurrence after TURBT without prior adjuvant therapy were eligible if the histopathologic evaluation of their completely resected tumor revealed an intermediate risk pTaG1 tumor (size>3cm, recurrent or multifocal tumor) or pTaG2 up to pT1 tumor (G1-3). Patients with pT1G3 tumor were eligible in case of a unifocal small tumor (≤2.5 cm).	MIBC or concomitant CIS, evidence of lymph node or distant metastasis, or a pT1G3 tumor≥2.5cm.	A. MMC 20 mg, 6 weekly instillations B. BCG RIVM 2 x 10^8 CFU, 6 weekly instillations c. MMC 20 mg, 6 weekly instillations followed by monthly instillations of MMC 20mg for 3 years

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Flanigan, 1986 RCT Medium	Duration: Mean: MMC, 13.5 months; thiotepa NR Method: Cystoscopy and cytology every 3 months for the first 2 years and every 6 months thereafter.	Screened: NR Randomized: 40 (25 vs. 15) Post randomization exclusions: None reported Total analyzed: 40 Per group analyzed: 25 vs. 22 (includes 7 cross-overs due to MMC toxicity)	Age: NR Male: NR Race: NR Smoking status: NR Stage/grade: Ta, G1 or G2: 2 vs. 1 T1, G1: 6 vs. 8 T1, G2: 13 vs. 11 T1, G3: 3 vs. 2 Focal Tis: 1 vs. 0 Functional status: NR
Friedrich, 2007 RCT Medium	Duration, median: 2.9 years Method: Cytology and cystoscopy every 3 months in the first 2 years and every 6 months thereafter	Screened: NR Randomized: 495 (179 vs. 163 vs. 153) Post randomization exclusions: None reported Loss to followup: 11% equally distributed between arms Analyzed: 495 (179 vs. 163 vs. 153)	Age (median): 68 vs. 67 vs. 67 Male: 79% vs. 80% vs. 82% Race: NR Smoking status: NR Stage/grade: TaG1: 15% vs. 12% vs. 5% TaG2: 54% vs. 45% vs. 54% TaG3: 2% vs. 3% vs. 2% T1G1: 3% vs. 3% vs. 2% T1G2: 22% vs. 31% vs. 27% T1G3: 3% vs. 6% vs. 11%

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Flanigan, 1986 RCT Medium	A vs. B Recurrence: 4/25 (16%) vs. 2/22 (9.1%), RR 1.76 (95% CI 0.36 to 8.70) Progression: 3/25 (12%) vs. 1/22 (4.5%), RR 2.64 (95% CI 0.30 to 23.6)	A vs. B Recurrence, by tumor stage: Ta, G1 or G2: 0 vs. 0 T1, G1: 0 vs. 0 T1, G2: 3/13 vs. 1/11 T1, G3: 1/3 vs. 1/2
Friedrich, 2007 RCT Medium	Patients with recurrences:46 (26%) vs. 41 (25%) vs. 16 (10%) % recurrence-free at 2 years: 126 (71%) vs. 112 (69%) vs. 135 (88%) % recurrence-free at 3 years:123 (69%) vs. 107 (66%) vs. 132 (86%), difference between groups p=0.001. Pairwise comparison C superior to A (log-rank test, p=0.0006), or B (log-rank test , p=0.0005)	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Flanigan, 1986 RCT Medium		Crossovers, MMC to Thiotepa due to AE: 7/25	NR	
Friedrich, 2007 RCT Medium		Withdrawals due to AE: 0 vs. 3 vs. 8 Dysuria: 12% vs. 17% vs. 20% Hematuria: 1% vs. 12% vs. 9% Fever: 2% vs. 9% vs. 2%	Fa. Medac GmbH	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Giannopoulos, 2003 RCT Medium	Greece Multicenter Number unclear (authors from 3 centers) Study years: January 1997 - February 2001	Superficial transitional cell carcinoma (TCC) of the bladder. Primary/ initial diagnosis. Stages Ta or T1; Grade G2. No more than 2 foci. Initial specimens sufficient to document absence of muscle invasion.	Previous history of cancer and immunodeficiency; Coexistence of CIS or high grade (G3) TCC; Suspicion of upper tract TCC.	A: Interferon-gamma 1b (IFN-γ 1b), 1.5 X 107 IU (or 0.5 mg), in 50 mL normal saline. Retained intravesically for 2.5 hours. Total 20 instillations. First instillation 2 weeks after TURBT; then once a week X 7, then once biweekly X 4, then once monthly X 8. B: Mitomycin C, 40 mg (in 50 mL normal saline). Retained intravesically for 2.5 hours. Total 20 instillations. First instillation 2 weeks after TURBT; then once a week X 7, then once biweekly X 4, then once monthly X 8.
Gontero, 2013 RCT Medium	Italy, Germany, USA Multicenter 2006-2010	Intermediate risk NMIBC (namely Ta-1, G1-2, multifocal or unique and recurrent, more than 3 cm in diameter) were eligible if they met additional criteria of WHO performance status 2 or less, age 85 years or younger, BCG naïve, disease-free and not treated with intravesical chemotherapy in the last 3 months	Presence of T1G3 disease or CIS, preoperative urinary cytology positive for high grade atypia	A. BCG 27 mg (Connaught strain) in 50 mL saline, 6 weekly instillations, maintenance: 3 weekly instillations at 3, 6 and 12 months B. Gemcitabine 2000 mg in 500mL saline, 6 weekly instillations, maintenance consisted of monthly instillations up to 1 year

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Giannopoulos, 2003 RCT Medium	Duration, median (range): 26.5 months (4 -45) vs. 24 months (3 - 49). Method: Cystoscopy and urine cytology, every 3 months for 1 year, and every 6 months thereafter. Random cold cup biopsies from bladder wall urothelium during cystoscopy at 6 months and 12 months. Hematological, renal, and hepatic function testing every 3 months for 1 year, and every 6 months thereafter.	Screened: NR Randomized: 123 Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 123 Per Group Analyzed (A vs. B): 60 vs. 63	A vs. B Age, median (range): 68 years (34 - 86) vs. 60 years (26 - 81); p < 0.966 Race: NR Sex (male): 80.0% (48/60) vs. 88.9% (56/63); p =0.27 Smoking status: NR Recurrent bladder cancer: None (all primary) Stage: Ta: 66.7% (40/60) vs. 60.3% (38/63); T1: 33.3% (20/60) vs. 39.7% (25/63) Grade: All G2 Functional Status: NR
Gontero, 2013 RCT Medium	Duration: 1 year Method: Cytology and cystoscopy every 3 months	Screened: NR Randomized: 120 (59 vs. 61) Post randomization exclusions: 5 (2 vs. 3) Lost to followup: None reported Analyzed: 88 (47 vs. 41)	Age (mean) : 68 vs. 67 Male: 85% vs. 87% Race: NR Smoking: NR Stage: pta: 42 (71%) vs. 42 (69%) pT1: 17 (29%) vs. 19 (31%) Grade: Grade 1: 20 (34%) vs. 17 (28%) Grade 2: 39 (66%) vs. 44 (72%)

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Giannopoulos, 2003 RCT Medium	A vs. B Recurrence-free at 1 year: 90.0% (54/60) vs. 76.2% (48/63) Recurrence-free for total study period: 73.3% (44/60) vs. 57.1% (36/63) Difference in recurrence-free survival time at 1 year, p=0.04 Difference in recurrence-free survival time for total study period, p = 0.051	NR
Gontero, 2013 RCT Medium	Patients with recurrence at 1 year: 14 (30%) vs. 16 (39%), p=0.83 Mean recurrence free survival: 10.4 months vs. 10.6 months, p=0.66 Progression: 3 (6%) vs. 5 (12%), p=0.71 Mean progression free survival: 11.6 months vs. 11.6 months, p=0.50	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Giannopoulos, 2003 RCT Medium	NR	NR	Scientific Committee of the Central National Health Council of the Greek Ministry of Health; Scientific Committee of Special Account for Research of the National and Kapodistrian University of Athens	
Gontero, 2013 RCT Medium		Local and systemic side effects: 40.4% vs. 34.1% (p=0.66) Dysuria: p=0.01 (in favor of gemcitabine) Withdrawals due to AE: 1 vs. 0 Dysuria: induction: 21 (36.8%) vs. 13 (23.2%), p=0.15 1 year: 15 (31.9%) vs. 4 (9.7%), p=0.01 Hematuria: induction 9 (15.8%) vs. 0 (0%), p=0.003 1 year: 11 (23.4%) vs. 4 (9.7%), p=0.15 Fever: induction10 (17.5%) vs. 0 (0%), p=0.001 1 year: 4 (8.5%) vs. 2 (4.8%), p=0.68	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Gulpinar, 2012 RCT Medium	Turkey Single center 2004-2006	Patients with intermediate or high risk for recurrence and progression according to the EAU guidelines were included. Patients with stage pTaG1or pTaG2 tumors were included if tumor size>3cm or recurrent or multifocal tumors. Patients with CIS, pTaG3 tumors and all pT1 tumors were included, no instillations of chemotherapy or immunotherapy during the previous 6 months before entering the study	Muscle-invasive bladder tumor, evidence of lymph-node metastasis or distant metastasis, upper urinary tract tumors, tumors that could not be completely removed transurethral, presence of a second primary malignancy.	A. MMC 40mg in 40mL saline administered within 6 hours of surgery followed by delayed BCG instillations once a week for 6 weeks at least 15 days from TURBT B. Delayed BCG instillations (once a week for 6 weeks) at least 15 days from TURBT
Gustafson, 1991 RCT Medium	Sweden Number sites: unclear. Authors from 4 centers. Study years: NR	Superficial bladder cancer. Recurrent included, unclear if primary included. Stages Ta or T1; Grade G1, G2, or G3. Single or multiple tumors.	None explicitly stated. However, no patient had previously been treated with radiotherapy, systemic or topical chemotherapy.	A: Mitomycin C. Dosages "varied according to individual patient's bladder capacity". Range: "5 mg in 20 ml" to "40 mg in 250 ml". First instillation approximately 2 weeks after TURBT. instillations weekly X 4 weeks, then monthly X 11 months. B: Doxorubicin. Dosages "varied according to individual patient's bladder capacity". Range: "10 mg in 20 ml" to "80 mg in 250 ml". First instillation approximately 2 weeks after TURBT. instillations weekly X 4 weeks, then monthly X 11 months. C: No adjuvant treatment. TURBT alone.

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Gulpinar, 2012 RCT Medium	Duration: Median 41 months vs. 41 months Method: Cystoscopy and cytology every third month for first 2 years and then every 6 months years 3 and 4	Screened: NR Randomized: 51 (25 vs. 26) Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 51 (25 vs. 26)	Age mean): A: 58 vs. 58 Male: 84% vs. 77% Race: NR Smoking: NR Stage: T1: 44% vs. 46% Grade: High Grade: 32% vs. 23% CIS: 16% vs. 19%
Gustafson, 1991 RCT Medium	Duration: Mean months (range): 47 (12-65) vs. 45 (14-69) vs. 35 (10-68) Method: Cystoscopy every 3 months during year 1; thereafter, every 6 months unless recurrence, in which case every 3 months. Micturition frequency, pain on micturition, other subjective symptoms recorded before and after each instillation. Blood tests (including CBC and creatinine) after 2nd and 4th instillation and every month, thereafter.	Screened: NR Randomized: 62 Postrandomization exclusions: NR Lost to followup: 2 Total Analyzed: 60 Per Group Analyzed: 19 vs. 20 vs. 21	A vs. B vs. C Age, mean (Overall; NR by group): 67 years Race: NR Sex (Overall male: female; NR by group): "Four to one" Smoking status: NR Recurrent bladder cancer: NR Stage: Ta: 89.5% (17/19) vs. 90.0% (18/20) vs. 95.2% (20/21); T1: 10.5% (2/19) vs. 10.0% (2/20) vs. 4.8% (1/21) Grade: G1: 36.8% (7/19) vs. 35.0% (7/20) vs. 33.3% (7/21); G2: 63.2% (12/19) vs. 65.0% (13/20) vs. 61.9% (13/21); G3: 0% (0/19) vs. 0% (0/20) vs. 4.8% (1/21) Functional Status: NR

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Gulpinar, 2012 RCT Medium	Patients with recurrence: 9 (36%) vs. 5 (19%) ,p=0.052 Median time to first recurrence: 8 months vs. 7 months, p=0.012 Progression to muscle invasive disease: 1 vs. 1 Recurrence-free survival: no difference between groups, p=0.959	
Gustafson, 1991 RCT Medium	A vs. B vs. C Recurrence: Tumor-free survival during treatment year: 52.6% (10/19) vs. 15% (3/20) vs. 14.3% (3/21) Tumor-free survival for duration of followup: 26.3% (5/19) vs. 10% (2/20) vs. 4.8% (1/21) Mean disease-free interval, months (A vs. B): 14 vs. 6, p=0.02 Recurrence rate/100 patient-months: 7.7 vs. 18.3 vs. 18.6, p=0.02 Progression: Increased stage: 0% (0/19) vs. 5% (1/20) vs. 4.8% (1/21) Increased grade: 0% (0/19) vs. 15% (3/20) vs. 9.5% (2/21) Increased stage and grade: 10.5% (2/19) vs. 10% (2/20) vs. 0% (0/21)	NR

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Gulpinar, 2012 RCT Medium		Rates of AE: p=0.457 between groups Dysuria: A: 2 (8%) vs. B: 3 (12%)	NR	
Gustafson, 1991 RCT Medium	NR	No significant changes in frequency of micturition. No serious side-effects detected by blood samples. Mild pain on micturition (A vs. B): 60 % vs. 45%	King Gustaf V Jubilee Foundation	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Hinotsu, 2011 RCT Medium	Japan Multicenter 2004-2006	Recurrent or multiple tumors with confirmed Ta or T1 transitional cell carcinoma; must have 1 of the following: (a) at least 3 tumors (b) recurrence is at least the third such event or © recurrence diagnosed within 12 months from previous TURBT for NMIBC	History of BCG instillation or an anthracycline anti-tumor drug within the 12 months following the day on which the TURBT was performed (1 course of BCG more than 12 months earlier permitted and MMC therapy allowed after a washout period of at least 4 weeks); stage T2 or higher; IV/IA anticancer/ chemotherapy, radiation	Within 1 month of TURBT: A. BCG 81 mg (Connaught strain) in 40 mL saline weekly for 6 weeks then once weekly for 3 weeks at 3, 6, 12,and 18 months from start of induction therapy B. BCG 81 mg (Connaught strain) in 40 mL saline weekly for 6 weeks C. Epirubicin 40 mg in 40 mL saline twice at 1-week interval and then 7 times at 2-week intervals
Hinotsu, 2006 RCT Low	Japan Number of sites: unclear 1998-2002	Histopathologically proven transitional cell carcinoma (Stage pTa or pT1 and grade 1 to 2)	Single primary lesion, previous BCG or doxorubicin instillations	A. BCG (Tokyo 172 strain) 80 mg in 40 mL saline-6 weekly instillations B. Doxorubicin 20 mg in 40 mL saline-17 instillations-twice performed once a week then once every other week seven times, then once a month eight times

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Hinotsu, 2011 RCT Medium	Duration: Median 2 years Method: Cystoscopy and cytology every 3 months for 3 years then every 6 months	Screened: NR Randomized: 116 Post-randomization exclusions: 5 in BCG maintenance group as had no maintenance instillations Loss to followup: None reported Analyzed: 110 (36 vs. 42 vs. 32)	Age ≤ 64: 17 vs. 22 vs. 11 Age > 64: 24 vs. 20 vs. 21 Male: 80% vs. 95% vs. 97% Race: NR Smoking: NR Stage: pTa: 29 (71%) vs. 29 (69%) vs. 24 (75%) pT1: 12 (29%) vs. 13 (31%) vs. 8 (26%) Grade: Grade 1: 5 (12%) vs. 10 (24%) vs. 4 (13%) Grade 2: 29 (71%) vs. 24 (57%) vs. 21 (68%) Grade 3: 7 (17%) vs. 8 (19%) vs. 7 (23%)
Hinotsu, 2006 RCT Low	Duration: Median 667 days Method: Cystoscopy every 3 months for 3 years and every 6 months thereafter	Screened: NR Randomized: 83 (41 vs. 42) Post-randomization exclusions: 3 found to be ineligible after registration (1 vs. 2) Loss to followup: None reported Analyzed: 80 (40 vs. 40)	Age (mean): 64 vs. 63 Male: 80% vs. 68% Race: NR Smoking: NR Stage: Ta: 19 (48%) vs. 21 (53%) T1: 21 (53%) vs. 19 (48%) Grade: Grade 1: 8 (20%) vs. 8 (20%) Grade 2: 32 (80%) vs. 30 (75%) Grade 3: 0 vs. 2 (5%)

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Hinotsu, 2011 RCT Medium	Recurrence: 5 (12%) vs. 14 (33%) vs. 22 (69%) Progression at time of recurrence: 0 vs. 3 (7%) vs. 7 (22%)	
Hinotsu, 2006 RCT Low	Recurrence: favored BCG, p=0.02; "the hazard of recurrence in the BCG group was about one half of that in the doxorubicin group"	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Hinotsu, 2011 RCT Medium		Dysuria: 93% vs. 69% vs. NR Hematuria: 93% vs. 71% vs. NR Fever: 43% vs. 26% vs. NR	Nippon Kayaku Co. Ltd. (current Japanese license holder for the BCG Connaught strain)	
Hinotsu, 2006 RCT Low		Dysuria: 28 vs. 15, p=0.024 Hematuria: 21 vs. 8, p=0.005 Fever: 13 vs. 7, p=0.043	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Huland, 1990 RCT Medium	Germany (Hamburg) Multicenter Study years: March 1983 - June 1985	Superficial bladder carcinoma (primary or recurrent). Stages Ta, T1 or Tis; Grade G1, G2 or G3. CIS. Single or multiple tumors.	"Prophylactic instillation not possible because of patient age, immobility or lack of cooperation". Grade 0 tumor.	A: Mitomycin C, 20 mg/20 mL. Total 42 instillations. Every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year. B: Mitomycin C, 20 mg/20 mL. Total 42 instillations. Every week X 8 weeks, then every 4 weeks for rest of 1st year and 2 additional years. C: Mitomycin C, 20 mg/20 mL. Total 20 instillations. Every week X 20 weeks. D: Doxorubicin, 50 mg/50 mL. Total 42 instillations. Every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year. For all groups: instillations started 4 to 6 weeks after discharge from hospital.
Jauhiainen, 1987 RCT High	Finland Single center Study years: NR	Superficial bladder cancer. Recurrent only ($\geq$ 3 recurrences). Stages Ta or T1; Grades G1, G2, or G3.	None explicitly stated.	A: MMC, range 20 mg to 40 mg. Dosages varied according to patient's bladder capacity. B: Doxorubicin, range: 50 mg to 100 mg. Dosages varied according to patient's bladder capacity. For A and B: Total installations NR. First instillation not less than 14 days after TURBT; then 5 times weekly, then monthly. A phosphate buffer (pH 7.4, 0.05M) was added to reduce bladder irritation.

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Huland, 1990 RCT Medium	Duration, mean: A vs. B vs. C vs. D: 26.7 vs. 27.4 vs. 26.7 vs. 30.2 months Method: Cystoscopy every 3 months.	Screened: 597 Randomized: 477 Postrandomization exclusions: 29 Lost to followup: NR Total Analyzed: 419 Per Group Analyzed: 209 vs. 96 vs. 75 vs. 39	A vs. B vs. C vs. D Age, mean (men/women): 61.1/67.5 vs. 66.3/68.1 vs. 65.1/64.6 vs. 68.0/58.3 Race: NR Sex (male): 82.3% (172/209) vs. 77.1% (74/96) vs. 77.3% (58/75) vs. 74.4% (29/39) Smoking status: NR Recurrent bladder cancer: 32.1% (67/209) vs. 25.0% (24/96) vs. 25.3% (19/75) vs. 43.6% (17/39) Stage: Ta: 73.7% (154/209) vs. 78.1% (75/96) vs. 76.0% (57/75) vs. 59.0% (23/39); T1: 23.0% (48/209) vs. 19.8% (19/96) vs. 21.3% (16/75) vs. 33.3% (13/39); Tis: 3.3% (7/209) vs. 2.1% (2/96) vs. 2.7% (2/75) vs. 7.7% (3/39) Grade: G1: 47.4% (99/209) vs. 58.3% (56/96) vs. 52.0% (39/75) vs. 43.6% (17/39); G2: 47.7% (99/209) vs. 35.4% (34/96) vs. 37.3% (28/75) vs. 38.5% (15/39); G3: 1.9% (4/209) vs. 4.2% (4/96) vs. 8.0% (6/75) vs. 10.3% (4/39) Functional Status: NR
Jauhiainen, 1987 RCT High	DurationL Mean (range): 23.6 months (8-43) vs. 23.3 months (4-48). Method: Followup with cystoscopy and biopsy cytology.	Screened: NR Randomized: 41 Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 41 Per Group Analyzed (A vs. B): 26 vs. 15	A vs. B Age (years), mean (range): 68.1 (40-82) vs. 65.2 (28-83) Male: 84% (42/50) of a larger series, of which only 41 were randomized. Race: NR Smoking status: NR Recurrent bladder cancer: 100% vs. 100% Stage: All Ta or T1, percentages NR, overall or by group. Grade: G1: 65.4% vs. 33.3%; G2: 26.9% vs. 46.7%; G3: 7.7% vs. 20.0% Functional Status: NR

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Huland, 1990 RCT Medium	A vs. B vs. C vs. D Recurrence: 15.3% (32/209) vs. 9.4% (9/96) vs. 17.3% (13/75) vs. 23.1% (9/39) Recurrence per 100 patient-months: 0.68 vs. 0.49 vs. 0.65 vs. 0.76 Progression of stage: 2.9% (6/209) vs. 1.0% (1/96) vs. 5.3% (4/75) vs. 7.7% (3/39) Progression of grade: 1.9% (4/209) vs. 1.0% (1/96) vs. 4.0% (3/75) vs. 10.3% (4/39)	A vs. B vs. C vs. D Recurrence among patients with primary tumor (n=288): By Stage: Ta: 9.6% (10/104) vs. 6% (3/50) vs. 15% (6/40) vs. 23.1% (3/13) T1: 14.7% (5/34) vs. 0% (0/17) vs. 13.3% (2/15) vs. 42.9% (3/7) CIS: 66.7% (2/3) vs. 0% (0/2) vs. 0% (0/1) vs. 0% (0/2) By Grade: G1: 7.9% (5/63) vs. 7.5% (3/40) vs. 14.3% (4/28) vs. 0% (0/9) G2: 12.7% (9/71) vs. 0% (0/24) vs. 13.0% (3/23) vs. 50% (4/8) G3: 9% (1/9) vs. 0% (0/3) vs. 0% (0/5) vs. 20% (1/5) Recurrence among patients with recurrent tumor in the past (n=131): By Stage: Ta: 28.0% (14/50) vs. 20% (5/25) vs. 29.4% (5/17) vs. 10% (1/10) T1: 7.1% (1/14) vs. 50% (1/2) vs. 0% (0/1) vs. 16.7% (1/6) CIS: 0% (0/4) vs. 0% (0/0) vs. 0% (0/1) vs. 100% (1/1) By Grade: G1: 13.9% (5/36) vs. 25% (4/16) vs. 9.1% (1/11) vs. 0% (0/8) G2: 35.7% (10/28) vs. 20% (2/10) vs. 80% (4/5) vs. 14.3% (1/7) G3: 0% (0/2) vs. 0% (0/3) vs. 0% (0/3) vs. 100% (2/2)
Jauhiainen, 1987 RCT High	Recurrence: 11.5% (3/26) vs. 40.0% (6/15) Disease-free interval: A > B, Mantel-Cox statistic p=0.0079. Progression of stage, multifocality, or grade: 7.7% (2/26) vs. 0.0% (0/15)	NR

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Huland, 1990 RCT Medium	NR	A vs. B vs. C vs. D Chemical cystitis: 25% vs. 12% vs. 18% vs. 48% Allergy: 2% vs. 2% vs. 1% vs. 2% Other: 6% vs. 4% vs. 10% vs. 16% Total: 33% vs. 18% vs. 29% vs. 66%	NR	
Jauhiainen, 1987 RCT High	NR	A vs. B Chemical cystitis: Mild: 7.7% (2/26) vs. 13.3% (2/15) Moderate: 7.7% (2/26) vs. 0.0% (0/15) Heavy: 3.9% (1/26) vs. 0.0% (0/15) Total: 19.2% (5/26) vs. 13.3% (2/15) General side effects: 0.0% (0/26) vs. 0.0% (0/15)	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Jimenez-Cruz, 1997 RCT Medium	Spain Multicenter	Recurrent histologically proved superficial transitional cell carcinoma of the bladder (Stage T1, grade 1 to 3)	Primary tumors, Stage pTa and infiltrative tumors, Previous treatment with interferon or BCG for bladder tumor	A. BCG (Pasteur F) 150mg in 50mL saline B. Interferon alpha-2a 54 MU in 50 mL saline instillations were weekly during the first month, biweekly for 2 months, and monthly for 9 months
Kaasinen, 2000 RCT Medium Finnbladder IV	Finland Multicenter 1992 to 1996	At least 2 histologically verified recurrent stage Ta or T1 grade 1 to 2 tumors without concomitant CIS, Grade 3 tumors also included		All patients received MMC 40 mg in 100 mL of buffered solution perioperatively followed by 4 weekly MMC instillations and then randomized to (in addition to MMC): A. BCG (OncoTICE) 5 x 10^8 colony-forming units in 100 mL saline monthly B. Interferon alpha-2b in 100 mL saline alternating with BCG monthly
Kaasinen, 2003 RCT Medium	Sweden, Norway, Finland Multicenter 1992-1997	High-grade primary, secondary, or concomitant (with pTa or pT1 tumor) carcinoma in situ of the urinary bladder	CIS in other parts of the urinary tract, previous radiotherapy or systemic chemotherapy	Six weekly instillations of: A. MMC 40 mg in 50 mL saline followed by alternating instillations of BCG (Connaught) 120 mg in 50 mL saline and MMC monthly up to one year B. BCG 120 mg followed by BCG monthly for one year

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Jimenez-Cruz, 1997 RCT Medium	Duration: mean months (21 vs. 18) Method: Urine cytology, bladder ultrasound and cystoscopy every 3 months for first year then every 4 months for second year	Screened: NR Randomized: 122 (61 vs. 61) Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 110 (61 vs. 49)	Age (mean): 67 vs. 64 Male: 87% vs. 82% Race: NR Smoking: NR Stage: T1: 61 vs. 61 Grade: Grade 1: 51% vs. 52% Grade 2: 43% vs. 41% Grade 3: 7% vs. 7%
Kaasinen, 2000 RCT Medium Finnbladder IV	Duration: Median 30.7 months Method: NR	Screened: NR Randomized: 236 (118 vs. 118) Post-randomization exclusions: 31 (due to randomization violations) Loss to followup: None reported Analyzed: 205 (102 vs. 103)	Age (mean): 68 vs. 67 Male: 72% vs. 66% Race: NR Smoking: NR Stage: pTa: 97% vs. 94% pT1: 3% vs. 5% pTa-1: 0 vs. 1% Grade: Grade 1: 64% vs. 63% Grade 2: 34% vs. 37% Grade 3: 2% vs. 0
Kaasinen, 2003 RCT Medium	Duration: Median 56 months Method: Cystoscopy, cytology, and biopsy of suspicious lesions every three months for two years and then according to local practice	Screened: NR Randomized: 323 (195 vs. .157) Post-randomization exclusions: 19 (6 vs. 12) Loss to followup: None reported Analyzed: 304 (159 vs. 145)	Age (mean): 71 vs. 70 Male: 79% vs. 82% Race: NR Smoking: NR Primary CIS: 47 vs. 44 Secondary CIS: pTa: 40 vs. 35 pT1: 26 vs. 22 Concomitant CIS: pTa: 17 vs. 20 pT1: 21 vs. 16 Grade of concurrent tumor: G1: 2 vs. 1 G2: 11 vs. 16 G3: 25 vs. 19

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Jimenez-Cruz, 1997 RCT Medium	Patients with recurrences 24 (39%) vs. 34 (69%) Disease-free interval (months): 93 vs. 84	
Kaasinen, 2000 RCT Medium Finnbladder IV	Probability of nonrecurrence at 2 years: 73% vs. 34% Probability of nonrecurrence at 5 years: 67% vs. 22%	
Kaasinen, 2003 RCT Medium	Complete response at 3 months: 119/150 (75%) vs. 120/145 (83%), p=0.6 Complete response at 1 year: 116/147 (79%) vs. 106/136 (78%) Disease-free interval at 60 months: 41% vs. 54% Death due to bladder cancer 13 vs. 10	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Jimenez-Cruz, 1997 RCT Medium		Cessation of treatment due to intolerance: 4 (7%) vs. 0 Dysuria, frequency, urgency: 85% vs. 0 Fever: 5% vs. 0	NR	
Kaasinen, 2000 RCT Medium Finnbladder IV		Cessation of instillation due to side effects: 1 vs. 3 Contracted bladder: 1 vs. 0	Finnish Cancer Foundation, Oreganon Teknika, Pharmacia-Upjohn, Roche and Schering Plough	
Kaasinen, 2003 RCT Medium		Withdrawals due to AE: NR BCG monotherapy showed significantly higher scores for local and systemic side-effects at 3 and 12 months Contracted bladders: 9 vs. 5	Nordic Cancer Union, Finnish Cancer Foundation, Connaught Laboratories Limited	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Krege, 1996 RCT Medium	Germany, Multicenter 1985-1992	histological evidence of superficial bladder cancer (stage pTa/1 grades 1 to 3), no intravesical chemotherapy during last 6 months or previous radiation	Primary stage pTa grade 1 tumor	A. TURBT only B. TURBT + MMC 20 mg in 50 mL saline every 2 weeks during year 1 and monthly during year 2 C. TURBT + BCG 120 mg (Connaught strain) in 50 mL saline and subcutaneous BCG 0.5 mg in the forearm weekly for 6 weeks and then monthly for 4 months
Lamm, 1991 RCT Medium	USA Multicenter 1983-1985	Transitional-cell carcinoma with tumors at stage Ta or T1 of any grade with two or more recurrences in the most recent 12 months, CIS, or both		A. BCG 120 mg (Connaught strain) in 50 mL saline and 0.5 mL administered percutaneously to inner thigh six weekly treatments with additional single intravesical and percutaneous treatments at 3, 6, 12, 18, and 24 months B. Doxorubin 50 mg in 50 mL saline 4 weekly treatments followed by 11 monthly treatments
Lamm, 1995 RCT Medium	USA Multicenter Study years NR	Histologically proven, completely resected Ta (noninvasive) or T1 (lamina propria invasive) transitional cell carcinoma and at increased risk for tumor recurrence	Stage T2 or higher tumors excluded; patient treated with agent or radiation therapy	1 to 2 weeks after tumor resection: A. Tice BCG: 5 x 10^8 CFU in 50 mL saline for 2 hours; treatments were weekly for 6 weeks then at 8 and 12 weeks; then monthly to one year B. Mitomycin C: 20 mg in 20 mL sterile water; treatments were weekly for 6 weeks then at 8 and 12 weeks; then monthly to one year

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Krege, 1996 RCT Medium	Duration: Mean 20 months Method: Evaluated after 3, 6, 9, 12, 18, 24, 30, and 36 months	Number screened: NR Randomized: 337 Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 336 (122 vs. 112 vs. 102)	Age (mean): 65 (not specified by group) Male: 75% vs. 84% vs. 80% Race: NR Smoking: NR Stage: Ta: 95 (78%) vs. 84 (74%) vs. 78 (77%) T1: 27 (22%) vs. 29 (26%) vs. 24 (24%) Grade: Grade 1: 47 (39%) vs. 40 (39%) vs. 36 (41%) Grade 2: 69 (57%) vs. 57 (51%) vs. 57 (56%) Grade 3: 6 (5%) vs. 12 (11%) vs. 4 (4%)
Lamm, 1991 RCT Medium	Duration: Median 65 months	Screened: NR Randomized: 285 (143 vs. 142) Post-randomization exclusions: 23 patients found to be ineligible (16 vs. 7) based on data or specimens available before randomization Loss to followup: None reported Analyzed: 262 (127 vs. 135)	Age (mean): 67 vs. 66 Male: 79% vs. 85% White: 90% vs. 82% Smoking: NR Stage: Ta: 79 (62%) vs. 80 (59%) T1: 22 (17%) vs. 28 (21%) Grade: Grade 1: 19 (15%) vs. 25 (19%) Grade 2: 38 (30%) vs. 45 (33%) Grade 3: 26 (20%) vs. 38 (28%)
Lamm, 1995 RCT Medium	Duration: Median 913 days Method: Cystoscopy and urinary cytology were performed every 3 months for 2 years then every 6 months	Screened: NR Randomized: 469 Post-randomization exclusions: 22 patients ineligible due to inappropriate pathology, failure to demonstrate increased risk of recurrence, presence of another primary cancer, residual papillary tumors following resection, prior use of study treatment Loss to followup: NR Analyzed: 447 (225 vs. 222)	Age (mean): 67 vs. 67 Male: 82% vs. 85% White: 93% vs. 94% Smoking: NR Stage: TaT1: 86% vs. 85% Grade: Grade 3: 29% vs. 32% CIS: 14% vs. 16%

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Krege, 1996 RCT Medium	Recurrence: 56 46%) vs. 30 (25%) vs. 26 (25%)	
Lamm, 1991 RCT Medium	Recurrence: 78 (61%) vs. 110 (81%) Mortality: 44 (35%) vs. 46 (34%) Complete response in CIS: 45 (70%) vs. 23 (47%), p<0.001	
Lamm, 1995 RCT Medium	Recurrence or death due to any cause: 44 months vs. 22 months (97/191 vs. 106/186) Disease worsening or death from any cause: No significant difference in time to disease worsening or death from any cause (87/191 vs. 106/186) Death: 11% (25/225) vs. 13% (28/222) Death due to bladder cancer: 4% (8/225) vs. 5% (12/222)	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Krege, 1996 RCT Medium		Cystitis: NR vs. 16% vs. 34% Hematuria: NR vs. 3% vs. 6% Fever: NR vs. 0 vs. 18	Ministry of Science and Technology, Germany	
Lamm, 1991 RCT Medium		Irritative bladder symptoms: 62% vs. 49% Hematuria: 39% vs. 27% Fever or chills: 42% vs. 8%	NR	
Lamm, 1995 RCT Medium		Withdrawals due to AE: NR Systemic toxicity: 181 vs. 80 realizations Bladder toxicity: 356 vs. 234 realizations Patient refusal or physician reluctance to restart treatment: 8% vs. 7%	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Lamm, 2000 RCT Medium Lerner, 2007 SWOG 8507	USA Multicenter 1986-1989	Histologically confirmed transitional cell carcinoma of the bladder within 6 months before enrollment; papillary tumors Ta or T1; 2 tumors (primary and recurrent or 2 recurrences) within 1 year, 3 or more within the most recent 6 months and/or CIS, responded to induction therapy with BCG	Stage T2 or higher, previous radiation therapy for bladder, planning concomitant chemotherapy or radiation therapy, received previous BCG treatments	At least 1 week following TURBT patients received BCG 81 mg (Connaught strain) in 50.5 mL saline and simultaneous percutaneous BCG 0.5 cc (10^7 CFU) to inner thigh weekly for 6 weeks, responders randomized to: A. BCG intravesically and percutaneously 3 successive weekly treatments at 3 months, 6 months and every 6 months to 3 years B. No BCG
Liu, 2006 RCT Medium	China Number sites: unclear Study years: May 1997 - February 1998	Superficial bladder carcinoma (primary or recurrent). Stages Ta or pT1; Grade G1 or G2.	No recurrence within 1 year prior to enrollment. CIS; muscle-invasive disease (stage pT2 or greater); age > 85 years; history of another cancer; tumor in upper urinary tract; uncontrollable UTIs.	A: Epirubicin, 80 mg (in 40 mL normal saline). Single intravesical instillation within 6 hours of TURBT. B: Epirubicin, 40 mg, intravesical instillation every week for 6 ~ 8 weeks, then every month for 10 months. C: Mitomycin C, 40 mg, intravesical instillation every week for 6 ~ 8 weeks, then every month for 10 months.

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Lamm, 2000 RCT Medium Lerner, 2007 SWOG 8507	Duration: Median 120 months Method: Cytology and cystoscopy every 3 months for 2 years then every 6 months for 2 years then yearly	Number screened: 660 Randomized: 550 Post-randomization exclusions: 12 deemed ineligible before randomization; 154 had evidence of disease at randomization and were not included Analyzed: 384 (192 vs. 192)	Age (mean): 67 vs. 67 Male: 90% vs. 83% Black men: 4% vs. 3% Smoking: NR CIS at induction: 66 (34%) vs. 64 (33%)
Liu, 2006 RCT Medium	Duration: 5 years until June 2003. Method: Cystoscopy and urinary cytology every 3 months X 2 years, then every 6 months X 3 years.	Screened: NR Randomized: 47 (16 vs. 15 vs. 16) Postrandomization exclusions: None Lost to followup: None Total Analyzed: 44 (14 vs. 15 vs. 15)	A vs. B vs. C Age (Overall; NR by group), mean: 62.2 ± 11.7 (range, 45 ~ 79) Race: NR Sex (male): NR Smoking status: NR Recurrent bladder cancer (Overall; NR by group): 23.4% (11/47) Stage and Grade: TaG1: 6.3% (1/16) vs. 0% (0/15) vs. 0% (0/16); TaG2: 6.3% (1/16) vs. 6.6% (1/15) vs. 6.3% (1/16); T1G1: 12.5% (2/16) vs. 26.7% (4/15) vs. 12.5% (2/16); T1G2: 75.0% (12/16) vs. 66.7% (10/15) vs. 81.3% (13/16) Functional Status: NR "There were no significant differences in patient characteristics among the 3 groups".

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Lamm, 2000 RCT Medium Lerner, 2007 SWOG 8507	5 year survival: 83% vs. 78%	
Liu, 2006 RCT Medium	A vs. B vs. C Tumor-free survival at 1 year: 100% (14/14) vs. 86.7% (13/15) vs.93.3% (14/15) Tumor-free survival at 2 years: 85.7% (12/14) vs. 80.0% (12/15) vs.66.7% (13/15) Tumor-free survival at 3 years: 71.4% (10/14) vs. 73.3% (11/15) vs.80.0% (12/15) Tumor-free survival at 5 years: 64.3% (9/14) vs. 66.7% (10/15) vs.60.0% (9/15) p > 0.05 Mean interval to recurrence, months: 8 vs. 4 vs. 5 Recurrence rate: 35.7% (5/14) vs. 33.3% (5/15) vs. 40% (6/15), p > 0.05	NR

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Lamm, 2000 RCT Medium Lerner, 2007 SWOG 8507		2 BCG related deaths	National Cancer Institute	
Liu, 2006 RCT Medium	NR	A vs. B vs. C Only local toxicities observed; No general toxicities encountered. Any side effect: 13.6% vs. 53.3% vs. 46.7%, p < 0.01 Dysuria or urinary frequency/urgency: 6.3% (1/16) vs. 13.3% (2/15) vs. 12.5% (2/16) Stricture of urethra: 0% (0/16) vs. 6.7% (1/15) vs. 6.3% (1/16)	Pharmacia Ltd.	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Lundholm,1996 RCT Medium Malmstrom, 1999 (5 year followup) Gardmark, 2007 (10 year followup)	Norway, Sweden Multicenter 1987-1992	Stage Ta, grades 1 to 3 or stage T1, grades 1 and 2 tumors were included provided there had been at least 3 tumor events during the prior 18 months. Patients with stage T1 grade 3 and those with primary or concomitant dysplasia or carcinoma in situ were included without having had prior tumor events, no chemotherapy during the past 6 months.	Previous or on-going intravesical treatment with Mitomycin C, BCG or radiotherapy	A. Mitomycin C 40mg in 50 mL phosphate buffer B. BCG 120 mg (Danish strain) in 40 mL saline Treatment for 6 weeks, monthly for up to 1 year and every 3 months during year 2. [Crossover initiated in A to B in 38 patients and B to A in 21 patients]
Mangiarotti, 2008 RCT Medium	Italy Number of sites: unclear. Study years NR	Nonmuscle invasive bladder cancer not previously treated with any chemotherapeutic or immunotherapeutic agent		A. MMC 40 mg in 50 mL saline weekly for 8 weeks then monthly for 12 months B. BCG (Tice strain) weekly for 6 weeks then monthly for 12 months
Martinez-Pineiro, 1990 RCT Medium 2nd interim report	Spain Number of sites: unclear. 1980-1988	Histologically proved superficial transitional cell carcinoma; Initially Ta or T1 tumors admitted, later only T1 cancer patients admitted	Previous treatment with any of the 3 study agents	A. Doxorubicin 50 mg in 50 mL saline B. BCG (Pasteur strain) 150 mg in 50 mL saline C. Thiotepa 50 mg in 50 mL saline First treatment within 14 days of TUR, treatments given weekly for 4 weeks, then monthly for 11 months

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Lundholm,1996 RCT Medium Malmstrom, 1999 (5 year followup) Gardmark, 2007 (10 year followup)	Duration: Median 39 months; 10 year followup: 123 months Method: Cystoscopy and cytology quarterly for 3 years then every 6 months for years 4 and 5	Screened: NR Randomized: 261 (130 vs. 131) Post randomization exclusions: 11 died shortly after randomization (5 vs. 6) Analyzed:250 (125 vs. 125)	Age (mean): 68 vs. 69 Male: 84% vs. 83% Race: NR Smoking status: NR Stage: Ta: 51 (48%) vs. 53 (42%) T1: 32 (26%) vs. 31 (25%) Dysplasia/Tis: 42 (34%) vs. 41(33%)
Mangiarotti, 2008 RCT Medium	Duration: Mean 66 months vs. 66 months Method: Cytology and cystoscopy every 3 months	Screened: NR Randomized: 96 Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 92 (46 vs. 46)	Age (mean): 64 vs. 64 Male: 76% vs. 70% Race: NR Smoking: NR Stage: Ta: 32 (70%) vs. 21 (46%) T1: 14 (30%) vs. 25 (54%) Grade: Grade 1: 26 (57%) vs. 31 (67%) Grade 2: 20 (43%) vs. 15 (33%)
Martinez-Pineiro, 1990 RCT Medium 2nd interim report	Duration: Median 3 years (range 3-97 months) Method: Cystoscopy and cytology every 3 months for 1 year then every 4 months for 2 years and then every 6 months thereafter	Screened: NR Randomized; 202 Post-randomization exclusions: None reported Loss to followup: 9 (also excluded were 1 for protocol violation and 7 for being too early) Analyzed: 176	Age (Median): 62 vs. 64 vs. 65 Male: 89% vs. 82% vs. 84% Race: NR Smoking: NR Stage: Ta: 21 (40%) vs. 18 (27%) vs. 23 (41%) T1: 32 (60%) vs. 49 (73%) vs. 33 (59%) Grade: Grade 1: 24 (45%) vs. 23 (34%) vs. 18 (32%) Grade 2: 18 (34%) vs. 29 (43%) vs. 24 (43%) Grade 3: 11 (21%) vs. 15 (22%) vs. 14 (25%)

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Lundholm,1996 RCT Medium Malmstrom, 1999 (5 year followup) Gardmark, 2007 (10 year followup)	Disease-free at 39 months: 43 (34%) vs. 62 (49%), p<0.03 Median time to recurrence: 14.9 months vs. 33.9 months Disease progression: 17 (14%) vs. 16 (13%) Mortality: 11 (9%) vs. 19 (15%) Died of bladder cancer: 4 (3%) vs. 6 (5%) <u>10 year followup:</u> Progression: 34 (27%) vs. 24 (19%) Mortality: 72 (58%) vs. 68 (54%) Died of bladder cancer: 26 (21%) vs. 19 (15%)	
Mangiarotti, 2008 RCT Medium	Recurrence: 23 (50%) vs. 23 (50%) Recurrence free interval: 27 months vs. 36 months (p=0.132)	
Martinez-Pineiro, 1990 RCT Medium 2nd interim report	Recurrence: 23 (43%) vs. 9 (13%) vs. 20 (36%) Months to recurrence (mean): 31 vs. 31 vs. 29 Progression: 4 (8%) vs. 1 (2%) vs. 2 (4%) Death due to metastatic disease: 1 vs. 0 vs. 0 Noncancer death: 0 vs. 0 vs. 1	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Lundholm,1996 RCT Medium Malmstrom, 1999 (5 year followup) Gardmark, 2007 (10 year followup)		Withdrawal due to adverse events: 10 (8%) vs. 16 (13%) Hematuria: 78 (63%) vs. 112 (91%) Irritative bladder symptoms: 87 (71%) vs. 100 (81%) Fever: 89 (72%) vs. 96(78%) Sepsis:0 vs. 3 (2%) Bladder contracture: 0 vs. 1 (1%)	NR <u>10 year followup</u>: Linner Hagstrand Memory Foundation	
Mangiarotti, 2008 RCT Medium		Cystitis: 10 (22%) vs. 19 (41%) Gross hematuria: 2 (4%) vs. 0 Fever: 0 vs. 2 (4%) Treatment discontinued: 11 (24%) vs. 2 (4%)	NR	
Martinez-Pineiro, 1990 RCT Medium 2nd interim report		Bladder irritability: 7 (13%) vs. 28 (42%) vs. 8 (14%) Cystitis: 0 vs. 11 (16%) vs. 0 Fever: 0 vs. 5 (7%) vs. 0 Contracted bladder: 0 vs. 1 (1%) vs. 0	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Melekos, 1993 RCT Medium	Greece Number of sites: unclear. Study years NR	Histologically proven superficial transitional cell carcinoma of the bladder; primary or recurrent neoplasms	Multifocal carcinoma in situ and another cancer or history of another cancer outside the bladder and who had had previous local or systemic chemotherapy or radiotherapy	2 weeks after last resection began 6 weekly instillations of: A. BCG 150 mg (Pasteur F strain) in 50 mL saline maintenance therapy every 3 months for first 2 years then every 6 months; if at high risk for recurrence and initially responsive to treatment then received a separate 4-week course at month 6 of followup B. Epirubicin: 50 mg in 50 mL saline maintenance therapy every 3 months for first 2 years then every 6 months if at high risk for recurrence and initially responsive to treatment then received a separate 4-week course at month 6 of followup C. TURBT alone
Melekos, 1996 RCT Medium	Greece Number of sites: unclear. Study years NR	Completely resectable recurrent (at least 2 recurrences in the most recent 12 months) or multiple (more than 2) papillary superficial bladder tumors Ta and T1 of any grade	Solitary-primary neoplasms, stage >T1, multifocal CIS, previous systemic chemotherapy or radiotherapy	A. Epirubicin 50 mg in 50 mL saline weekly for 4 weeks beginning within 2 days of TURBT B. BCG 5 x 10^8 CFU (Tice strain) in 50 mL saline weekly for 6 weeks beginning approximately 10 days after TURBT Those free of recurrence then received a single maintenance dose every 3 months during the first 2 years and then every 6 months thereafter until the end of the second year of followup; for T1 or TaG2/G3 instead of a single dose at 6 months, patients received 3 weekly doses at months 3 and 6 of followup

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Melekos, 1993 RCT Medium	Duration: Total months: 1784 vs. 1745 vs. 603 Method: Cystoscopy and urinary cytology every 3 months for first 2 years than every 6 months thereafter	Screened: NR Randomized: 190 (2:2:1) Post-randomization exclusions: 29 patients ineligible due to protocol violation, loss to followup, or other reason Analyzed: 161 (62 vs. 67 vs. 32)	Age (mean): 67 vs. 66 vs. 68 years Male: 82% vs. 84% vs. 84% Race: NR Smoking: NR Stage: Ta: 66% vs. 63% vs. 66% T1: 34% vs. 37% vs. 34% Grade: Grade 1: 44% vs. 46% vs. 41% Grade 2: 44% vs. 37% vs. 44% Grade 3: 13% vs. 16% vs. 16% Tis: 6% vs. 4% vs. 6%
Melekos, 1996 RCT Medium	Duration: Median followup: 43 months vs. 43 months Method: Cystoscopy and urinary cytology every 3 months for first 2 years than every 6 months thereafter	Screened: NR Randomized: 132 Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 119 (61 vs. 58)	Age (mean): 67 vs. 65 Male: 87% vs. 90% Race: NR Smoking: NR Stage: Ta: 38 (62%) vs. 34 (59%) T1: 23 (38%) vs. 24 (41%) Grade: Grade 1: 12 (20%) vs. 12 (21%) Grade 2: 35 (57%) vs. 34 (59%) Grade 3: 14 (23%) vs. 12 (21%)

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Melekos, 1993 RCT Medium	Recurrence: 32% vs. 40% vs. 59% Interval before recurrence: 18 months vs. 16 months vs. 11 months Progression: 6% vs. 9% vs. 22% Muscle invasion: 3% vs. 4% vs. 13%	
Melekos, 1996 RCT Medium	Recurrence: 34 (56%) vs. 26 (45%) Progression: 10 (16%) vs. 7 (12%)	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Melekos, 1993 RCT Medium		Withdrawals due to AE: NR Cystitis:79% vs. 34% vs. NR Fever: 27% vs. 3% vs. NR Flu-like illness:13% vs. 0% vs. NR Macroscopic hematuria: 23% vs. 15% vs. NR Reduced bladder volume: 0% vs. 1% vs. NR Treatment delay: 5% vs. Epirubicin 8% vs. NR	NR	
Melekos, 1996 RCT Medium		Cystitis: 38% vs. 67% Macroscopic hematuria: 16% vs. 24% Treatment delayed: 12% vs. 5%	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Mohsen, 2010 RCT Medium	Egypt Number of sites: unclear. 2003-2006	At least 2 histologically verified recurrent stage Ta or T1 during the preceding 1.5 years		A. MMC 40 mg in 50 mL saline immediately after resection and then 4 weekly instillations; then BCG 5 x 10^8 in 50 mL saline monthly for postoperative months 2 through 12 B. BCG 5 X 10^8 in 50 mL saline with no perioperative instillations, then weekly for 6 weeks then monthly for postoperative months 3 through 12
Nepple, 2010 RCT Medium	USA Multicenter 1999-2003	Histologically confirmed CIS, Ta, T1 urothelial cancer diagnosed within 8 weeks	Prior BCG treatment for bladder cancer	A. BCG 50 mg (TICE) 6 weekly instillations then 3 weekly instillations of BCG 16.6 mg at 4, 7, 13, 19, 25 and 37 months B. BCG 50 mg (TICE) plus INF alpha-2b 50 MU 6 weekly instillations then 3 weekly instillations of BCG 16.6 mg at 4, 7, 13, 19, 25 and 37 months Patients were also randomized to regular or mega-dose vitamins

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Mohsen, 2010 RCT Medium	Duration: Mean 24 months Method: Cytology and cystoscopy every 3 months	Screened: NR Randomized: 56 Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 56 (29 vs. 27)	Age (mean): 48 vs. 48 Male: 69% vs. 67% Race: NR Smoking: NR Stage: pTa: 15 (52%) vs. 14 (52%) pT1: 14 (48%) vs. 13 (48%)
Nepple, 2010 RCT Medium	Duration: 24 months Method: Cystoscopy and cytology every 3 months for 24 months then semiannually for 2 years then annually thereafter	Screened: NR Randomized: 670 (324 vs. 346) Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 670 (324 vs. 346)	Age: 68 Male: 76% Race: NR Smoking: NR CIS: 8%

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Mohsen, 2010 RCT Medium	Recurrence: 9 (31%) vs. 16 (70%) Median time to first recurrence: 9 months vs. 6 months	
Nepple, 2010 RCT Medium	Recurrence: 104 (32%) vs. 127 (37%)	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Mohsen, 2010 RCT Medium		NR	NR	
Nepple, 2010 RCT Medium		Constitutional symptoms: 58 (18%) vs. 38 (11%) Fever: 36 (11%) vs. 17 (5%)	Schering-Plough Corp and Mission Pharmacal	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Niijima, 1983 [see also Akaza, 1987] RCT Medium	Japan Multicenter Study years: April 1980 - 1985	Histologically proven superficial bladder cancer (primary or recurrent). Stages Ta or T1; Grade not specified. Absence of tumor after TURBT.	Tis superficial cancer; other therapies, such as chemotherapy, immunotherapy, and/or radiotherapy within 3 or 4 weeks before initiation of study; severe cardiovascular, renal, hepatic or hematopoietic disturbances; simultaneous presence of another cancer.	A: Doxorubicin, 30 mg (in 30 mL saline). B: Doxorubicin, 20 mg (in 40 mL saline). C: Mitomycin C: 20 mg (in 40 mL saline). D: No adjuvant treatment. TURBT alone. For A, B, and C: First instillation within 1 week of TURBT. Twice weekly X 4 weeks (Total: 8 doses)

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Niijima, 1983 [see also Akaza, 1987] RCT Medium	Duration: 5 years, maximum; Mean/Median NR Method: Cystoscopy and urinary cytology studies at 12-week intervals during the observation period.	Screened: NR Randomized: 707 (192 vs. 176 vs. 185 vs. 154) Post-randomization exclusions: NR Lost to followup: NR Total Analyzed: 575* Per Group Analyzed: (149 vs. 148 vs. 139 vs. 139) * Nonevaluated patients due to protocol violations, cessation of instillation, adverse effects, or other reasons. Not quantified overall or by group.	A vs. B vs. C vs. D Age (years), average: 62.3 vs. 62.9 vs. 62.9 vs. 62.9 Sex (male): 82.6% (123/149) vs. 75.7% (112/148) vs. 74.8% (104/139) vs. 74.1% (103/139) Race: NR Smoking status: NR Recurrent bladder cancer: 29.5% (44/149) vs. 31.1% (46/148) vs. 33.8% (47/139) vs. 35.3% (49/139) Stage: NR Grade: NR Functional Status: NR Size: < 1 cm: 40.3% (60/149) vs. 37.2% (55/148) vs. 43.9% (61/139) vs. 46.0% (64/139); 1-3 cm: 43.0% (64/149) vs. 52.7% (78/148) vs. 38.8% (54/139) vs. 48.2% (67/139); 3-5 cm: 14.8% (22/149) vs. 74.3% (11/148) vs. 12.2% (17/139) vs. 5.0% (7/139) Number of tumors: 1: 64.4% (96/149) vs. 63.5% (94/148) vs. 48.2% (67/139) vs. 60.4% (84/139); 2-4: 26.2% (39/149) vs. 25.7% (38/148) vs. 39.6% (55/139) vs. 30.2% (42/139); 5+: 80.5% (12/149) vs. 10.8% (16/148) vs. 11.5% (16/139) vs. 9.4% (13/139) * From Akaza, 1987. No data provided on stage or grade, but reported "the number of patients were approximately the same in all four groups" and "no significant differences were found" (no statistical testing reported).

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Niijima, 1983 [see also Akaza, 1987] RCT Medium	A vs. B vs. C vs. D Recurrence-free survival rate at 540 days*: 56.6% vs. 52.0% vs. 42.4% vs. 38.5%, generalized Wilcoxon test: A vs. D, $p < 0.05$ B vs. D, $p < 0.05$ C vs. D, $p < 0.10$ NR for other treatment group comparisons.	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Niijima, 1983 [see also Akaza, 1987] RCT Medium	NR	A vs. B vs. C (NR for group D) Pollakiuria: 33.8% vs. 28.3% vs. 33.1% Dysuria: 36.9% vs. 27.5% vs. 27.4% Hematuria: 20.0% vs. 11.6% vs. 9.7% Pyuria: 23.8% vs. 19.6% vs. 8.9%	Ministry of Health and Welfare of Japan	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Ojea, 2007 RCT Medium	Spain Multicenter 1995-1998	Intermediate risk with stages TaG2 and T1G1-2 superficial bladder tumors without carcinoma in situ	TaG1 tumors; concurrent or previous muscle-invasive disease; concurrent or previous tumor in upper urinary tract or prostatic urethra, intravesical treatment with MMC or BCG during previous 6 months; another malignancy except basal cell carcinoma of skin; previous pelvic irradiation	14-21 days after transurethral resection with histological confirmation of bladder cancer, patients received 6 weekly instillations then another 6 instillations one every 2 weeks; if a recurrence was diagnosed a further TURBT was performed and the treatment continued A. BCG 27 mg (Connaught strain) B. BCG 13.5 mg (Connaught strain) C. Mitomycin C: 30 mg
Oosterlinck, 2011 RCT Medium	Belgium, Sweden, Portugal, Italy, Turkey, the Netherlands, United Kingdom Multicenter 2001-2005	Primary, concurrent, or recurrent biopsy-proven CIS, no pretreatment with BCG and no intravesical treatment with chemotherapeutic agents within 3 months prior to TUR		15-28 days after TUR: A. MMC 40 mg in 50 mL saline weekly for six weeks followed by BCG (Tice strain 5 x 10^8 CFU in 50 mL saline) weekly for six weeks B. BCG (Tice strain 5 x 10^8 CFU in 50 mL saline) weekly for six weeks, then 3 weeks of rest, then 3 weeks of BCG Maintenance therapy for complete responders was three weekly maintenance instillations at 6, 12, 18, 24, 30 and 36 months; maintenance for group 1 was 1 MMC then 2 BCG instillations
Porena, 2010 RCT Medium	Italy Single center 2004-2006	Superficial TCC; high risk superficial bladder cancer according to EAU guidelines	Concomitant tumors, UTIs, altered function	14 days after second look TURBT patients received 6 weekly instillations of: A. BCG 5x10^8 CFU (Tice strain) in 50 mL of saline, maintenance therapy at 3,6,12,18,24,30, and 36 months B. Gemcitabine 2,000 mg in 50 ml; maintenance therapy at 3,6,12,18,24,30, and 36 months

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Ojea, 2007 RCT Medium	Duration, median: 57 months vs. 61 months vs. 53 months Method: Cystoscopy every 3 months during first year and then every 4 months for the next 4 years	Screened: NR Randomized: 430 Post-randomization exclusion: 33 patients did not complete treatment and were withdrawn from study but were followed for recurrence and other end points Loss to followup: NR Analyzed: 397 (125 vs.135 vs. 137)	Age (mean): 65 vs. 65 vs. 64 Male: 88% vs. 86% vs. 87% Race: NR Smoking: NR Stage: TaG2: 16% vs. 14% vs. 9% T1G1: 22% vs. 23% vs. 23%
Oosterlinck, 2011 RCT Medium	Duration: Median 4.7 years Method: Cystoscopy and cytology every 3 months for 3 years then every 6 months for 2 years and then yearly thereafter	Screened: NR Randomized: 96 (48 vs. 48) Post-randomization exclusions: 13 (7 vs. 6) Loss to followup: NR Analyzed: 83 (41 vs. 42)	Age (Median): 68 vs. 70 Male: 92% vs. 81% Race: NR Smoking: NR Stage: pTa: 17 (35%) vs. 11 (23%) pT1: 10 (21%) vs. 14 (29%) pTx: 0 vs. 1 (2%) Missing: 0 vs. 1 (2%) CIS: 5 (10%) vs. 4 (8%) No papillary lesions: 21 (44%) vs. 21 (44%)
Porena, 2010 RCT Medium	Duration: mean 44 months Method; In tumor free cases, urinary cytology and cystoscopy were performed every 3 months for the first 2 years then every 6 months for the following 3 years, then annually;	Screened: 74 Randomized: 64 (32 vs. 32) Post-randomization exclusions: None reported Lost to followup: None reported Analyzed for recurrence 64 (32 vs. 32)	Age (mean): 69 vs. 70 years Male: 88% vs. 81% Race: NR Smoking: NR Stage: Ta-T1 G3: 88% vs. 81% T1 G3 or CIS:13% vs. 19%

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Ojea, 2007 RCT Medium	Recurrence: 27% vs. 36% vs. 39% Progression: 10% vs. 13% vs. 9%	
Oosterlinck, 2011 RCT Medium	Complete response (ITT): 28 (58%) vs. 26 (54%) Complete response (per-protocol): 25 (61%) vs. 26 (62%) Progression (ITT): 1 (2%) vs. 1 (2%) Progression (per-protocol): 1 (2%) vs. 1 (2%) Recurrence (ITT): 23 (48%) vs. 26 (54%) Mortality: 7 (15%) vs. 11 (23%) Death not due to bladder cancer: 2 vs. 2	
Porena, 2010 RCT Medium	Recurrence: 28% vs. 53% (p=0.037) Interval before recurrence: 39 months vs. 26 months (p=0.042) Persistence of high-risk disease: 44% vs. 41% (p=NS) Progression: 0 vs. 0 (p=NS)	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Ojea, 2007 RCT Medium		Withdrawals due to AE: NR Local toxicity 65% vs. 64% vs. 30% Systemic toxicity: 11% vs. 11% vs. 5%	NR	
Oosterlinck, 2011 RCT Medium		Chemical cystitis: (16%) Dysuria: (24%) Fever: 9 No difference between groups Sepsis: 0 vs. 1 Withdrawal due to AE: 2 vs. 1	Grants from National Cancer Institute (USA), Fonds Cancer (FOCA) in Belgium and from Kyowa Hakko Ltd and Organon Teknika (now part of Merck)	
Porena, 2010 RCT Medium		Withdrawals due to AE: NR Severe local toxicity: 13% vs. 0% Moderate local toxicity: 0% vs. 9% Systemic toxicity: 6% vs. 0% Postpone/suspend treatment: 13% vs. 0%	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Rajala, 1999 [see also Rajala, 2002] RCT Medium	Finland Multicenter Study years: December 1991 - September 1994	Superficial bladder cancer; Primary only. Stages pTa or pT1; Grade G1, G2 or G3.	Recurrent bladder cancer; invasive disease (stage ≥ pT2); CIS.	A: Interferon-α-2b, 50 million units (in 100 mL physiological saline). Single intravesical instillation immediately after TUR, retained in bladder X 2 hours. B: Epirubicin, 100 mg (in 100 mL physiological saline). Single intravesical instillation immediately after TUR, retained in bladder X 2 hours. C: No adjuvant treatment. TURBT alone.
Rajala, 2002 [see also Rajala, 1999] RCT Medium	Finland Multicenter Study years: December 1991 - September 1994	Superficial bladder cancer; Primary only. Stages pTa or pT1; Grade G1, G2 or G3.	Recurrent bladder cancer; invasive disease (stage ≥ pT2); CIS.	A: Interferon-α-2b, 50 milliunits (in 100 mL physiological saline). Single intravesical instillation immediately after TUR, retained in bladder X 2 hours. B: Epirubicin, 100 mg (in 100 mL physiological saline). Single intravesical instillation immediately after TUR, retained in bladder X 2 hours. C: No adjuvant treatment. TURBT alone.

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Rajala, 1999 [see also Rajala, 2002] RCT Medium	Duration: Overall duration of study was 2 years. Mean/median followup durations NR. Method: Cystoscopy and urinary cytology every 3 months X 2 years.	Screened: 283 Randomized: 283 Postrandomization exclusions: 40 Lost to followup: NR Total Analyzed: 200 (66 vs. 68 vs. 66)	A vs. B vs. C Age: NR Race: NR Sex (male): 81.8% (54/66) vs. 70.6% (48/68) vs. 65.2 (43/66) Smoking status: NR Recurrent bladder cancer: None; All primary. Stage: pTa: 80.3% (53/66) vs. 79.4% (54/68) vs. 83.3% (55/66); pT1: 19.7% (13/66) vs. 20.6% (14/68) vs. 16.7% (11/66) Grade: G1: 43.9% (29/66) vs. 50.0% (34/68) vs. 57.6% (38/66); G2: 43.9% (29/66) vs. 26.8% (25/68) vs. 31.8% (21/66); G3: 12.1% (8/66) vs. 13.2% (9/68) vs. 10.6% (7/66) Functional Status: NR Multiplicity: Single tumor: 77.3% (51/66) vs. 76.5% (52/68) vs. 71.2% (47/66); Multiple tumors: 22.7% (15/66) vs. 23.5% (16/68) vs. 28.8% (19/66)
Rajala, 2002 [see also Rajala, 1999] RCT Medium	Duration: Median 72 months (range 6-102). Method: Cystoscopy and urinary cytology every 3 months X 1 year. Thereafter, followup cystoscopy according to the practice at each center.	Screened: 283 Randomized: 283 [see comment] Postrandomization exclusions: 40 [see comment] Lost to followup: NR Total Analyzed: 200 (66 vs. 68 vs. 66)	A vs. B vs. C Age, mean: 66.3 vs. 65.1 vs. 64.6 Race: NR Sex (male): 81.8% (54/66) vs. 70.6% (48/68) vs. 65.2 (43/66) Smoking status: NR Recurrent bladder cancer: None; All primary. Stage: pTa: 80.3% (53/66) vs. 79.4% (54/68) vs. 83.3% (55/66); pT1: 19.7% (13/66) vs. 20.6% (14/68) vs. 16.7% (11/66) Grade: G1: 43.9% (29/66) vs. 50.0% (34/68) vs. 57.6% (38/66); G2: 43.9% (29/66) vs. 26.8% (25/68) vs. 31.8% (21/66); G3: 12.1% (8/66) vs. 13.2% (9/68) vs. 10.6% (7/66) Functional Status: NR Multiplicity: Single tumor: 77.3% (51/66) vs. 76.5% (52/68) vs. 71.2% (47/66); Multiple tumors: 22.7% (15/66) vs. 23.5% (16/68) vs. 28.8% (19/66)

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Rajala, 1999 [see also Rajala, 2002] RCT Medium	A vs. B vs. C Recurrence: 63.7% (42/66) vs. 33.8% (23/68) vs. 60.6 (40/66)	A vs. B vs. C Recurrence by stage: Ta: 64.2% (34/53) vs. 35.2% (19/54) vs. 56.4% (31/55), p < 0.05 T1: 61.5% (8/13) vs. 28.6% (4/14) vs. 81.8% (9/11), p < 0.01 Recurrence by grade: G1: 51.7% (15/29) vs. 20.6% (7/34) vs. 52.6% (20/38), p < 0.01 G2: 70.0% (20/29) vs. 44.0% (11/25) vs. 66.7% (14/21), p=0.09 G3: 87.5% (7/8) vs. 55.6% (5/9) vs. 85.7% (6/7), p=NS Recurrence by tumor multiplicity: Single: 62.7% (32/51) vs. 26.9% (14/52) vs. 55.3% (26/47), p < 0.01 Multiple: 66.7% (10/15) vs. 56.3% (9/16) vs. 73.7% (14/19), p=NS
Rajala, 2002 [see also Rajala, 1999] RCT Medium	A vs. B vs. C Recurrence: 68.2% (45/66) vs. 45.6% (31/68) vs. 72.7 (48/66), p=0.002 Recurrence-free at 72 months: 31.4% vs. 50.8% vs. 23.7% Recurrence-free survival: B > A or C, p=0.002 Median time to first recurrence, months (95% CI): 12 (9-15) vs. [not attained] vs. 9 (5-13)	A vs. B vs. C Recurrence by stage: Ta: 67.9% (36/53) vs. 46.3% (25/54) vs. 70.9% (39/55) T1: 69.2% (9/13) vs. 42.9% (6/14) vs. 81.8% (9/11) Recurrence by grade: G1: 58.6% (17/29) vs. 38.2% (13/34) vs. 65.8% (25/38) G2: 72.4% (21/29) vs. 52.0% (13/25) vs. 81.0% (17/21) G3: 87.5% (7/8) vs. 55.6% (5/9) vs. 85.7% (6/7) Recurrence by tumor multiplicity: Single: 64.7% (33/51) vs. 42.3% (22/52) vs. 70.2% (33/47) 2 tumors: 70.0% (7/10) vs. 33.3% (3/9) vs. 83.3% (10/12) 3 tumors: 100% (3/3) vs. 80.0% (4/5) vs. 33.3% (1/3) ≥ 4 tumors: 100% (2/2) vs. 100% (2/2) vs. 100% (4/4)

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Rajala, 1999 [see also Rajala, 2002] RCT Medium	NR	A vs. B vs. C Fever: 6% (4/66) vs. 0% (0/68) vs. 1.5% (1/66) Dysuria: 1.5% (1/66) vs. 5.9% (4/68) vs. 0% (0/66)	NR	
Rajala, 2002 [see also Rajala, 1999] RCT Medium	NR	NR	Finnish Cancer Foundation; Pharmacia; Roche and Schering-Plough	Study is followup of Rajala, 1999. Description of followup cystoscopy internal after year 1 is not consistent with Rajala, 1999. Number randomized and postrandomization exclusion taken from Rajala, 1999.

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Rintala, 1991 RCT Medium Jarvinen, 2009 FinnBladder I (20 year followup)	Finland Multicenter 1984-1987	Frequently recurrent TaT1 tumors and/or CISTa-T1 cancers with a minimum of two episodes of recurrence during the preceding 1.5 years	Urethral or prostatic involvement	2 weeks after TURBT 5 weekly instillations then monthly instillations up to 2 years of: A. MMC dose and volume adjust for bladder capacity but averaged 30-40 mg in 150-200 mL phosphate buffer B. BCG 75 mg (Pasteur strain F)
Rintala, 1995 RCT Medium Jarvinen, 2012 FinnBladder II with 17 year followup of CIS	Finland Multicenter 1987-1992	Primary, secondary, or concomitant CIS	Ta or T1	MMC perioperatively then 4 weekly instillations of MMC then randomized to: A. MMC monthly monotherapy B. MMC alternated with BCG monthly (Pasteur strain F 75 mg in 50 mL saline) MMC dose and volume of phosphate buffer were adjusted according to bladder capacity

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Rintala, 1991 RCT Medium Jarvinen, 2009 FinnBladder I (20 year followup)	Duration; mean 28 months; 20 year followup of TaT1: median followup overall 8.5 years; median followup of 17 patients still alive 19.4 years Method: Cytology and cystoscopy every 3 months for first 2 years then between 6 and 12 months thereafter according to clinician judgment	Screened: NR Randomized: 109 (7 patients randomized to BCG but tested PPD-negative were transferred, according to protocol to the MMC group; 23 patients with persistent disease at 6 months were transferred to the second-line instillation (at least 8 MMC patients and 10 BCG patients were transferred) Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: Unclear but at least 85 (41 vs. 44) <u>20 year followup:</u> Analyzed: 89 patients with TaT1 disease without CIS (45 vs. 44)	Age (mean) 67 vs. 68 Male: 71% vs. 76% Race: NR Smoking: NR Stage: TIS: 12 (21%) vs. 6 (12%) Ta-T1: 46 (79%) vs. 45 (88%) Grade: Grade 1: 33 (57%) vs. 35 (69%) Grade 2: 19 (33%) vs. 12 (24%) Grade 3: 6 (10%) vs. 4 (8%) 20 year followup of TaT1: Age (mean) 67 vs. 68 Male: 67% vs. 77% Stage: Ta: 29 (64%) vs. 31 (70%) T1: 4 (9%) vs. 3 (7%) Grade: Grade 1: 13 (29%) vs. 16 (36%) Grade 2: 19 (42%) vs. 17 (39%) Grade 3: 1 (2%) vs. 1 (2%)
Rintala, 1995 RCT Medium Jarvinen, 2012 FinnBladder II with 17 year followup of CIS	Duration: mean followup 33 months; 17 year followup of CIS: median followup 7.2 years Method: Cytology and cystoscopy every 3 months for first 2 years and then annually or according to clinician's decision	Screened: NR Randomized (subgroup): 68 (40 vs. 28) Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 68 (40 vs. 28)	Age (mean): 68 vs. 66 Male: 78% vs. 86% Race: NR Smoking: NR Primary CIS: 15 (38%) vs. 15 (54%) Secondary CIS: 15 (38%) vs. 2 (7%) Concomitant CIS: 10 (25%) vs. 11 (39%)

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Rintala, 1991 RCT Medium Jarvinen, 2009 FinnBladder I (20 year followup)	TIS Complete response: 12 (58%) vs. 10 (40%) TaT1 Complete response at 6 months: 70% vs. 88% TaT1 Complete response at 12 months: 67% vs. 90% TaT1 Complete response at 2 years: 79% vs. 97% <u>20 year followup of TaT1</u>: Recurrence: 36 (80%) vs. 26 (59%) Progression: 10 (22%) vs. 4 (9%) Died from bladder cancer: 9 (20%) vs. 4 (9%) Overall mortality: 80% vs. 82%	
Rintala, 1995 RCT Medium Jarvinen, 2012 FinnBladder II with 17 year followup of CIS	Complete response 3 months: 45% vs. 71%, p=0.047 Complete response 6 months: 50% vs. 75%, p=0.047 Complete response 12 months: 59% vs. 82%, 0.062 Complete response 24 months: 47% vs. 74%, p=0.041 Progression: 4 vs. 2 <u>17 year followup of CIS:</u> Recurrence: 35 (88%) vs. 19 (68%), p=0.06 Progression: 14 (35%) vs. 8 (28%), p=0.59 Died from bladder carcinoma: 12 (30%) vs. 8 (29%) Overall mortality: 30 (75%) vs. 20(71%)	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Rintala, 1991 RCT Medium Jarvinen, 2009 FinnBladder I (20 year followup)		Instillations discontinued due to side effects: 2 (9%) vs. 9 (20%)	Finnish Cancer Foundation, Academy of Finland Paolo Foundation, Research and Science Foundation of Farmos <u>20 year followup of TaT1:</u> Funding/support and role of the sponsor: None	
Rintala, 1995 RCT Medium Jarvinen, 2012 FinnBladder II with 17 year followup of CIS		Chemical cystitis: 1 vs. 0 Bladder contraction: 1 vs. 0	Finnish Cancer Foundation, Academy of Finland and Paulo Foundation	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Rintala, 1996 RCT Medium FinnBladder II	Finland Multicenter 1987-1992	recurrent stage Ta or T1 papillary transitional cell carcinoma		MMC perioperatively then 4 weekly instillations of MMC then randomized to: A. MMC monthly monotherapy B. MMC alternated with BCG monthly (Pasteur strain F 75 mg in 50 mL saline) MMC dose and volume of phosphate buffer were adjusted according to bladder capacity
Sekine, 2001 RCT Medium	Japan Single center 1988-1999	Tis with or without T1 bladder cancer	NR	A: BCG (type of BCG, dose, and number and timing of instillations NR) B: MMC, 20 mg and doxorubicin, 30 mg sequential therapy (number and timing of instillations NR)

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Rintala, 1996 RCT Medium FinnBladder II	Duration: mean followup 34 months but focus is on 2-year instillation period Method; Cytology and cystoscopy every 3 months for first 2 years and then annually or according to clinician's decision	Screened: NR Randomized (subgroup): 188 Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 182 (90 vs. 92)	Age (mean): 69 vs. 68 Male: 76% vs. 75% Race: NR Smoking: NR Grade: Grade 1: 49 (53%) vs. 55 (58%) Grade 2: 40 (43%) vs. 39 (41%) Grade 3: 4 (4%) vs. 1 (1%)
Sekine, 2001 RCT Medium	Duration: Mean 47 months (range 3 to 143 months) Method: Cystoscopy and urine cytology every 3 months and urography every 12 months	Screened: NR Randomized: 42 (21 vs. 21) Postrandomziation exclusions NR Lost to followup: NR Total analyzed: 42 (21 vs. 21)	Age: NR Male: 81% vs. 81% Race: NR Smoking status: NR pTis: All With pT1 or pT0 tumor: 67% vs. 43% G2: 67% vs. 62% Functional status: NR

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Rintala, 1996 RCT Medium FinnBladder II	Patents with recurrence: 58 (64%) vs. 57 (62%) Median time to first recurrence: 12.4 months vs. 6.9 months Median time to treatment failure: 30 months vs. 28 months Progression based on muscle infiltration or metastases: 3 vs. 3	
Sekine, 2001 RCT Medium	A vs. B Compete response to initial therapy (no residual CIS and negative urine cytology for at least 4 weeks): 86% (18/21) vs. 81% (17/21), RR 1.06 (95% CI 0.81 to 1.39) within 2 months of completion of therapy Complete response, including crossover therapy: 90% (19/21) vs. 100% (21/21), RR 0.90 (95% CI 0.79 to 1.04) Recurrence after complete response: 11% (2/21) vs. 52% (11/21), RR 0.18 (95% CI 0.05 to 0.72) Progression: 14% (3/21) vs. 10% (2/21), RR 1.50 (95% CI 0.28 to 8.08) Bladder cancer mortality: 10% (2/19) vs. 4.8% (1/21), RR 2.21 (95% CI 0.22 to 22.5)	G2: 93% (13/14) vs. 85% (11/13), RR 1.10 (95% CI 0.83 to 1.44) G3: 71% (5/7) vs. 75% (6/8), RR 0.95 (0.51 to 1.76)

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Rintala, 1996 RCT Medium FinnBladder II		Discontinued instillations due to side effects: 6 vs. 6	Finnish Cancer Foundation, Academy of Finland and Paulo Foundation	
Sekine, 2001 RCT Medium	NR	NR	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Shuin, 1994 RCT High	Japan Multicenter Study years: April 1990 - December 1993	Recurrent superficial bladder cancer (recurrent only). Stages Ta or T1; Grade G1 or G2.	None reported	A: Epirubicin, 30 mg (in 40 mL saline), retained in bladder for at least 2 hours. Timing of first instillation not specified. instillations every 2 weeks X 3 months, then every 4 weeks for remainder of 1 year. B: Doxorubicin, 30 mg (in 40 mL saline), retained in bladder for at least 2 hours. Timing of first instillation not specified. instillations every 2 weeks X 3 months, then every 4 weeks for remainder of 1 year.
Tsushima, 1987 RCT Medium	Japan Number sites: Unclear (multicenter) Study years: 1981-end date NR	Superficial bladder tumors (primary or recurrent). Stage: Ta or T1;	Grade 3 tumor; Receipt of preoperative intravesical chemotherapy.	A: Doxorubicin, 50 mg (in 100 mL physiological saline). B: MMC, 30 mg (in 100 mL physiological saline). C: No adjuvant treatment. TURBT or TUC alone. For A and B: Total 58 installations: Six times in first 2 weeks after TURBT, then on 2 consecutive days every 4 weeks X 2 years. If recurrence, repeat TURBT or TUC and resume 2 consecutive days every 4 weeks until 2 years after initial treatment.

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Shuin, 1994 RCT High	Duration: 43 months Method: NR	Screened: NR Randomized: 68 (33 vs. 35) Postrandomization exclusions: 3 (1 vs. 2) Lost to followup: NR Total analyzed: 65 (32 vs. 33)	A vs. B Age: < 40 years: 6% vs. 3% 40-49 years: 3% vs. 9% 50-59 years: 9% vs. 24% 60-69 years: 25% vs. 21% ≥ 70: 56% vs. 42%, chi-square test for age, p=NS Race: NR Sex (male): 81% (26/32) vs. 82% (27/33), p=NS Smoking status: NR Recurrent bladder cancer: 100% (recurrent only) Stage Ta: 69% (22/32) vs. 64% (21/33) Stage T1: 25% (8/32) vs. 27% (9/33) Stage unknown: 6% (2/32) vs. 9% (3/33), chi-square test for stage, p=NS Grade G1: 50% (16/32) vs. 39% (13/33) Grade G2: 59% (19/32) vs. 61% (20/33), chi-square test for grade, p=NS Functional status: NR
Tsushima, 1987 RCT Medium	Duration: 15 months vs. 21 months vs. 13 months Method: Cystoscopy every 3 months.	Screened: NR Randomized: 134 Postrandomization exclusions: 2 Lost to followup: 20 Total Analyzed: 103 Per Group Analyzed (A vs. B vs. C): 33 vs. 37 vs. 33	A vs. B vs. C Age (average), years: 66.1 (not specified by group); age range (years): 28-89 Male: 84.8% vs. 81.1% vs. 81.8% Race: NR Smoking: NR Recurrent bladder cancer: 39.4% vs. 16.2% vs. 33.3% Stage: All Ta or T1, NR by group. Grade: G1: 27.3% vs. 35.1% vs. 27.3%; G2: 63.6% vs. 64.9% 66.7%; Other: 9.1% vs. 0.0% vs. 6.1% Functional Status: NR Number: Solitary: 51.5% vs. 54.1% vs. 45.5%; Multiple: 48.5% vs. 45.9% vs. 54.5% Papillary: 84.9% vs. 94.6% vs. 84.9% Nonpapillary: 9.1% vs. 5.4% vs. 9.1%

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Shuin, 1994 RCT High	A vs. B Recurrence: 25% (8/32) vs. 27% (9/33), chi-square test, p=NS Recurrence-free period, mean (range): 9.7 months (4 to 17) vs. 8.5 months (3 to 16), "no significant difference" (type of statistical testing and p-value not specified). Progression: "There has been no case of grade G3 or invasive cancer in either group."	NR
Tsushima, 1987 RCT Medium	A vs. B vs. C Recurrence: 18.2% (6/33) vs. 35.1% (13/37) vs. 63.6% (21/33) Recurrence rate:19.7% vs. 23.9% vs. 70.0% (1 year); 26.4% vs. 36.6% vs. 77.5% (2 years); A vs. C, generalized Wilcoxon test, p < 0.001; B vs. C, generalized Wilcoxon test, p < 0.01	A vs. B vs. C Solitary tumor: Recurrence: 11.8% (2/17) vs. 25.0% (5/20) vs. 40.0% (6/15) Recurrence rate:18.0% vs. 5.0% vs. 41.7% (1 year); 18.0% vs. 31.0% vs. 61.2% (2 years); A vs. C, generalized Wilcoxon test, p=NS; B vs. C, generalized Wilcoxon test, p=NS Multiple tumors: Recurrence: 25.0% (4/16) vs. 47.1% (8/17) vs. 83.3% (15/18) Recurrence rate: 21.7% vs. 43.7% vs. 92.6% (1 year); 31.5% vs. 43.7% vs. 92.6% (2 years); A vs. C, generalized Wilcoxon test, p < 0.001; B vs. C, generalized Wilcoxon test, p < 0.05

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Shuin, 1994 RCT High	NR	A vs. B Pollakisuria: 16% (5/32) vs. 6% (2/33), chi-square test, p=NS Dysuria: 16% (5/32) vs. 6% (2/33), chi-square test, p=NS Hematuria: 13% (4/32) vs. 6% (2/33), chi-square test, p=NS	NR	
Tsushima, 1987 RCT Medium	NR	A vs. B (NR for group C) Bladder irritability: 7.1% (3/42) vs. 8.3% (4/48) Renal dysfunction: 2.4% (1/42) vs. 0.0% (0/48) Itching: 2.4% (1/42) vs. 2.1% (1/48) Macrohematuria: 0.0% (0/42) vs. 2.1% (1/48) Total: 11.9% (5/42) vs. 10.4% (5/48)	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
van der Meijden, 2001 RCT Medium Sylvester, 2010 (9 year followup)	Europe Multicenter 1992-1997	Intermediate or high risk superficial bladder tumors; single or multiple, primary or recurrent, completely resectable stages Ta-T1, G1 to G3, biopsy proven TCC	Primary solitary tumor, T2 or greater, CIS, age>85, previously treated with doxorubicin, epirubicin, or BCG, intravesical treatment during previous 3 months	A. Epirubicin 50 mg in 50 mL saline weekly for 6 consecutive weeks starting within 24 hours of transurethral resection B. BCG 5x10^8 CFU (Tice strain) for 6 consecutive weeks starting 7-15 days after transurethral resection C. BCG + isoniazid: BCG 5x10^8 CFU (Tice) for 6 consecutive weeks starting 7-15 days after transurethral resection plus 300 mg INH orally the day before, same day and day after instillation Median duration of treatment: 12 months vs. 18 months vs. 12 months
Witjes, 1993 RCT Medium The Dutch Cooperative Trial Witjes, 1996	The Netherlands Multicenter 1987-1990	Histologically proven papillary pTa-pT1 transitional cell transitional cell carcinoma of the bladder with or without CIS	Previous local or systemic cancer therapy or radiotherapy	A. MMC 30mg in 50mL saline once a week for 4 weeks and thereafter once a month for 5 months. If a superficial recurrence or persistent CIS after 6 months, 3 additional monthly instillations given B. BCG-Tice C. BCG RIVM BCG 5X108 bacilli in 50mL saline, administered once a week for 6 weeks. At the time of first superficial recurrence or persistent CIS at 3 or 6 months, a second 6 week course with BCG instillations was given after complete TURBT or biopsy.

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
van der Meijden, 2001 RCT Medium Sylvester, 2010 (9 year followup)	Duration, median: 4 years (initial report); 9 years (subsequent report) Method: Cystoscopy and urine cytology every 3 months during first 3 years and then every 6 months	Screened: NR Randomized: 957 Post-randomization exclusions: 120 (32 had no tumor, 31 had muscle invasive tumor, 37 had CIS, 20 ineligible for other reasons) Loss to followup: 169 prematurely stopped treatment due to concomitant disease, refusal or loss to followup. In another 137 patients further followup data were required Analyzed: 837 (279 vs. 281 vs. 277)	Age (mean): 67 vs. 66 vs. 66 Male: 79% vs. 75% vs. 78% Race: NR Smoking: NR Stage: Ta: 63% vs. 60% vs. 63% T1: 33% vs. 37% vs. 35% Grade: Grade 1: 38% vs. 37% vs. 36% Grade 2: 48% vs. 47% vs. 49% Grade 3: 11% vs. 13% vs. 12%
Witjes, 1993 RCT Medium The Dutch Cooperative Trial Witjes, 1996	Duration, median: 32 months Method: Cystoscopy every 3 months for 2 years, every 4 months in years 3 and 4 and every 6 months thereafter	Screened: NR Randomized: 469 (156 vs. 154 vs. 159) Post-randomization exclusions: 17 (ineligible) Loss to followup: None reported although 15 patients excluded for "different reasons" Analyzed: 437 (148 vs. 140 vs. 149)	Age (mean): 66 vs. 66 vs. 66 Male: 80% vs. 86% vs. 87% Race: NR Smoking status: NR G1: 24 (16%) vs. 28 (20%) vs. 32 (22%) pTaG2: 55 (37%) vs. 48 (34%) vs. 54 (36%) G3: 4 (4%) vs. 5 (4%) vs. 4 (3%) CIS: 12 (8%) vs. 23 (16%) vs. 15 (10%)

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
van der Meijden, 2001 RCT Medium Sylvester, 2010 (9 year followup)	Recurrence at 3 years: 51% vs. 35% vs. 36% Time to first recurrence at 3.5 years: BCG with or without INH significantly prolonged time to first recurrence vs. Epirubicin Progression to muscle invasive disease: 7% (19/279) vs. 3% (9/281) vs. 5% (15/277) Death at 3.9 years: 19% vs. 15% vs. 19% Death due to bladder cancer: 4% vs. 2% vs. 3% 9 year followup: Recurrence: 53% vs. 37% vs. 40% Progression: 9% vs. 7% vs. 8% Death: 38% vs. 30% vs. 32% Death due to bladder cancer: 7% vs. 3% vs. 4% With BCG arms pooled (epirubicin vs. BCG) hazard ratios (combines intermediate and high risk): Recurrence: 0.62 (0.50 to 0.76) Progression: 0.84 (0.51 to 1.39) Death: 0.76 (0.59 to 0.96) Death due to bladder cancer: 0.47 (0.25 to 0.89)	
Witjes, 1993 RCT Medium The Dutch Cooperative Trial Witjes, 1996	% Disease-free, all papillary tumors 1 year: 76% vs. 68% vs. 69% 2 year: 65% vs. 54% vs. 62% % Disease-free, grade 3 papillary tumors 1 year: 79% vs. 55% vs. 64% 2 year: 0 vs. 46% vs. 50% Complete response in patients with CIS (N=50) 5 (42%) vs. 16 (70%) vs. 7 (47%), p=0.20 5 year followup: % Disease-free (all papillary tumors): 57% vs. 36% vs. 54% Response rate (CIS): 8 (67%) vs.17 (74%) vs. 9 (60%) Recurrence: 58/136 (43%) vs. 75/117 (64%) vs. 62/134 (46%)	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
van der Meijden, 2001 RCT Medium Sylvester, 2010 (9 year followup)		Withdrawals due to AE: 16 (6%) vs. 31 (12%) vs. 44 (17%) Bacterial cystitis: 26% vs. 26% vs. 23% Chemical cystitis 31% vs. 42% vs. 45% Macroscopic hematuria: 17% vs. 35% vs. 30%	National Cancer Institute	
Witjes, 1993 RCT Medium The Dutch Cooperative Trial Witjes, 1996		Drug-induced cystitis: 26 (18%) vs. 42 (30%) vs. 48 (32%), p=0.009 Systemic side-effects: 6 (4%) vs. 38 (27%) vs. 27 (18%) Sepsis: 0 vs. 1 vs. 0 Withdrawals due to AE: 14 (total) Intercurrent death=10 (total)	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Witjes, 1998 RCT Medium	The Netherlands Multicenter 1991-1993	Histologically proved primary multiple (more than 2 tumors) or recurrent multiple (2 or more tumors) stage pTa or pT1 transitional cell carcinoma, solitary or multiple grade III tumors and primary or concomitant CIS	Previous radiotherapy, intravesical or systemic chemotherapy within 3 months of the study	A. MMC 40 mg in 50 mL saline weekly for 4 weeks followed by BCG (Tice strain) 5 x 10^8 in 50 mL saline weekly for 6 weeks B. MMC 40 mg in 50 mL saline weekly for 10 weeks
Zincke, 1985 RCT Medium	USA Single center Study years NR	Transitional cell cancer, any grade, Ta or Tis	Previous systemic or intravesical treatment with chemotherapy, previous pelvic radiotherapy, limited bladder capacity, urinary incontinence, second malignancy	A. MMC 40 mg in 40 mL distilled water B. Thiotepa 60 mg in 60 mL distilled water Biweekly treatment for a total of 5 treatments. If no tumor was present at the first 3-month assessment the treatment interval was lengthened to every 4 weeks for 6 months. If there still was no recurrence, there was no further treatment. If tumor recurred during the primary treatment, patients were given the opposite drug.

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Witjes, 1998 RCT Medium	Duration: Median 32 months (range 2-65 months) Method: cystoscopy and cytology every 3 months until recurrence	Screened: NR Randomized: 182 (90 vs. 92) Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 182 (90 vs. 92)	Age: NR Male: NR Race: NR Smoking: NR Stage: pTa: 43 (48%) vs. 36 (39%) pT1: 36 (40%) vs. 47 (51%) Grade: Grade 1: 19 (21%) vs. 16 (17%) Grade 2: 42 (47%) vs. 44 (48%) Grade 3: 18 (20%) vs. 24 (26%) CIS: 29 (32%) vs. 36 (39%)
Zincke, 1985 RCT Medium	Duration: Mean 16.1 months overall Method: Cystoscopy and cytology every 3 months for 1 year, then every 6 months for 1 year, and yearly thereafter	Screened: NR Randomized: 51 vs. 54 Postrandomization exclusions: 9 vs. 13 Lost to followup: None reported Analyzed: 42 vs. 41	Age (mean): 64 Male: 71/83 Race: NR Smoking: NR Tumor grade: G1: 16/29 vs. 13/29 G2: 23/47 vs. 24/47 G3, G4: 3/7 vs. 4/7

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Witjes, 1998 RCT Medium	Recurrence: 35 (39%) vs. 42 (46%), p=0.36 Progression: 5 (6%) vs. 4 (4%), p=0.70 Mortality: 21 (23%) vs. 14 (15%), p=0.16 Disease-related mortality: 5 vs. 8	
Zincke, 1985 RCT Medium	Recurrence: 14/42 (33%) vs. 12/41 (29%), RR 1.14 (95% CI 0.60 to 2.16) Percent free of recurrence at 1 year: 67% vs. 78%	Recurrence numbers NR, but reported no difference according to tumor grades

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Witjes, 1998 RCT Medium		Chemical cystitis: 37 (41%) vs. 29 (32%) Fever (occurrences): 11 vs. 3 Patients without side effects: 29 (32%) vs. 38 (41%)	NR	
Zincke, 1985 RCT Medium	A vs. B, log rank p-value Recurrence, months from diagnosis to treatment: <1 month: 3/18 vs. 1/20, p=0.3 ≥ 1 month: 11/24 vs. 11/21, p=0.8 Recurrence, age: <65 years: 7/20 vs. 2/21, p=0.04 ≥65 years: 7/22 vs. 10/20, 0.2	Myelosuppression: 4 vs. 3 Cystitis: 4 vs. 1 Rash and contact dermatitis: 2 vs. 0	NR	

Please see Appendix C. Included Studies for full study references.

Table E4. Key Question 3c: Trials of treatment dose and duration

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Akaza, 1987 RCT (Also Akaza 1992) Study Two Medium	Japan Number sites: Unclear Study years: July 1982 1985	Histologically proven superficial bladder cancer (primary only). Stages Ta or T1; Grade G1 or G2. Absence of tumor after TURBT.	Tis superficial cancer; other therapies, such as chemotherapy, immunotherapy, and/or radiotherapy within 3 or 4 weeks before initiation of study; severe cardiovascular, renal, hepatic or hematopoietic disturbances; simultaneous presence of another cancer.	A: Doxorubicin, 30 mg (in 30 mL saline). B: Doxorubicin, 20 mg (in 40 mL saline). C: Mitomycin C: 20 mg (in 40 mL saline). D: No adjuvant treatment. TURBT alone. For A, B, and C: First instillation within 1 week of TURBT. Once weekly X 2 weeks then once every 2 weeks X 14 week, ther once monthly X 8 months, then once every 3 month X 1 year (Total: 21 doses over 2 years)
Ali-El-Dein, 1997 (British J Urol) RCT Medium	Egypt Single Center Study years: January 1992 - February 1996	Transitional cell carcinoma (TCC) of the bladder (primary or recurrent). G2 or G3, multiple recurrent, pT1, aneuploidy, or ≥3 cm; pTa if multiple, large (≥ 3 cm), recurrent and/or grade 2-3 tumors.	Prior pelvic radiotherapy or chemotherapy; Abnormal cardiac, hematologic, renal, or bladder function; CIS.	A: Epirubicin, 50 mg (in 50 mL normal saline); Single instillation immediately after TURBT. Retained intravesically for 2 hours. B: Epirubicin, 50 mg (in 50 mL normal saline); Initial instillation 1 - 2 weeks after TURBT. Retained intravesically for 2 hours; Then, instillations once a week X 7, then once monthly X 10 to complete 1 year of treatment. C: No adjuvant treatment. TURBT alone.

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Akaza, 1987 RCT (Also Akaza 1992) Study Two Medium	Duration: 3.5 years, maximum; Mean, median NR Method: Cystoscopy and urinary cytology studies at 12-week intervals throughout study period	Screened: NR Randomized: 665 (170 vs. 175 vs. 164 vs. 156) Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 607 Per Group Analyzed: (151 vs. 158 vs. 150 vs. 148)	A vs. B vs. C vs. D Age (years), average: 63.1 vs. 62.1 vs. 62.3 vs. 62.0 Male: 80.1% vs. 82.3% vs. 82.0% vs. 81.1% Race: NR Smoking status: NR Recurrent bladder cancer: 19.7% vs. 17.7% vs. 18.0% vs. 18.9% Stage: NR Grade: NR Functional Status: NR Size: >3 cm: 14.6% vs. 11.4% vs. 11.3% vs. 6.8% Proportion with single tumor: 64.2% vs. 55.7% vs. 55.3% vs. 66.9%
Ali-El-Dein, 1997 (British J Urol) RCT Medium	Duration, mean: 32.2 months Method: Cysto-urethroscopy, cytology, and DNA flow cytometry 8 weeks after resection, then every 3 months during first 2 years, and every 6 months thereafter during the next 2 years.	Screened: 181 Randomized: 179 Postrandomization exclusions: none Lost to followup: NR Total Analyzed: 168 Per Group Analyzed (A vs. B vs. C): 55 vs. 59 vs. 54	A vs. B vs. C Age, mean years: 52.1 vs. 55 vs. 53.4 Race: NR Sex (male): 67.3% vs. 74.6% vs. 70.4% Smoking status: NR Recurrent bladder cancer: 47.2% vs. 52.5% vs. 44.4%, p = 0.5 Stage: pTa: 16.3% vs. 25.4% vs. 18.5%; pT1: 83.7% vs. 74.6% vs. 81.5%, p=0.4. Grade: G1: 10.9% vs. 18.6% vs. 25.9%; G2: 54.5% vs. 55.9% vs. 53.7%; G3: 34.5% vs. 25.4% vs. 20.4%, p=0.2. Functional Status: NR Size: $\geq$ 3 cm: 35% (19/55) vs. 29% (17/59) vs. 37% (20/54)

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Akaza, 1987 RCT (Also Akaza 1992) Study Two Medium	A vs. B vs. C vs. D Recurrence-free survival rate at 1 year: 74.8% vs. 75.0 vs. 76.3% vs. 66.7% Recurrence-free survival rate at 2 years: 62.3% vs. 59.1 vs. 62.3% vs. 51.8% Recurrence-free survival at 1260 days, generalized Wilcoxon test: A > D, p < 0.05 B > D, p < 0.05 C > D, p < 0.05 Long-term (median, 6.6 years) followup in subgroup of 158 patients Recurrence/year (number of recurrences/total observation period: 0.473 vs. 0.512 vs. 0.472 vs. 0.510 Progression (in stage, grade, or both): 43.2% (19/44) vs. 31.0% (13/42) vs. 26.8% (11/41) vs. 38.7% (12/31); RR 1.40 (95% CI 0.79 to 2.45) for A vs. B	NR
Ali-El-Dein, 1997 (British J Urol) RCT Medium	A vs. B Recurrence: 23.6% (13/55) vs. 25.4% (15/59), p=0.8. Mean interval to first recurrence, months: 16 vs. 18 Recurrence rate per 100 patient-months: 0.79 vs. 0.84 Progression: 5.5% (3/55) vs. 3.4% (2/59)	A vs. B Recurrence Ta: 0.0% (0/9) vs. 0.0% (0/15) T1: 28.3% (13/46) vs. 34.1% (15/44) G1: 0.0% (0/6) vs. 27.3% (3/11) G2: 10.0% (3/30) vs. 27.3% (9/33) G3: 52.6% (10/19) vs. 20.0% (3/15), RR 2.63 (95% CI 0.88 to 7.89) $\geq$ 3 cm: 21.1% (4/19) vs. 41.2% (7/17), RR 0.51 (95% CI 0.18 to 1.45)

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Akaza, 1987 RCT (Also Akaza 1992) Study Two Medium	NR	A vs. B vs. C (NR for group D) Pollakiuria: 16% vs. 18.7% vs. 23.8% Dysuria: 25.6% vs. 25.2% vs. 27.0% Hematuria: 13.6% vs. 7.3% vs. 11.1% Pyuria: 10.4% vs. 10.6% vs. 19.8% "No significant systemic side effects"	Ministry of Health and Welfare of Japan	
Ali-El-Dein, 1997 (British J Urol) RCT Medium	NR	A vs. B Any adverse event: 21.8% (12/55) vs. 25.4% (15/59), p=0.8. Mild toxicity: 75.0% (9/12) vs. 66.7% (10/15) , p=0.8. Severe toxicity (i.e., requiring permanent or temporary discontinuation of treatment): 25.0% (3/12) vs. 33.3% (5/15) , p=0.7. Contracted bladder: 0.0% (0/12) vs. 6.7% (1/15) Hematuria: 16.7% (2/12) vs. 20.0% (3/15) UTI: 8.3% (1/12) vs. 6.7% (1/15) No patients with systemic toxicity.	No financial support received	Note: Possible overlap of some study subjects (group B) with those in Ali-El-Dein, 1997 (J Urol)

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Au, 2001 RCT Medium	USA, Europe, and Canada Multicenter 1992-2000	Transitional cell carcinoma of bladder at high risk for recurrence based on 1) two or more episodes of Ta, Tis, or T1 cancers, 2) multifocal (≥3 papillary tumors or Tis involving ≥25% of bladder surface and/or in two or more biopsy sites), 3) tumors >5 cm, G3, or DNA aneuploidy	Treatment with mitomycin C within 56 weeks, prior T2-T4 bladder cancer, concurrent cancer, pregnant, WBC <4000/mm3, platelets <100,000/mm3, Cr ≥2.0 mg/dL, Karnofsky performance score <50	A: Mitomycin C 40 mg/20 mL sterile water, 6 instillations (once weekly for 6 weeks), optimized by instruction to refrain from fluids for 8 hour prior to and during instillations, oral doses of 1.3 g sodium bicarbonate the night before, Foley to empty bladder prior to instillation for post void residual <10 ml B: Mitomycin C 20 mg/20 mL sterile water, 6 instillations (once weekly for 6 weeks), without additional optimization measures

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Au, 2001 RCT Medium	Duration: 5 years Method: Cystoscopy and cytology every 3 months for 2 years, every 6 months for years 3-5, and once yearly thereafter	Screened: NR Randomized: 230 (119 vs. 111) Postrandomization exclusions: 29 (17 vs. 12) Loss to followup: 2 (1 vs. 1) Analyzed: 201 (102 vs. 99)	Age (median): 68 vs. 65 Male: 74% vs. 75% White race: 93% vs. 95% Smoking status: NR Ta: 64% vs. 68% T1: 28% vs. 22% CIS: 8.4% vs. 9.9% G1/2: 75% vs. 75% G3: 25% vs. 25% Unifocal: 44% vs. 43% Primary: 30% vs. 31% Recurrent: 70% vs. 69% Prior BCG: 26% vs. 28%

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Au, 2001 RCT Medium	Percent recurrence-free at 5 years: 41% vs. 25% Recurrences: 51% (61/119) vs. 66% (73/111), RR 0.78 (95% CI 0.63 to 0.97) Time to recurrence (median, months): 29 vs. 12 (p=0.005)	Percent recurrence-free at 5 years Multifocal: 35% vs. 19% Unifocal: 50% vs. 32% Ta: 41% vs. 25% T1: 41% vs. 23% Papillary: 41% vs. 24% Recurrent: 37% vs. 24% Grade I/II: 38% vs. 23% No prior intravesical treatment: 30% vs. 27% Prior intravesical treatment: 44% vs. 23% Recurrences Multifocal: 58% (39/67) vs. 70% (44/63) Unifocal: 42% (22/52) vs. 60% (29/48) Ta: 51% (39/76) vs. 67% (50/75) T1: 52% (17/33) vs. 64% (16/25) Papillary: 51%(56/109) vs. 66% (66/100) CIS: 50% (5/10) vs. 64% (7/11) Recurrent: 57% (47/83) vs. 68% (52/77) Primary: 39% (14/36) vs. 62% (21/34) G3: 50% (15/30) vs. 61% (17/28) G1/2: 52% (46/89) vs. 67% (56/83) No prior intravesical treatment: 65% (26/40) vs. 68% (25/37) Prior intravesical treatment: 49% (21/43) vs. 68% (27/40) Time to recurrence (median, months) Multifocal: 16 vs. 7.9 (p=0.008) Unifocal: 44 vs. 17 (p=0.12) Ta: 30 vs. 13 (p=0.01) T1: 13 vs. 7.1 (p=0.29) Papillary: 29 vs. 12 (p=0.008) CIS: 34 vs. 14 (p=0.30) Recurrent: 18 vs. 9.5 (p=0.04) Primary: 34 vs. 14 (p=0.03) G3: 34 vs. 13 (p=0.31) G1/2: 29 vs. 12 (p=0.008) No prior intravesical treatment: 12 vs. 9.5 (p=0.50) Prior intravesical treatment: 29 vs. 7.1 (p=0.04)

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Au, 2001 RCT Medium		Discontinuation of treatment due to adverse events: 1.8% (2/111) vs. 1.9% (2/106) Dysuria: 33% (37/111) vs. 18% (19/106), RR 1.86 (95% CI 1.15 to 3.02) Cystitis: 23% (26/111) vs. 16% (17/106), RR 1.46 (95% CI 0.84 to 2.53) Urinary frequency: 24% (27/111) vs. 31% (33/106) Urinary urgency: 22% (24/111) vs. 26% (28/106) Hematuria: 26% (29/111) vs. 23% (24/106) Fever: 3.6% (4/111) vs. 4.7% (5/106) Fatigue: 18% (20/111) vs. 19% (20/106) Nausea: 10% (11/111) vs. 8.5% (9/106)		

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Badalament, 1987 RCT Medium	USA Single center August 1981 - July 1984	Recurrent Ta, T1, or Tis bladder cancer without immediate indication for cystectomy who underwent BCG induction therapy	NR	A: BCG Pasteur strain 120 mg (in 50 mL sterile saline) weekly for 6 weeks starting at 2-3 weeks after TURBT, then monthly B: BCG Pasteur strain 120 mg (in 50 mL sterile saline) weekly for 6 weeks
Bouffioux, 1995 RCT Medium	Europe Multicenter 1983-1986	Completely resectable, Ta or T1 (0 or A), papillary transitional cell carcinoma of the bladder (single or multiple, primary or recurrent), previous intravesical treatment with cytotoxic drugs other than mitomycin C allowed if >3 months prior	Another cancer, previous treatment with local or systemic chemotherapy within 3 months, radiation therapy within 12 months, survival of 3 years unlikely, BUN or creatinine >50% above the upper limit or normal, WBC <3,000/mm3, platelet count, <100,000/mm3, untreated UTI	Initial randomization: A. Mitomycin C 30 mg/50 mL saline or doxorubicin 50 mg, 9 instillations starting on day of TURBT (once weekly for 4 weeks, then once monthly for 5 months) B. Mitomycin C 30 mg/50 mL saline or doxorubicin 50 mg, 9 instillations, starting between days 7 and 15 after TURBT (once weekly for 4 weeks, then once monthly for 5 months) Second randomization at 6 months: A: Continued instillations once a month for 6 months, total 15 B: No maintenance

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Badalament, 1987 RCT Medium	Duration, median 22 months (range 3 to 44 months) Method: Cystoscopy 3-5 weeks after induction, then every 3 months, with cytology	Screened: NR Randomized: 93 (47 vs. 46) Postrandomization exclusions: None reported Loss to followup: NR Analyzed: Unclear	Age, median: 62 vs. 64 years Male: 87% vs. 87% Race: NR Smoking status: NR Recurrent: All Unifocal: 45% vs. 35% Tumor stage: NR Tumor grade: NR Concurrent Tis: 77% vs. 78% Persistent tumor after BCG induction: 34% vs. 37%
Bouffioux, 1995 RCT Medium	Duration, average: 2.75 to 6.5 years (varied by outcome) Method: Cystoscopy every 3 months during year 1, every 4 months during year 2, every 6 months thereafter	Screened: NR Randomized: 965 underwent initial randomization (483 to early treatment, 482 to delayed treatment), 626 underwent second randomization (312 to maintenance and 313 to no maintenance) Postrandomization exclusions: 113 Loss to followup: 18 Analyzed: 834 (417 received mitomycin C, 417 doxorubicin)	Age: <50 8.2%, 50-59 20%, 60-69 34%, 70-79 31%, >80 7.1% Male: 81% Race: NR Smoking status: NR Primary: 44% Recurrent: 56% Ta: 57% T1: 41% CIS: 1.1% G1: 41% G2: 45% G3: 13% Gx: 0.7% Tumor >3 cm: 17% Single tumor: 52%

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Badalament, 1987 RCT Medium	Mortality: 0% (0/47) vs. 0% (0/46) at median 22 months Progression: 26% (12/47) vs. 20% (9/46) at median 22 months, RR 1.31 (95% CI 0.61 to 2.80) Reduction in number of tumors per patient-month: 0.071 vs. 0.148 (p=0.77) Disease-free interval: No difference Progression-free interval: No difference	
Bouffioux, 1995 RCT Medium	Early vs. delayed treatment Time to first recurrence: 43% (161/374) vs. 49% (187/378) after 2.75 years (p=0.18, log-rank test) Recurrence rate: 0.27 vs. 0.33 (p=0.08) Progression to invasive bladder cancer: 11% (40/374) vs. 10% (38/378) after 6.5 years Distant metastasis: 6% (24/412) vs. 6% (17/412) Second primary: 7% (28/412) vs. 6% (25/412) Mortality: 19% (78/412) vs. 21% (86/412) (p=0.60) Maintenance vs. no maintenance Time to first recurrence: 43% (130/303) vs. 50% (156/314) after 3 years (p=0.20, log-rank test) Recurrence rate: 0.23 vs. 0.28 (p=0.20) Progression to invasive bladder cancer: 9% (26/303) vs. 8% (25/314) Distant metastasis: 4% (12/304) vs. 4% (13/314) Second primary: 5% (15/304) vs. 7% (21/314) (p=0.41) Mortality: 17% (53/304) vs. 20% (63/314)	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Badalament, 1987 RCT Medium		Only reported for maintenance arm Discontinued due to adverse events: 45% (21/47) Dysuria: 89% (42/47) Frequency/urgency: 85% (40/47) Hematuria: 57% (27/47) Fever/chills: 43% (20/47) Flu-like symptoms: 13% (6/47) Suprapubic pain: 6% (3/47)	NR	
Bouffioux, 1995 RCT Medium		Early vs. delayed Chemical cystitis requiring delay or discontinuation of therapy: 3% vs. 0% with mitomycin C, 2.2% vs. 0.5% with doxorubicin Systemic toxicity requiring discontinuation of instillations: 1.8% with mitomycin C, 0.8% with doxorubicin	NR	Two parallel trials of mitomycin C and doxorubicin analyzed together

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Colombo, 2012 RCT Medium	Italy Single center 2010-2011	Recurrent, single, small (<1.5 cm) bladder cancers following TURBT of low-grade NMIBC	Positive urinary cytology, severe dysplasia, UTI, Eastern Cooperative Oncology Group performance status >1, hydronephrosis, laboratory test abnormalities	A: Mitomycin C (MMC), 40 mg (in 40 mL saline) three instillations per week for 2 weeks, prior to TURBT B: Mitomycin C (MMC), 40 mg (in 40 mL saline) one instillation per week for 6 weeks, prior to TURBT

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Colombo, 2012 RCT Medium	Duration, 9 to 11 days following end of instillations Method: Cystoscopy with 14 days of completion of therapy	Screened: NR Randomized: 54 Postrandomization exclusions: NR Loss to followup: NR Analyzed: 54 (27 vs. 27)	Age, mean: 65 vs. 60 years Male: 70% vs. 85% Race: NR Smoking status: Not reported Recurrent: 100% Stage: NR (all low-grade) Grade: NR (all low-grade) Tumor size: Mean 8.9 vs. 9.5 mm Single tumor: 100%

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Colombo, 2012 RCT Medium	A vs. B Complete response (absence of residual tumor on histology): 70% (19/27) vs. 44% (12/27), RR 1.58 (95% CI 0.97 to 2.58) Progression: 0% (0/27) vs. 0% (0/27)	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Colombo, 2012 RCT Medium		A vs. B Grade 3 or 4 systemic toxicity or discontinuation due to systemic toxicity: No cases Urinary frequency: 69% (18/26) vs. 67% (16/24) Chemical cystitis: 42% (8/19) vs. 47% (8/17) Urinary incontinence: 15% (4/26) vs. 27% (6/22) Hematuria: 31% (8/26) vs. 52% (13/25) Lower urinary tract pain: 38% (10/26) VS. 29% (6/21)	Reports no funding	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Ersoy, 2013 RCT High	Turkey Single center 2006-2010	Primary low-risk nonmuscle-invasive bladder cancer (NMIBC). Stage Ta, Grade G1. Solitary tumor; Size < 3 cm.	"Medium or high risk NMIBC"; Muscle-invasive bladder cancer; Suspected bladder perforation.	A: Mitomycin C (MMC), 40 mg (in 40 mL sterile saline) intravesical; infusion within 6 hours of TURBT; MMC retained in bladder for 2 hours. B: Urinary alkalinization prior to MMC instillation: Sodium bicarbonate, 1.3 g, orally X 3 doses (night before TURBT, morning of TURBT, 30 minutes prior to MMC). Mitomycin C (MMC), 40 mg (in 40 mL sterile saline) intravesical; infusion within 6 hours of TURBT; MMC retained in bladder for 2 hours. C: No drugs given in the first 6 hours after TURBT.
Fellows, 1994 RCT Medium	UK Multicenter 1988-1991	Histologically proven recurrent multiple pTa/pT1 bladder tumors difficult to control endoscopically	lymphatic or blood borne metastasis, upper tract tumors, intravesical chemotherapy during the previous 3 months were ineligible, immunodeficiency	A: BCG Evans strain (1-5 x 10^9 CFU) B: BCG Pasteur strain (1-3 x 10^9 CFU) Six weekly instillations

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Ersoy, 2013 RCT High	Duration, median: A vs. B vs. C: 51 vs. 50 vs. 54 months, p = 0.815 Method: Cystoscopy: month 3, month 12, then annually for 5 years.	Screened: NR Randomized: 53 Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 49 Per Group Analyzed (A vs. B vs. C): 11 vs. 15 vs. 23	A vs. B vs. C Age, mean: 59.3 vs. 63.5 vs. 61.9 years, p=0.716 Race: NR Male: 81.8% vs. 86.7% vs. 95.7%, p=0.395 History of smoking: 63.6% vs. 73.3% vs. 91.3%; p=0.124 Recurrent bladder cancer: None Stage: Ta: 100% vs. 100% Grade: G1: 100% vs. 100% Functional Status: NR
Fellows, 1994 RCT Medium	3 months Method: Cystoscopy 3 months after start of BCG	Screened: Not reported Randomized: 99 Postrandomization exclusions: 2 Lost to followup: 1 Analyzed: 51 vs. 46	Age (mean): 67.6 vs. 64.7 years Male: 34/51 (67%) vs. 33/46 (72%) Race: Not reported Smoking status: Not reported Recurrent bladder cancer: All Stage of disease: Ta: 34/51 (67%) vs. 38/46 (83%) T1: 11/51 (22%) vs. 5/46 (11%) Functional status: Not reported

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Ersoy, 2013 RCT High	A vs. B Recurrence free at 1 year: 100% vs. 86.7%, p=0.132 Recurrence free at 3 years: 100% vs. 79.4%, p=0.132 Recurrence free at 5 years: 100% vs. 79.4%, p=0.173 Mean time to recurrence, months (95% CI): NR vs. 34.8 (28.5-41.1)	NR
Fellows, 1994 RCT Medium	Responders at three months (marker tumor response and no new tumors): 12/51 vs. 18/43, p=0.064	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Ersoy, 2013 RCT High	A vs. B vs. C Recurrence free survival according to sex, (p=0.769): Male, 1-year: 90.9%; 3-years: 85.9%; 5-years: 85.9% Female, 1-year: 100.0%; 3- years: 66.7%; 5-years: NR Mean time to recurrence according to sex, months (95% CI): Male: 53.0 (47.7-58.2) Female: 44.9 (28.6-61.1) Recurrence free survival according to history of smoking (p =0.645): None, 1-year: 100.0%; 3-year: 85.7%; 5-years: 85.7% Present, 1-year: 89.7%; 3- years: 84.2%; 5-years: 84.2% Mean time to recurrence according to history of smoking, months (95% CI): None: 54.9 (45.8-64.1) Present: 52.1 (46.3-57.9)	NR	NR	
Fellows, 1994 RCT Medium		Severe AEs: Frequency: 4/51 vs. 5/46 Dysuria: 2/51 vs. 2/46 Hematuria: 1/51 vs. 2/46 Fever/Malaise: 2/51 vs. 1/46 Joint pain: 1/51 vs. 0/46 Hepatic dysfunction: 0/51 vs. 0/46	Not reported	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Flamm, 1990 RCT Medium	Austria Single center 1979-1981	Primary or recurrent transitional cell carcinoma of the bladder, otherwise not specified	Previous radiotherapy of the bladder, intravesical therapy within the last 6 months	A: Doxorubicin 50 mg/50 mL saline weekly for 6 weeks, then monthly for 2 years B: Doxorubicin 50 mg/50 mL saline weekly for 6 weeks
Friedrich, 2007 RCT Medium	Germany Multicenter 1995-2002	Patients with primary transitional cell carcinoma of the bladder or patients with tumor recurrence after TURBT without prior adjuvant therapy were eligible if the histopathologic evaluation of their completely resected tumor revealed an intermediate risk pTaG1 tumor (size >3 cm, recurrent or multifocal tumor) or pTaG2 up to pT1 tumor (G1-3). Patients with T1G3 tumor were eligible in case of a unifocal small tumor (≤2.5 cm).	MIBC or concomitant CIS, evidence of lymph node or distant metastasis, or a pT1G3 tumor≥2.5cm.	A. MMC 20 mg, 6 weekly instillations B. BCG RIVM 2 x 10^8 CFU, 6 weekly instillations C. MMC 20 md, 6 weekly instillations followed by monthly instillations of MMC 20 mg for 3 years

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Flamm, 1990 RCT Medium	Duration: 5 years Method: Cystoscopy every 3 months for 2 years, then every 6 months	Screened: NR Randomized: 160 Postrandomization exclusions: NR Loss to followup: Unclear Analyzed: 146 (70 vs. 76)	Age (mean): 67 vs. 69 years Male: 64% vs. 63% Race: NR Smoking status: NR Primary: 70% vs. 72% Recurrent: 30% vs. 28% Ta: 49% vs. 51% T1: 51% vs. 49% Concomitant Tis: 8.6% vs. 5.3% G1: 51% vs. 47% G2: 29% vs. 38% G3: 20% vs. 14% Solitary: 44% vs. 51% Tumor weight <5 g: 60% vs. 53%
Friedrich, 2007 RCT Medium	Duration, median: 2.9 years Method: Cytology and cystoscopy every 3 months in the first 2 years and every 6 months thereafter	Screened: NR Randomized: 495 (179 vs. 163 vs. 153) Postrandomization exclusions: None reported Loss to followup: 11% equally distributed between arms Analyzed: 495 (179 vs. 163 vs. 153)	Age (median): 68 vs. 67 vs. 67 Male: 79% vs. 80% vs. 82% Race: NR Smoking status: NR Stage/grade: TaG1: 15% vs. 12% vs. 5% TaG2: 54% vs. 45% vs. 54% TaG3: 2% vs. 3% vs. 2% T1G1: 3% vs. 3% vs. 2% T1G2: 22% vs. 31% vs. 27% T1G3: 3% vs. 6% vs. 11%

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Flamm, 1990 RCT Medium	Recurrence: 47% (33/70) vs. 42% (32/76), RR 1.1 (95% CI 0.78 to 1.6) Time to first recurrence (months): 16 vs. 13 (p=0.78) Recurrence rate: 1.7 vs. 1.4 per 100 patient-months (p>0.1) Progression: 19% (13/70) vs. 20% (15/76), RR 0.94 (95% CI 0.48 to 1.8) All-cause mortality: 21% (15/70) vs. 24% (18/76), RR 0.90 (95% CI 0.49 to 1.7) Bladder cancer mortality: 13% (9/70) vs. 13% (10/76), RR 0.95 (95% CI 0.41 to 2.2)	Recurrence rate (per 100 patient-months) (p>0.1 in all subgroups) Primary: 1.33 vs. 1.03 Recurrent: 2.85 vs. 2.65 Solitary: 0.67 vs. 0.98 Multiple: 2.77 vs. 2.03 <5 g: 1.62 vs. 1.51 >5 g: 1.98 vs. 1.36 Ta: 1.45 vs. 1.23 T1: 2.03 vs. 1.69
Friedrich, 2007 RCT Medium	A vs. C Recurrence: 26% (46/179) vs10% (16/153), RR 2.5 (95% CI 1.5 to 4.2) Percent recurrence-free at 2 years: 71% (126/179) vs. 88% (135/153) Percent recurrence-free at 3 years:69% (123/179) vs. 86% (132/153) (log-rank test, p=0.0006) Recurrence-free interval: Adjusted HR 0.38 (95% CI 0.21 to 0.69) for C vs. A after adjustment for facility, primary/recurrent, stage/grade	A vs. C Percent recurrence-free at 3 years TaG2: 70% vs. 90% (log-rank, p=0.009) T1G2: 74% vs. 81% (log-rank, p=0.29) Primary bladder cancer: 70% vs. 85% (log-rank, p=0.01) Recurrent bladder cancer: 59% vs. 92% (log-rank, p=0.005)

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Flamm, 1990 RCT Medium		Chemical cystitis: 12.8% vs. 11.8%	NR	
Friedrich, 2007 RCT Medium		Withdrawals due to AE: 0 vs. 3 vs. 8 Dysuria: 12% vs. 20% Hematuria: 1% vs. 9% Fever: 2% vs. 2%	Fa. Medac GmbH	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Fukui, 1992 RCT High	Japan Single center 1986-1989	Ta, T1, or Tis transitional cell carcinoma of the bladder who had complete response (disappearance of cystoscopically visible tumors and normalization of urinary cytology, and negative biopsies in patients with CIS) to 5 weeks induction therapy with sequential mitomycin c and Adriamycin		A: MMC 20 mg (in 20 mL saline) on day 1 and Adriamycin 40 mg (in 20 mL saline) on day 2 for 5 weeks, followed by maintenance therapy once monthly for 12 months B: MMC 20 mg (in 20 mL saline) on day 1 and Adriamycin 40 mg (in 20 mL saline) on day 2 for 5 weeks, No maintenance therapy
Gardmark, 2005 RCT High	Sweden Multicenter 2002-2004	Recurrent multiple Ta G1/2 bladder cancer, with all lesions except one marker lesion resected	Intravesical therapy within 3 months for chemotherapy or 6 months for BCG, chronic cystitis, laboratory test abnormalities, Eastern Cooperative Oncology Group performance status >2	A: Gemcitabine 2000 mg (in 100 mL saline) once weekly for 6 weeks B: Gemcitabine 2000 mg (in 100 mL saline) twice weekly for 3 weeks C: Gemcitabine 2000 mg (in 100 mL saline) single instillation

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Fukui, 1992 RCT High	Duration: Unclear Method: Cystoscopy and urine cytology every 3 months	Screened: 98 patients underwent induction therapy Randomized: 51 (25 vs. 26) Postrandomization exclusions: NR Loss to followup: NR Analyzed: 25 vs. 26	Age (mean): 63 vs. 68 years (Tis); 63 vs. 65 years (Ta or T1) Male: 58% vs. 82% (Tis); 85% vs. 93% (Ta or T1) Race: NR Smoking status: NR Ta or T1: 48% vs. 42% Tis: 52% vs. 58% G1 (Ta or T1 tumors): 23% vs. 20% G2: 62% vs. 67% G3: 15% vs. 13% Functional status: NR Multifocal (Ta or T1): 77% vs. 54%
Gardmark, 2005 RCT High	Duration: 9 weeks after initial instillation Method: Cystoscopy	Screened: NR Randomize: 32 Postrandomization exclusions: NR Lost to followup: NR Analyzed: 30 (10 vs. 11 vs. 11)	Age (mean): 67 years (overall) Male: 77% (overall) Race: NR Smoking status: NR Ta: 100% G1: 47% (overall) G2: 53% (overall) Multifocal: NR

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Fukui, 1992 RCT High	A vs. B Recurrence: 36% (9/25) vs. 65% (17/26), RR 0.55 (95% CI 0.30 to 1.0) Progression: 12% (3/25) vs. 3.8% (1/26), RR 3.12 (95% CI 0.35 to 28.0)	A vs. B Nonrecurrence, according to stage: Ta or T1: 59% vs. 38% (p>0.05) Tis: 73% vs. 24% (p<0.05) Recurrence, according to stage: Ta or T1: 38% (5/13) vs. 60% (9/15) Tis: 33% (4/12) vs. 73% (8/11) Progression, according to stage: Ta or Ta: 0% (0/13) vs. 0% (0/15) Tis: 25% (3/12) vs. 9.1% (1/11)
Gardmark, 2005 RCT High	A vs. B vs. C Complete response (complete disappearance of marker lesion and no new tumor): 44% (4/9) vs. 40% (4/10) vs. 10% (1/10)	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Fukui, 1992 RCT High		NR by treatment group	NR	
Gardmark, 2005 RCT High		1 patient in twice-weekly group discontinued due to nausea/vomiting, 1 patient in once-weekly group delayed therapy for 1 week due to thrombocytopenia	Lilly Corporation	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Giannakopoulos, S, 1998 RCT Medium	Greece Number sites: Unclear (authors from 3 centers) Study years: NR	Superficial transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Stages Ta or T1; Grade G2.	Stage ≥ T2. Grade G1 or G3 (any stage). CIS; Other concomitant malignancy; Serious systemic disease; Previous intravesical chemotherapy or immunotherapy; TCC of upper urinary tract; Previous systemic chemo/immunotherapy or pelvic radiation therapy	A: No adjuvant treatment. TURBT alone. B: Interferon-α-2b (IFN-α-2b), 40 MU (in 50 mL normal saline). C: Interferon-α-2b (IFN-α-2b), 60 MU (in 50 mL normal saline). D: Interferon-α-2b (IFN-α-2b), 80 MU (in 50 mL normal saline). For Groups B - D: First instillation after histological verification of stage and grade; 48 - 72 hours after TURBT. Retained intravesically for 1 hour; patient position changed every 15 minutes. Instillations once a week X 2 months, then once every 15 days X 4 months, then once monthly X 6 months.
Glashan, 1990 RCT Medium	USA, Europe, Australia, Canada Multicenter 1985-1988	Carcinoma in situ of the bladder and positive post-biopsy cytology	Invasive bladder cancer, other malignancy	A: Interferon α-2b 100 million units (in 30 mL sterile water) B: Interferon α-2b 10 million units (in 30 mL sterile water) First instillation within 1 month of positive cytology, administered once weekly for twelve weeks, then monthly through one year

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Giannakopoulos, S, 1998 RCT Medium	Duration: 36 months Method: Cystoscopy and urine cytology, every 3 months for 18 months, and every 6 months thereafter.	Screened: NR Randomized: 89 Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 89 Per Group Analyzed (A vs. B vs. C vs. D): 20 vs. 22 vs. 24 vs. 23	A vs. B vs. C vs. D Age, mean: 61.6 vs. 62.1 vs. 60.9 years vs. 61.9 years; p > 0.10 Race: NR Male: 80.0% vs. 81.8% vs. 79.2% vs. 82.6% ; p > 0.10 Smoking status: NR Recurrent bladder cancer: NR Stage: Ta: 60.0% vs. 59.1% vs. 62.5% vs. 56.5%; T1: 40.0% vs. 40.9% vs. 37.5% vs. 43.5%; p > 0.10 Grade: All G2 Functional Status: NR
Glashan, 1990 RCT Medium	Duration: 36 months Method: Cystoscopy and cytology every 3 months	Screened: NR Randomized: 85 Postrandomization exclusions: 2 Lost to followup: NR Analyzed: 80 (43 vs. 37)	Age (median): 67 years (overall) Male: NR Race: NR Smoking status: NR Recurrent bladder cancer: 51% vs. 42% Stage: 0: 83% vs. 84%; Ta: 17% vs. 16% Grade: NR WHO performance status 0 or 1: 89% vs. 92%

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Giannakopoulos, S, 1998 RCT Medium	B vs. C vs. D Recurrence: 36.4% (8/22) vs. 29.2% (7/24) vs. 21.7% (5/23); Differences between B, C, and D, p > 0.10. Recurrence-free survival time, months (mean): 21.4 vs. 26.1 vs. 30.0; B vs. C, p=0.02, B vs. D, p < 0.01; C vs. D, p=NS. Recurrence rate per 100 patient-months: 1.19 vs. 0.88 vs. 0.63; B vs. C, p="significant", B vs. D, p="significant"; C vs. D, p=0.026. Progression: 13.6% (3/22) vs. 4.2% (1/24) vs. 4.3% (1/23); B vs. C, p = NS, B vs. D, p=NS; C vs. D, p=NS	B vs. C vs. D Simple recurrence rate according to stage: Ta: 50.0% (4/8) vs. 57.1% (4/7) vs. 40.0% (2/5); For all comparisons between groups, p > 0.10. T1: 50.0% (4/8) vs. 42.9% (3/7) vs. 60.0% (3/5); For all comparisons between groups, p > 0.10. Recurrence-free survival time according to stage, Mean months (SD): Ta: 23.3 (6.65) vs. 28.5 (7.55) vs. 31.5 (6.36); B vs. C, p=0.05, B vs. D, p < 0.001; C vs. D, p=NS. T1: 23.3 (6.65) vs. 28.5 (7.55) vs. 31.5 (6.36); B vs. C, p=0.048, B vs. D, p < 0.001; C vs. D, p < 0.01. Recurrence rate per 100 patient-months according to stage: Ta: 0.96 vs. 0.78 vs. 0.44; Differences between B, C, and D, p=NS. T1: 1.55 vs. 1.05 vs. 0.8; Results "similar" to stage Ta, no p=values reported.
Glashan, 1990 RCT Medium	Complete response (resolution of Tis, negative cytology, and no transitional cell carcinoma tumors present): 43% (20/47) vs. 5.3% (2/38) at 12 m, RR 8.09 (95% CI 2.02 to 32.4); 21% (10/47) vs. 2.1% (1/47) at >24 m, RR 10.0 (95% CI 1.33 to 75.0) Progression: 13% (6/47) vs. 37% (14/38) at 12 m, RR 0.35 (95% CI 0.15 to 0.82) Cystectomy: 15% (7/47) vs. 18% (7/38), RR 0.81 (95% CI 0.31 to 2.10)	NR

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Giannakopoulos, S, 1998 RCT Medium	NR	No side effects of the drugs were noted. No adverse reactions noted. Five patients (groups NR) developed fevers and were found to have urinary tract infections.	NR	
Glashan, 1990 RCT Medium	NR	Flu-like symptoms: 14% (8/47) vs. 8% (3/38), RR 2.2 (95% CI 0.61 to 7.57) Withdrawal due to adverse events: None	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Gruenwald, 1997 RCT Medium	Israel Single center 1992-1994	Multifocal (≥3) tumors of any stage or grade, ≥3 recurrences within 12 months (regardless of stage), concomitant Tis, stage T1, or grade G3	NR	A: Pasteur strain BCG 120 mg/50 mL saline (begun within 1 month after TURBT, once weekly for 12 weeks) B: Pasteur strain BCG 120 mg/50 mL saline (begun within 1 month after TURBT, once weekly for 6 weeks)
Hendricksen, 2008 RCT Medium	the Netherlands Multicenter 1998-2004	≤85 years of age, solitary T1 tumor, or multiple primary or recurrent T1 or Ta G1-G3 urothelial cell carcinoma of the bladder in whom complete TURBT was possible	Prior epirubicin therapy (other intravesical therapy allowed), intravesical therapy within 6 months, solitary Ta tumor, CIS, or tumors ≥2, concurrent malignancy, history of other malignancy within 5 years, uncontrollable UTI, previous systematic cancer therapy or radiotherapy, urothelial cell carcinoma in prostatic urethra or upper urinary tract, pregnant or lactating, immunodeficiency, hypersensitivity to anthracyclines	A. Epirubicin 50 mg/50 mL saline, 9 instillations over 6 months (once weekly for 4 weeks started within 2 weeks of TURBT, then once monthly for 5 months) B. Epirubicin 50 mg/50 mL saline, 10 instillations over 6 months (within 48 hours of TURBT, once weekly for 4 weeks starting within 2 weeks of TURBT, once monthly for 5 months) C: Epirubicin 50 mg/50 mL saline, 11 instillations over 12 months (once weekly for 4 weeks starting within 2 weeks of TURBT, once monthly for 5 months, once every three months for 6 months)

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Gruenwald, 1997 RCT Medium	Duration, median: 29 months Method: Cystoscopy and cytology every 3 months during year 1, every 6 months during year 2	Screened: NR Randomized: 75 Postrandomization exclusions: 5 (2 vs. 3) Loss to followup: None reported Analyzed: 70 (40 vs. 30)	Age (mean): 69 vs. 68 years Male: 90% vs/ 88% Race: NR Smoking status: NR Recurrences in last 12 months: 40% vs. 25% Ta: 30% vs. 30% T1: 70% vs. 70% Tis: 10% vs. 10% G1: 6.6% vs. 2.5% G2: 63% vs. 55% G3: 30% vs. 42% Tumor size: NR Single: NR
Hendricksen, 2008 RCT Medium	Duration, median (A and B, NR for C): 7 years Method: Cystoscopy every 3 months for a year, then every 6 months for a year, annually thereafter.	Screened: NR Randomized: 1000 Postrandomization exclusions: 269 (101 vs. 91 vs. 77) Loss to followup: NR Analyzed: 731 (239 vs. 238 vs. 254)	Age (mean): 67 years (overall) Male: 80% (overall) Race: NR Smoking status: NR Ta: 79% vs. 82% vs. 74% T1: 21% vs. 18% vs. 26% G1: 45% vs. 42% vs. 38% G2: 45% vs. 46% vs. 49% G3: 8.8% vs. 11% vs. 12% Single tumor: 20% vs. 18% vs. 22% Primary: 48% vs. 46% vs. 52% Recurrent: 52% vs. 54% vs. 48% Prior intravesical therapy: 17% vs. 15% vs. 12%

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Gruenwald, 1997 RCT Medium	Bladder cancer and all-cause mortality: 3.3% (1.30) vs. 5.0% (2/40), RR 0.67 (95% CI 0.06 to 7.0) Percent recurrence-free: 70% (21/30) vs. 55% (22/40), RR 1.27 (95% CI 0.88 to 1.83); adjusted OR 2.17 (95% CI 0.9 to 5.22) (adjusted for stage and number of recurrences) Time to recurrence: 12.9 vs. 12.3 months Recurrence: 13% (4/30) vs. 20% (8/40) at 1 year, RR 0.67 (95% CI 0.22 to 2.0); 30% (9/30) vs. 45% (18/40) at 2 years, RR 0.67 (95% CI 0.35 to 1.27) Progression: 10% (3/30) vs. 5.0% (2/40), RR 2.0 (95% CI 0.36 to 11.2) Radical cystectomy: 6.7% (2/30) vs. 5.0% (2/40), RR 1.33 (95% CI 0.20 to 8.9)	Greater difference in risk estimates favoring 12 week course in patients with higher risk cancer, based on stage and number of recurrences in the year before treatment (data NR)
Hendricksen, 2008 RCT Medium	Percent recurrence-free at 5 years: 44.4% vs. 42.7% vs. 45.0% (p=0.712, log-rank) % progression-free at 5 years: 90.0% vs. 87.7% vs, 88.2% (p=0.593, log-rank)	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Gruenwald, 1997 RCT Medium		Dysuria or frequency: 40% (12/30) vs. 30% (12/40) Hemorrhagic cystitis: 13% (4/30) vs. 7.5% (3/40) Fever (mild): 30% (9/30) vs. 22% (9/40) Severe side effects: 6.7% (2/30) vs. 2.5% (1/40)	NR	Terminated early due to unavailability of Pasteur strain BCG
Hendricksen, 2008 RCT Medium		Therapy stopped or delayed due to side effects: 15% (39/266) vs. 22% (62/286) vs. 22% (61/277) Chemical cystitis: 32% (84/266) vs. 33% (95/286) vs. 24% (66/277) Hematuria: 13% (36/266) vs. 19% (54/286) vs. 11% (30/277) Systemic side effects: 13% (35/266) vs. 14% (40/286) vs. 14% (37/277)	Pfizer, the Netherlands	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Hinotsu, 2011 RCT Medium	Japan Multicenter 2004-2006	Recurrent or multiple tumors with confirmed Ta or T1 transitional cell carcinoma; must have 1 of the following: (a) at least 3 tumors (b) recurrence is at least the third such event or with recurrence diagnosed within 12 months from previous TURBT for NMIBC	History of BCG instillation or an anthracycline anti-tumor drug within the 12 months following the day on which the TURBT was performed (1 course of BC more than 12 months earlier permitted and MMC therapy allowed after a washout period of at least 4 weeks); stage T2 or higher; IV/IA anticancer/ chemotherapy, radiation	Within 1 month of TURBT: A. BCG 81 mg (Connaught strain) in 40 mL saline weekly for 6 weeks then once weekly for 3 weeks at 3, 6, 12,and 18 months from start of induction therapy B. BCG 81 mg (Connaught strain) in 40 mL saline weekly for 6 weeks C. Epirubicin 40 mg in 40 mL saline twice at 1-week interval and then 7 times at 2-week intervals
Hoeltl, 1991 RCT Medium	Austria Single center Study years NR (publication date 1991)	Primary G1 or G2 papillary transitional cell carcinoma of bladder stages Ta, T1, or TIS or recurrent G1/Ta or T1 bladder cancer; Karnofsky performance status ≥50%	Prior intravesical or systemic chemotherapy or immunotherapy, other cancers, pelvic irradiation within 3 months, Cr >2.5, bilirubin >1.12, WBC <2500, platelet count <100,000	A: Interferon alfa-2b 100 x 106 IU (100 MU)/30 mL sterile water (once weekly for 10 weeks, then once monthly for 1 year total of therapy) B: Interferon alfa-2b 10 x 106 IU (10 MU)/30 mL sterile water (starting within 36 hours of TURBT, once weekly for 10 weeks, then once monthly for 1 year total of therapy) C: Ethoglucid 1.13 g/100 mL sterile water (once weekly for 10 weeks, then once monthly for 1 year total of therapy)

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Hinotsu, 2011 RCT Medium	Duration, median: 2 years Method: Cystoscopy and cytology every 3 months for 3 years then every 6 months	Screened: NR Randomized: 116 Postrandomization exclusions: 5 in BCG maintenance group as had no maintenance instillations Loss to followup: None reported Analyzed: 110 (41 vs. 42 vs. 32)	Age ≤ 64: 17 vs. 22 vs. 11 Age > 64: 24 vs. 20 vs. 21 Male: 80% vs. 95% vs. 97% Race: NR Smoking: NR Stage: pTa: 71% vs. 69% vs. 75% pT1: 29% vs. 31% vs. 26% Grade 1: 12% vs. 24% vs. 13% Grade 2: 71% vs. 57% vs. 68% Grade 3: 17% vs. 19% vs. 23%
Hoeltl, 1991 RCT Medium	Duration, mean: 36.5 months Method: Cystoscopy and urine cytology every 3 months for 1 year, then every 6 months	Screened: NR Randomized: 44 Postrandomization exclusions: 10 Loss to followup: NR Analyzed: 34 (14 vs. 14 vs. 16)	Age (mean): 68 vs. 68 vs. 73 years Male: 55% vs. 60% vs. 77% Race: NR Smoking status: NR Ta: 0% vs. 7.7% vs. 10% T1: 91% vs. 85% vs. 80% Tis: 9.1% vs. 7.7% vs. 10% G1: 73% Vs. 77% vs. 70% G2: 18% vs. 15% vs. 20% G3: 9.1% vs. 7.7% vs. 10% Single tumor: 36% vs. 54% vs. 50% Primary: 36% Vs. 46% vs. 50% Recurrent: 64% vs. 54% vs. 50%

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Hinotsu, 2011 RCT Medium	A vs. B Recurrence: 12% (5/41) vs. 33% (14/42), RR 0.37 (95% CI 0.14 to 0.92) Progression at time of recurrence: 0% (0/41) vs. 7.1% (3/42), RR 0.15 (0.01 to 2.7) Recurrence-free survival: 85% vs. 65% (p=0.02)	
Hoeltl, 1991 RCT Medium	A vs. B Recurrence rate: 2.76 vs. 4.4 per 100 months Percent recurrence-free: 54.5% (6/11) vs. 46.2% (6/13), RR 1.2 (95% CI 0.53 to 2.62) Time to recurrence (mean, months): 22.4 vs. 22.2 Progression (recurrence of G2 or G3 cancer, ≥T2, or metastatic): 36.4% (4/11) vs. 7.7% (1/13), RR 4.7 (95% CI 0.62 to 36)	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Hinotsu, 2011 RCT Medium		A vs. B Urinary frequency: 93% (39/42) vs. 71% (30/42), RR 1.3 (95% CI 1.1 to 1.6) Dysuria: 93% (39/42) vs. 69% (29/42), RR 1.3 (95% CI 1.1 to 1.7) Hematuria: 93% (39/42) vs. 71% (30/42), RR 1.3 (95 %CI 1.1 to 1.6) Fever: 43% (18/42) vs. 26% (11/42), RR 1.6 (95% CI 0.88 to 3.0)	Nippon Kayaku Co. Ltd. (current Japanese license holder for the BCG Connaught strain)	
Hoeltl, 1991 RCT Medium		A vs. B Local toxicity (chemocysstitis, dysuria): 0% (0/11) vs. 0% (0/13) Systemic side effects: None observed	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Huland, 1990 RCT Medium	Germany (Hamburg) Multicenter Study years: March 1983 - June 1985	Superficial bladder carcinoma (primary or recurrent). Stages Ta, T1 or Tis; Grade G1, G2 or G3. CIS. Single or multiple tumors.	"Prophylactic instillation not possible because of patient age, immobility or lack of cooperation". Grade 0 tumor.	A: Mitomycin C, 20 mg/20 ml. Total 42 instillations. Every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year. B: Mitomycin C, 20 mg/20 ml. Total 42 instillations. Every week X 8 weeks, then every 4 weeks for rest of 1st year and 2 additional years. C: Mitomycin C, 20 mg/20 ml. Total 20 instillations. Every week X 20 weeks. D: Doxorubicin, 50 mg/50 ml. Total 42 instillations. Every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year. For all groups: Instillations started 4 to 6 weeks after discharge from hospital.
Inamoto, 2013 RCT Medium	Japan Single center 2008-2009	Histologically proven, single or multiple, primary or recurrent, stage Ta, T1, grades 1-3 urothelial carcinoma of the bladder, or carcinoma in situ.	tumor size >3cm, age <20 years, ECOG performance status 3 or 4, pneumonitis, active TB, strong positive PPD skin test, intravesical treatment within previous 1 month, intravenous or intraarterial chemotherapy for bladder cancer, grade >2 dysuria	A: Tokyo 172 strain BCG 40mg in 40 mL of saline B: Connaught strain BCG 81 mg in 40 mL of saline Given for six consecutive weeks starting 14 days after TURBT

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Huland, 1990 RCT Medium	Duration, mean: A vs. B vs. C vs. D: 26.7 vs. 27.4 vs. 26.7 vs. 30.2 months Method: Cystoscopy every 3 months.	Screened: 597 Randomized: 477 Postrandomization exclusions: 29 Lost to followup: NR Total Analyzed: 419 Per Group Analyzed: 209 vs. 96 vs. 75 vs. 39	A vs. B vs. C vs. D Age, mean (men/women): 61.1/67.5 vs. 66.3/68.1 vs. 65.1/64.6 vs. .68.0/58.3 Race: NR Male: 82.3% vs. 77.1% vs. 77.3% vs. 74.4% Smoking status: NR Recurrent bladder cancer: 32.1% vs. 25.0% vs. 25.3% vs. 43.6% Stage: Ta: 73.7% vs. 78.1% vs. 76.0% vs. 59.0%; T1: 23.0% vs. 19.8% vs. 21.3% vs. 33.3%; Tis: 3.3% vs. 2.1% vs. 29.3% vs. 7.7% Grade: G1: 47.4% vs. 58.3% vs. 52.0% vs. 43.6%; G2: 47.7% vs. 35.4% vs. 37.3% vs. 38.5%; G3: 1.9% vs. 4.2% vs. 8.0% vs. 10.3%; CIS: 3.3% vs. 2.1% vs. 2.7% vs. 7.7% Functional Status: NR
Inamoto, 2013 RCT Medium	Duration: Median followup: 16.4 months vs. 16.5 months Method: Cystoscopy and urine cytology every 3 months	Screened: NR Randomized: 38 Post randomization exclusions: 0 Lost to followup: 0 Analyzed: 18 vs. 20	Age (mean): 71.0 vs. 72.7 years Race: NR Male: 14/18 (78%) vs. 17/20 (85%) Smoking status: NR Recurrent bladder cancer: 28% vs. 20% Stage: Ta: 8/18 (44%) vs. 6/20 (30%) T1: 10/18 (56%) vs. 12/20 (60%) Functional status: NR

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Huland, 1990 RCT Medium	A vs. B vs. C Recurrence: 15.3% (32/209) vs. 9.4% (9/96) vs. 17.3% (13/75) Recurrence per 100 patient-months: 0.68 vs. 0.49 vs. 0.65 Progression of stage: 2.9% (6/209) vs. 1.0% (1/96) vs. 5.3% (4/75) Progression of grade: 1.9% (4/209) vs. 1.0% (1/96) vs. 4.0% (3/75)	A vs. B vs. C Primary bladder cancer (n=288) Ta: 9.6% (10/104) vs. 6% (3/50) vs. 15% (6/40) T1: 14.7% (5/34) vs. 0% (0/17) vs. 13.3% (2/15) CIS: 66.7% (2/3) vs. 0% (0/2) vs. 0% (0/1) G1: 7.9% (5/63) vs. 7.5% (3/40) vs. 14.3& (4/28) G2: 12.7% (9/71) vs. 0% (0/24) vs. 13.0% (3/23) G3: 9% (1/9) vs. 0% (0/3) vs. 0% (0/5) Recurrent bladder cancer (n=131) Ta: 28.0% (14/50) vs. 20% (5/25) vs. 29.4% (5/17) vs. 10% (1/10) T1: 7.1% (1/14) vs. 50% (1/2) vs. 29.4% (5/17) vs. 10% (1/10) CIS: 0% (0/4) vs. 0% (0/0) vs. 0% (0/1) vs. 100% (1/1) G1: 13.9% (5/36) vs. 25% (4/16) vs. 9.1% (1/11) vs. 0% (0/8) G2: 35.7% (10/28) vs. 20% (2/10) vs. 80% (4/5) vs. 14.3% (1/7) G3: 0% (0/2) vs. 0% (0/3) vs. 0% (0/3) vs. 100% (2/2)
Inamoto, 2013 RCT Medium	Recurrence-free survival: 72.2% vs. 83.5%, log rank p= 0.698	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Huland, 1990 RCT Medium	NR	A vs. B vs. C Chemical cystitis: 25% vs. 12% vs. 18% Allergy: 2% vs. 2% vs. 1% Other: 6% vs. 4% vs. 10% Total: 33% vs. 18% vs. 29%	NR	
Inamoto, 2013 RCT Medium		All AEs: 14/18 (77%) vs. 14/20 (70%), p=0.7718 AEs in more than 10% of patients: Pollakisuria: 3/18 (16.7%) vs. 6/20 (31.6%), p=0.5637 Hematuria: 4/18 (22.2%) vs. 1/20 (5.3%), 0.0833 Miction pain: 4/18 (22.2%) vs. 1/20 (5.3%), p=0.0455 Fever: 2/18 (11.1%) vs. 7/20 (36.8%)	Japan BCG laboratory	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Irie, 2003 NRCT Low	Japan Single center 1996-2001	Superficial papillary bladder cancer, no prior BCG or chemotherapeutic agents, stage Ta or T1	NR	A. BCG (Tokyo 172 strain) 40 mg/40 mL saline, 6 instillations weekly starting 7-50 days after TURBT B: BCG (Tokyo 172 strain) 80 mg/40 mL saline, 6 instillations weekly starting 7-50 days after TURBT
Koga, 2004 RCT Medium	Japan Multicenter 1993-1995	New, untreated transitional cell carcinoma of the bladder, Ta or T1 disease, no residual tumor based on cystoscopy and cytology	Other active neoplasms or serious complications, urothelial carcinoma orf the renal pelvis or ureter	A: Epirubicin 30 mg/30 mL saline 19 times (within 24 hours of TURBT, then 2-3 days, 1 week, and 2 weeks after TURBT, then once every 2 weeks for 12 weeks, then once a month for 9 months) B: Epirubicin 30 mg/30 mL saline 9 times (within 24 hours of TURBT, then 2-3 days, 1 week, and 2 weeks after TURBT, then once every 2 weeks for 10 weeks)
Koga, 2010 RCT Medium	Japan Multicenter 2002-2005	Histologically-confirmed Ta, T1 transitional cell carcinoma or CIS of bladder, responded to induction therapy	History of BCG intravesical instillation therapy, severe bladder irritation before start of drug administration, infravesical instillation therapy with an anticancer drug within 3 weeks before start of BCG	BCG 80 mg (Tokyo strain) within 4 weeks of biopsy or TURBT and repeated weekly for 8 weeks; patients with complete response were randomized to: A. BCG 80 mg (Tokyo strain) within 3 months of randomization followed by instillations at 3, 6, and 9 months B. No BCG

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Irie, 2003 NRCT Low	Duration, mean: 27.5 months in 40 mg group and 20 months in 80 mg group Method: Cystoscopy and cytology every 3 months for 2 years, then every 6 months	Screened: NR Randomized: NR Postrandomization exclusions: NR Loss to followup: NR Analyzed: 80 (41 vs. 39)	Age (mean): 62 vs. 62 years Male: 80% vs. 90% Race: NR Smoking status: NR Ta: 22% vs. 31% T1: 78% vs. 69% Concurrent CIS: 0% vs. 7.7% G1: 56% vs. 41% G2: 31% vs. 44% G3: 4.9% vs. 15% Primary: 93% vs. 84% Recurrent: 7% vs. 16% Unifocal: 63% vs. 64%
Koga, 2004 RCT Medium	Duration, median: 30.6 months Method: Cytology every month, cystoscopy every 3 months for 2 years, then every 6 months	Screened: NR Randomized: 171 Postrandomization exclusions: 21 Loss to followup: 22 (14 vs. 8) Analyzed: 150 (77 vs. 73)	Age (mean): 66 vs. 64 years Male: 71% vs. 75% Race: NR Smoking status: NR Primary: All Ta: 79% vs. 85% T1: 21% vs. 15% G1: 21% vs. 29% G2: 65% vs. 63% G3: 14% vs. 8.2% Unifocal: 61% vs. 60% >3 cm: 5.2% vs. 8.2%
Koga, 2010 RCT Medium	Duration: Median 27 vs. 29 months Method: Cytology and cystoscopy 2 months after randomization and then every 3 months for 3 years and thereafter every 6 months	Number screened: 63 Randomized: 53 (26 vs. 27) Post-randomization exclusions: 2 in BCG group withdrew before start of maintenance instillations Loss to followup: None reported Analyzed: 51 (24 vs. 27)	Age <70: 9 vs. 14 Age ≥70 : 15 vs. 13 Male: 79% vs. 78% Race: NR Smoking: 15 (63% vs. 20 (74%) Stage: Ta/T1: 3 (13%) vs. 2 (7%) CIS: 21 (88%) vs. 25 (93%)

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Irie, 2003 NRCT Low	Recurrence: 28% (11/40) vs. 16% (5/31), RR 1.71 (95% CI 0.66 to 4.40) Progression: 5.0% (2/40) vs. 6.4% (2/31), RR 0.78 (95% CI 0.12 to 5.20)	
Koga, 2004 RCT Medium	Percent recurrence-free at 3 years: 85.2% vs. 63.9% (p=0.005) Recurrence: 13.0% (10/77) vs. 31.5% (23/77); unadjusted HR 0.39 (0.18 to 0.82), adjusted HR 0.36 (0.17 to 0.78) (adjusted for multiplicity and tumor stage)	
Koga, 2010 RCT Medium	Recurrence: 1 (4%) vs. 7 (26%), p=0.078 Progression: 0 vs. 1 (4%) Mortality: 2 (8%) vs. 2 (7%) Died due to bladder cancer: 0 vs. 1 (4%)	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Irie, 2003 NRCT Low	No statistically significant effects of sex or age on recurrence in multivariate analysis	Discontinuation of treatment due to adverse effects: 2% (1/40) vs. 21% (8/39), RR 0.12 (95% CI 0.02 to 0.93) Fever: 6% (2/35) vs. 13% (5/39), RR 0.45 (95% CI 0.09 to 2.15) Bladder irritability: 27% (10/37) vs. 53% (20/38), RR 0.51 (95% CI 0.28 to 0.94) Gross hematuria: 9% (3/34) vs. 23% (7/30), RR 0.38 (95% CI 0.11 to 1.33)	NR	
Koga, 2004 RCT Medium		Severe local toxicity: 5.2% (4/77) vs. 8.2% (6/73), RR 0.63 (95% CI 0.19 to 2.15) Discontinuation of instillation due to pain: 1.3% (1/77) vs. 0% (0/73) Systemic toxicity (fatigue, low grade fever): 0% (0/77) vs. 2.7% (2/73) Microhematuria (mild, moderate, severe): 30% (23/77) vs. 16% (12/73) Dysuria (mild, moderate, severe): 38% (29/77) vs. 37% (27/73) Frequency (mild, moderate, severe): 32% (25/77) vs. 30% (22/73)	NR	
Koga, 2010 RCT Medium		Dysuria: 17% vs. NR	Japan BCG Laboratory Co. Ltd.	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Koontz, 1981 (treatment) RCT Medium	USA Multicenter 1974-1977	Incompletely resected NMIBC (single or multiple) or Tis or carcinoma on random biopsy	WBC <3000, platelet count <100,000, hemoglobin <10, low bladder capacity, urinary extravasation or severe vesicoureteral reflux, pregnant, chemotherapy within 1 month	A: Thiotepa 30 mg/30 mL distilled water (once weekly for 4 weeks, repeated after 4 weeks) B: Thiotepa 60 mg/60 mL distilled water (once weekly for 4 weeks, repeated after 4 weeks)
Kuroda, 2004 RCT Medium	Japan Multicenter 1994-1996	Primary or recurrent superficial transitional cell carcinoma of the bladder (Ta or T1, G1 or G2)	CIS or G3 tumors, primary and solitary bladder cancer, other severe illness	A. Epirubicin 20 mg/40 mL saline, 17 instillations over 12 months (starting about 7 days after TURBT, once weekly for 2 weeks, once every other week for 14 weeks, once a month for 8 months) B: Epirubicin 30 mg/40 mL saline, 12 instillations over 12 months (starting about 7 days after TURBT, once weekly for 2 weeks, once every other week for 14 weeks, once a month for 3 months) C: Epirubicin 40 mg/40 mL saline, 9 instillations over 4 months (starting about 7 days after TURBT, once weekly for 2 weeks, once every other week for 14 weeks)

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Koontz, 1981 (treatment) RCT Medium	Duration: 4 weeks after 2 4-week treatment courses Method: Cystoscopy at 4 weeks after fourth instillation and 4 weeks after eight instillation	Screened: NR Randomized: 101 Postrandomization exclusions: 6 Loss to followup: NR Analyzed: 95 (50 vs. 45)	Age (median): 65 years Male: 82% Race: NR Smoking status: NR Primary: NR Ta: 46% T1: 24% Tis: 21% G1: 33% G2: 35% G3: 28% Unifocal: 19% ≥3 cm: 25%
Kuroda, 2004 RCT Medium	Duration, median: 3.5 years Method: Cystoscopy every 3 months	Screened: NR Randomized: 622 Postrandomization exclusions: NR Loss to followup: NR Analyzed: 614 (205 vs. 204 vs. 205)	Age 50-59: 18% vs. 19% vs. 19% Age 60-69: 36% vs. 40% vs. 33% Age ≥70: 41% vs. 35% vs. 40% Male: 78% vs. 78% vs. 83% Race: NR Smoking status: NR Ta: 51% vs. 49% vs. 448% T1: 48% vs. 48% vs. 47% G1: 35% vs. 34% vs. 35% G2: 65% vs. 63% vs. 60% Primary: 54% vs. 54% vs. 55% Recurrent: 46% vs. 46% vs. 45% >3 cm: 12% vs. 8.3% vs. 5.9% Unifocal: 17% vs. 18% vs. 19%

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Koontz, 1981 (treatment) RCT Medium	Success (slight or moderate reduction of tumor, or complete remission): 70% (35/50) vs. 58% (26/45), RR 1.21, 95% CI 0.89 to 1.65 after first course; 48% (24/50) vs. 47% (21/45), RR 1.03, 95% CI 0.67 to 1.57) after second course	
Kuroda, 2004 RCT Medium	Percent recurrence-free at 1 year: 67% vs. 73% vs. 74% Percent recurrence-free at 2 years: 49% vs. 55% vs. 60% Percent recurrence-free at 4 years: 36% vs. 46% vs. 44% Time to recurrence (median, days): 688 vs. 1007 vs. 1186 (p=0.04 for dose-response) Mortality: 5.4% (11/205) vs. 6.4% (13/204) vs. 8.8% (18/205); RR 0.84 (95% CI 0.39 to 1.8) for A vs. B, RR 0.61 (95% CI 0.30 to 1.3) for A vs. C, and RR 0.73 (95% CI 0.37 to 1.4) for B vs. C Bladder cancer mortality: 1.5% (3/205) vs. 1.5% (3/204) vs. 2.4% (5/205), RR 1.0 (95% CI 0.20 to 4.9) for A vs. B, 0.60 (95% CI 0.15 to 2.5) for A vs. C, and RR 0.60 (95% CI 0.15 to 2.5) for B vs. C	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Koontz, 1981 (treatment) RCT Medium		Leukopenia (WBC <3000): 2.0% (1/50) vs. 13% (6/45), RR 0.15 (95% CI 0.02 to 1.20) Thrombocytopenia (platelets <100,000): 6.0% (3/50) vs. 0% (0/45) UTI: 2.0% (1/50) vs. 2.2% (1/45)	NR	
Kuroda, 2004 RCT Medium		Frequency (mild, moderate, severe): 22% vs. 35% vs. 29% Pain on urination (mild, moderate, severe): 21% vs. 32% Vs. 30% Dysuria (mild, moderate, severe): 12% vs. 17% vs. 15% Hematuria (mild, moderate, severe): 19% vs. 25% vs. 20%	Pfizer Inc. Oncology Japan	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Lamm, 2000 RCT Medium Lerner, 2007 SWOG 8507	USA Multicenter 1986-1989	Histologically confirmed transitional cell carcinoma of the bladder within 6 months before enrollment; papillary tumors Ta or T1; 2 tumors (primary and recurrent or 2 recurrences) within 1 year, 3 or more within the most recent 6 months and/or CIS, responded to induction therapy with BCG	Stage T2 or higher, previous radiation therapy for bladder, planning concomitant chemotherapy or radiation therapy, received previous BCG treatments	At least 1 week following TURBT patients received BCG 81 mg (Connaught strain) in 50.5 mL saline and simultaneous percutaneous BCG 0.5 cc (10^7 CFU) to inner thigh weekly for 6 weeks, responders randomized to: A. BCG intravesically and percutaneously 3 successive weekly treatments at 3 months, 6 months and every 6 months to 3 years B. No BCG
Liu, 2006 RCT Medium	China Number sites: unclear Study years: May 1997 - February 1998	Superficial bladder carcinoma (primary or recurrent). Stages Ta or T1; Grade G1 or G2	No recurrence within 1 year prior to enrollment. CIS; muscle-invasive disease (stage pT2 or greater); age > 85 years; history of another cancer; tumor in upper urinary tract; uncontrollable UTIs.	A: Epirubicin, 80 mg (in 40 mL normal saline). Single intravesical instillation within 6 hours of TURBT. B: Epirubicin, 40 mg, intravesical instillation every week for 6 ~ 8 weeks, then every month for 10 months. C: Mitomycin C, 40 mg, intravesical instillation every week for 6 ~ 8 weeks, then every month for 10 months.

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Lamm, 2000 RCT Medium Lerner, 2007 SWOG 8507	Duration: Median 120 months Method: Cytology and cystoscopy every 3 months for 2 years then every 6 months for 2 years then yearly	Number screened: 660 Randomized: 550 Post-randomization exclusions: 12 deemed ineligible before randomization; 154 had evidence of disease at randomization and were not included Analyzed: 384 (192 vs. 192)	Age (mean): 67 vs. 67 Male: 90% vs. 83% Black men: 4% vs. 3% Smoking: NR CIS at induction: 66 (34%) vs. 64 (33%)
Liu, 2006 RCT Medium	Duration: All patients followed-up for 5 years until June 2003. Method: Cystoscopy and urinary cytology every 3 months X 2 years, then every 6 months X 3 years.	Screened: NR Randomized: 47 (16 vs. 15 vs. 16) Postrandomization exclusions: None Lost to followup: None Total Analyzed: 44 (14 vs. 15 vs. 15)	A vs. B vs. C Age (overall mean): 62.2 years Race: NR Sex (male): NR Smoking status: NR Recurrent bladder cancer, overall: 23.4% Stage and Grade: TaG1: 6.3% vs. 0% vs. 0%; TaG2: 6.3% vs. 6.6% vs. 6.3%; T1G1: 12.5% vs. 26.7% vs. 12.5%; T1G2: 75.0% vs. 66.7% vs. 81.3% Functional Status: NR

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Lamm, 2000 RCT Medium Lerner, 2007 SWOG 8507	5 year survival: 83% vs. 78%	
Liu, 2006 RCT Medium	A vs. B Tumor-free survival at 1 year: 100% (14/14) vs. 86.7% (13/15), RR 1.15 (95% CI 0.91 to 1.44) Tumor-free survival at 2 years: 85.7% (12/14) vs. 80.0% (12/15), RR 1.07 (95% CI 0.77 to 1.49) Tumor-free survival at 3 years: 71.4% (10/14) vs. 73.3% (11/15), RR 0.89 (95% CI 0.59 to 1.35) Tumor-free survival at 5 years: 64.3% (9/14) vs. 66.7% (10/15), RR 0.96 (95% CI 0.57 to 1.64) Mean interval to recurrence, months: 8 vs. 4 vs. 5 Recurrence rate: 35.7% (5/14) vs. 33.3% (5/15), RR 1.07 (95% CI 0.39 to 2.92)	NR

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Lamm, 2000 RCT Medium Lerner, 2007 SWOG 8507		2 BCG related deaths	National Cancer Institute	
Liu, 2006 RCT Medium	NR	A vs. B Any side effect: 13.6% vs. 53.3% Dysuria or urinary frequency/urgency: 6.3% (1/16) vs. 13.3% (2/15) Stricture of urethra: 0% (0/16) vs. 6.7% (1/15) No systemic adverse events	Pharmacia Ltd.	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Malmström, 2002 RCT Medium	Europe (multinational) Multicenter Study years: NR	Histologically confirmed transitional cell carcinoma (TCC) of the bladder (primary or recurrent). Multiple tumors only. Stages Ta or T1; Grade G1 or G2. Karnofsky performance status > 70%; No other malignancy within 5 years of the study, except nonmelanoma skin cancer; Age ≥ 18 years; Not pregnant and on appropriate birth control.	Previous exposure to any interferon or mitomycin-C; Pelvic radiation or treatment with any cytotoxic, immunological or chemotherapeutic agent for benign conditions within 5 years of the study; Abnormal hepatic, renal or bone marrow function, or coagulation disorder; Serious infection or genitourinary surgery within 1 month of study; Bladder capacity < 150 mL and/or bladder obstruction with residual urine volume > 100 mL after spontaneous voiding; Chronic UTI; Previous exposure to any experimental drug within 4 weeks; Any significant medical or psychiatric illness preventing informed consent or following study procedures; History of TCC of upper tract and/or disease limited to prostatic urethra.	A: Interferon-α, 30 MU (in 30 mL sterile water). Retained in bladder X 2 hrs; patient moved from side to side every 30 min. First installation 1 to 2 weeks after TURBT or biopsy, then weekly X 12 weeks. B: Interferon-α, 50 MU (in 30 mL sterile water). Same procedure as A. C: Interferon-α, 80 MU (in 30 mL sterile water). Same procedure as A. D: Mitomycin-C, 40 mg (in 40 mL sterile water). Retained in bladder X 2 hrs; patient moved from side to side every 30 min. First instillation 1 to 2 weeks after TURBT or biopsy, then weekly X 8 weeks.

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Malmström, 2002 RCT Medium	Method: followup at 9 weeks and 13 weeks for all treatment groups and at 9 weeks only for control group. Cystoscopy at week 9 for both groups.	Screened: NR Randomized: 115 (29 vs. 28 vs. 29 vs. 29) Postrandomization exclusions: 1 Lost to followup: None Total Analyzed: 110 (27 vs. 27 vs. 27 vs. 29)	A vs. B vs. C vs. D Age, % ≥ 70 years: 17% vs. 46% vs. 21% vs. 45% Race: All Caucasian, except one Asian (male) and one Arab (male), groups NR Male: 86% vs. 79% vs. 90% vs. 86% Smoking status: NR Recurrent bladder cancer: NR Stage/Grade: TaG1: 41% vs. 29% vs. 31% vs. 21%; TaG2: 38% vs. 43% vs. 52% vs. 48%; T1G1: 3% vs. 7% vs. 7% vs. 10% ; T1G2: 14% vs. 21% vs. 10% vs. 21% Functional Status: Normal activity: 79% vs. 82% vs. 76% vs. 83%

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Malmström, 2002 RCT Medium	A vs. B vs. C Complete response (macroscopic disappearance of marker lesion): 19% (5/27) vs. 30% (8/27) vs. 26% (7/27) at 9 weeks; 19% (5/27) vs. 33% (9/27) vs. 41% (11/27) at 13 weeks (p>0.05 for all comparisons)	NR

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Malmström, 2002 RCT Medium	NA	A vs. B vs. C vs. D Adverse events reported: 37% (10/27) vs. 37% (10/27) vs. 48% (13/27) vs. 55% (16/29)* Adverse events with frequency ≥ 10%, reported by treatment group: A: None B: Fever (11%); Pain (11%) C: Fever (11%); Pain (15%); Micturition frequency (11%) D: Pain (10%); Dysuria (10%); Hematuria (14%); Micturition disorder (14%); Micturition frequency (28%); UTI (10%) * Reported as "55% (26/29)"; error presumed to be with number of events.	Schering-Plough	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Martinez-Pineiro, 2002 RCT Medium	Spain Multicenter 1991-1992	Primary or recurrent TaG2/3 or T1G1-3 bladder cancer with or without CIS; primary Tis; recurrent TaG1 cancers	Previous BCG, severe infection or active tuberculosis, untreatable urinary infection, concomitant urothelial tumor, reduced bladder capacity to <200 ml, elevated Cr, bilirubin and hepatic enzymes >2 times upper limit of normal, expected survival <2 years, other malignancy	A: BCG Connaught strain 81 mg, 12 instillations (starting 7 to 14 days after TURBT, once weekly for 6 weeks, then once every 2 weeks for 12 weeks) B: BCG Connaught strain 27 mg, 12 instillation (starting 7 to 14 days after TURBT, once weekly for 6 weeks, then once every 2 weeks for 12 weeks)
Martinez-Pineiro, 2005 RCT Medium	Spain Multicenter 1995-1999	T1G3 and Tis bladder cancer	NR	A: BCG Connaught strain 81 mg, 12 instillations (starting 7 to 14 days after TURBT, once weekly for 6 weeks, then once every 2 weeks for 12 weeks) B: BCG Connaught strain 27 mg, 12 instillation (starting 7 to 14 days after TURBT, once weekly for 6 weeks, then once every 2 weeks for 12 weeks)

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Martinez-Pineiro, 2002 RCT Medium	Duration, median: 69 months Method: NR	Screened: NR Randomized: 500 (252 vs. 248) Postrandomization exclusions: None reported Loss to followup: NR Analyzed: 499 (252 vs. 247)	Age (mean): 64 vs. 63 years Male: 89% vs. 91% Race: NR Smoking status: NR Primary: 61% vs. 62% Recurrent: 39% vs. 38% Solitary: 56% vs. 57% >3 cm: 18% vs. 19% Ta: 24% vs. 27% T1: 67% vs. 66% Tis primary: 3.2% vs. 2.0% Tis Ta: 0.8% vs. 1.2% Tis T1: 5.1% vs. 3.2% G1: 17% vs. 18% G2: 60% vs. 67% G3: 24% vs. 15% High-risk (T1G3, Tis, ≥2 relapses, ≥3 lesions, or ≥3 cm): 75% vs. 71%
Martinez-Pineiro, 2005 RCT Medium	Duration, median: 61 months Method: NR	Screened: NR Randomized: 155 (81 vs. 73) Postrandomization exclusions: None reported Loss to followup: 12 (6 vs. 6) Analyzed: 155	Age (mean): 66 vs. 68 years Male: 94% vs. 90% Race: NR Smoking status: NR Primary: 70% vs. 70% Recurrent: 30% vs. 30% Solitary: 46% vs. 48% >3 cm: 18% vs. 19% T1G3: 56% vs. 60% Tis primary: 18% vs. 11% TisTaG3: 6.1% Vs. 5.1% TisT1G3: 20% vs. 23%

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Martinez-Pineiro, 2002 RCT Medium	Recurrence: 28% (71/252) vs. 31% (76/247), RR 0.92 (95% CI 0.70 to 1.20) Disease-free interval (B vs. A): HR 1.09 (95% CI 0.79 to 1.51) Progression: 12% (29/252) vs. 13% (33/247), RR 0.86 (95% CI 0.54 to 1.37) Progression-free survival (B vs. A): HR 1.17 (95% CI 0.71 to 1.93) All-cause mortality: 20% (51/252) vs. 22% (55/247), RR 0.93 (95% CI 0.66 to 1.31) Survival time (B vs. A): HR 1.08 (95% CI 0.74 to 1.58) Bladder cancer mortality: 7.9% (20/252) vs. 7.3% (18/247), RR 1.09 (95% CI 0.59 to 2.01) Cancer-free survival (B vs. A): HR 1.25 (95% CI 0.53 to 2.94) Cystectomy: 4.8% (12/252) vs. 6.1% (15/247), RR 0.78 (95% CI 0.37 to 1.64)	Recurrent High-risk tumors: 30% (56/190) vs. 37% (65/177), RR 0.80 (95% CI 0.60 to 1.08) Progression High-risk tumors: 15% (28/190) vs. 16% (29/177), RR 0.90 (95% CI 0.56 to 1.45) ≥3 tumors: standard dose superior (p=0.04)
Martinez-Pineiro, 2005 RCT Medium	Recurrence: 39% (32/82) vs. 45% (33/73), RR 0.86 (95% CI 0.60 to 1.25) Disease-free interval (B vs. A): HR 1.23 (95% CI 0.75 to 2.00) Progression: 24% (20/82) vs. 26% (19/73), RR 0.94 (95% CI 0.54 to 1.61) Progression-free survival (B vs. A): HR 1.08 (95% CI 0.58 to 2.03) All-cause mortality: 29% (24/82) vs. 29% (21/73), RR 1.01 (95% CI 0.62 to 1.67) Bladder cancer mortality: 12% (10/82) vs. 15% (11/73), RR 0.81 (95% CI 0.36 to 1.79) Cancer-free survival (B vs. A): HR 1.25 (95% CI 0.53 to 2.94) Cystectomy: 8.4% (7/82) vs. 9.5% (7/73), RR 0.89 (95% CI 0.33 to 2.42)	No effect of primary vs. recurrent, single or multiple, small or large, or T category on efficacy of doses for survival

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Martinez-Pineiro, 2002 RCT Medium		Local side effects: 67% (168/252) vs. 55% (135/247), RR 1.22 (95% CI 1.06 to 1.41) Severe (grade 3 or 4) local side effects: 18% (44/252) vs. 6.5% (16/247), RR 2.70 (95% CI 1.56 to 4.65) Systemic side effects: 32% (80/252) vs. 15% (38/247), RR 2.06 (95% CI 1.46 to 2.91) Severe systemic side effects: 3.6% (9/252) vs. 4.4% (11/247), RR 0.80 (95% CI 0.34 to 1.90) Withdrawal due to side effects: 9.1% (23/252) vs. 4.0% (10/247), RR 2.25 (95% CI 1.10 to 4.64)	NR	
Martinez-Pineiro, 2005 RCT Medium		Local side effects: 70% (57/82) vs. 48% (35/72), RR 1.43 (95% CI 1.08 to 1.89) Severe (grade 3 or 4) local side effects: 20% (16/82) vs. 11% (8/73), RR 1.78 (95% CI 0.81 to 3.92) Systemic side effects: 16% (13/82) vs. 5.5% (4/73), RR 2.89 (95% CI 0.99 to 8.48) Severe systemic side effects: 0% (0/82) vs. 1.4% (1/73), RR 0.30 (95% CI 0.01 to 7.18) Withdrawal due to side effects: 12.2% (10/83) vs. 9.6% (7/73), RR 1.26 (95% CI 0.50 to 3.13)	INIBSA	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Masters, 1999 RCT Medium	UK Multicenter 1991-1993	Primary or recurrent Ta or T1 bladder cancer	Previous malignancy, pelvic radiotherapy, WHO performance status >2, UTI	A: Epirubicin 50 mg/50 mL saline, 5 instillations (starting 10-14 days after TURBT, every 3 months for 12 months) B: Epirubicin 100 mg/50 mL saline, 5 instillations (starting 10-14 days after TURBT, every 3 months for 12 months) First 102 patients had a marker tumor left after initial TURBT (0.5 cm)

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Masters, 1999 RCT Medium	Duration: 834 vs. 774 days Method: Cystoscopy every 3 months	Screened: NR Randomized: 126 Postrandomization exclusions:4 Lost to followup: None reported Analyzed: 122 (61 vs. 61)	Age (median): 70 vs. 70 years Male: 80% vs. 64% Race: NR Smoking status: NR Ta: 70% vs. 72% T1: 20% vs. 23% Tis: 3.3% vs. 0% Tx: 3.3% vs. 3.3% G1: 44% vs. 51% G2: 41% vs. 43% G3: 8.2% vs. 1.6% Gx: 3.3% vs. 0% Primary: 34% vs. 48% Recurrent: 62% vs. 52% Solitary: 21% vs. 21%

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Masters, 1999 RCT Medium	Recurrence: 44% (27/61) vs. 56% (34/61), HR 0.68 (95% CI 0.41 to 1.13) Recurrence rate: 0.52 vs. 0.58 per patient-year, RR 0.90 (0.58 to 1.52)	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Masters, 1999 RCT Medium		UTI: 31% (19/61) vs. 21% (13/61), RR 1.46 (95% CI 0.79 to 2.69) Bladder spasm: 15% (9/61) vs. 44% (27/61), RR 0.33 (95% CI 0.17 to 0.65) Withdrawal or incomplete therapy due to adverse events: 11% (7/61) vs. 23% (14/61), RR 0.50 (95% CI 0.22 to 1.15)	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Matsumura, 1992 RCT Medium	Japan Multicenter 1987-1989	Ta, T1, or Tis transitional cell carcinoma of the bladder; primary with multiple lesions or recurrent with one or more lesions	NR	A: Doxorubicin 20 mg/40 mL saline, 21 instillations (following TURBT, once weekly for 2 weeks, then every 2 weeks for 14 weeks, once monthly for 8 months, and once every three months for 1 year) B: Doxorubicin 20 mg/40 mL saline, 6 instillations (over 2 weeks prior to TURBT) C: No doxorubicin

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Matsumura, 1992 RCT Medium	Duration, median: 240 days Method: NR	Screened: NR Randomized: 443 (182 vs. 126 vs. 135) Postrandomization exclusions: 91 Loss to followup: 26 Analyzed: 284 (126 vs. 75 vs. 83)	Age 50-59: 15% vs. 20% vs. 13% Age 60-69: 34% vs. 32% Vs. 31% Age ≥70: 43% vs. 44% vs. 42% Male: 82% Vs. 79% vs. 84% Race: NR Smoking status: NR Ta: 33% vs. 35% vs. 33% T1: 43% vs. 35% vs. 36% Tis: 0.8% vs. 2.7% vs. 3.6% Tx: 20% vs. 24% vs. 25% G0: 2.4% vs. 8.0% vs. 2.4% G1: 33% vs. 35% vs. 33% G2: 37% vs. 31% vs. 36% G3: 4.0% vs. 4.0% vs. 0% Gx: 20% vs. 19% vs. 28% Primary: 40% vs. 35% vs. 49% Recurrent: 60% vs. 65% vs. 51% >3 cm: 42% vs. 51% vs. 42% Unifocal: 26% vs. 23% vs. 24% Prior intravesical therapy with doxorubicin: 15% vs. 8% vs. 9.6% Prior intravesical therapy without doxorubicin: 13% vs. 5.3% vs. 6.0% No prior therapy: 53% vs. 69% vs. 64%

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Matsumura, 1992 RCT Medium	Percent recurrence-free at 1 year: 63.8% vs. 49.0% (p>0.05 for A vs. B) Percent recurrence-free at 2 years: 38.2% vs. 18.8% (p<0.05 for A vs. B)	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Matsumura, 1992 RCT Medium		A vs. B Urinary frequency: 10.3% (13/126) vs. 17.3% (13/75) Pain on urination: 10.3% (13/126) vs. 12.0% (9/75) Dysuria: 3.2% (4/126) vs. 4.0% (3/75) Hematuria: 4.0% (5/126) vs. 8.0% (6/75) Pyuria: 4.0% (5/126) vs. 9.3% (7/75)	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Mitsumori, 2004 RCT Medium	Japan Multicenter 1998-2001	Recurrent or primary Ta or T1 bladder cancer	Solitary papillary tumor, Tis, uncontrollable UTI, previous muscle-invasive bladder cancer, other malignancy	A: Epirubicin 30 mg/40 mL saline, 6 instillations (starting 1 week after TURBT once every 2 weeks for 12 weeks, total 180 mg) B: Epirubicin 30 mg/40 mL saline, 6 instillations (3 instillations within first 5-7 days after TURBT, then once every 2 weeks for 6 weeks, total 180 mg) C: Epirubicin 30 mg/40 mL saline, 12 instillations (starting 1 week after TURBT, once weekly for 12 weeks, total 360 mg) D: Epirubicin 30 mg/40 mL saline, 12 instillations (3 instillations within first 5-7 days after TURBT, then once weekly for 9 weeks, total 360 mg)
Morales, 1992 RCT High	Canada Single center 1979-1988	Tis or T1 transitional cell carcinoma of the bladder with residual neoplasm; in patients with recurrences must have had a least 2 histologically documented but completely ablated tumors on 2 separate cystoscopic studies in the last 12 months	NR	A: Armand Frappier BCG 60 mg weekly for 6 weeks B: Armand Frappier BCG 120 mg weekly for 6 weeks

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Mitsumori, 2004 RCT Medium	Duration, median: 13.3 months Method: Cystoscopy and urine cytology every 3 months for 3 years, then every 6 months	Screened: NR Randomized: 91 Postrandomization exclusions: 15 Loss to followup: 7 Analyzed: 69 (22 vs. 25 vs. 12 vs. 10)	Age (median): 68 years Male: 74% Race: NR Smoking status: NR Primary: 66% Recurrent: 34% Ta: 62% T1: 38% G1: 15% G2: 64% G3: 21% ≥2 cm: 30% Solitary: 43%
Morales, 1992 RCT High	Duration, mean: 21 months Method: Cystoscopy at 4, 12, and 24 weeks, then at 6 to 12 months	Screened: NR Randomized: 97 (49 vs. 48) Postrandomization exclusions: NR Loss to followup: NR Analyzed: 97	Age: NR Sex: NR Race: NR Smoking status: NR Primary or recurrent: NR Ta: 44% vs. 45% T1: 15% vs. 16% Tis: 23% vs. 22% Grade: NR

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Mitsumori, 2004 RCT Medium	Recurrence rates A vs. B vs. C vs. D: 30% (6/20) vs. 25% (6/24) vs. 8.3% (1/12) vs. 0% (0/10) at 6 months, 50% (10/20) vs. 35% (8/23) vs. 45% (4/9) vs. 12% (1/8) at 12 months (p=0.04 for A vs. D with log-rank test, otherwise p>0.05) A or B (180 mg) vs. C or D (360 mg): 27% (12/44) vs. 5% (1/22) at 6 months; 42% (18/43) vs. 29% (5/17) at 12 months (p=0.01, log-rank test) A or C (starting 1 week after TURBT) vs. B or D (early instillations): 22% (7/32) vs. 18% (6/34) at 6 months; 48% (14/29) vs. 29% (9/31) at 12 months (p=0.36, log-rank test) In multivariate regression, total dose (180 vs. 360 mg, AOR 0.32, 95% CI 0.11 to 0.92) and urine cytology (I-II vs. III-IV AOR 3.11, 95% CI 1.08 to 8.94) independent predictors for local recurrence; delayed vs. early not significant (AOR 0.91, 95% CI 0.37 to 2.23)	
Morales, 1992 RCT High	Recurrence-free: 37% (18/49) vs. 67% (32/48), RR 0.55 (95% CI 0.36 to 0.84)	Recurrence-free Ta: 41% (9/22) vs. 67% (14/21), RR 0.61 (95% CI 0.34 to 1.10) T1: 0% (0/8) vs. 56% (5/9), RR 0.10 (95% CI 0.01 to 1.58) Tis: 45% (5/11) vs. 73% (8/11), RR 0.62 (95% CI 0.30 to 1.31)

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Mitsumori, 2004 RCT Medium		Side effects (irritated bladder, UTI, or hematuria): 23% (5/22) vs. 24% (6/25) vs. 25% (3/12) vs. 40% (4/10) (P>0.05)	NR	
Morales, 1992 RCT High		Side effects (not otherwise defined): 12% (6/49) vs. 33% (16/48), RR 0.37 (95% CI 0.16 to 0.86)	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Mukherjee, 1992 RCT High Kaisary, 1987	UK Single center 1984 - unclear end date	Multiple recurrent superficial bladder tumors that were increasingly difficult to keep under endoscopic control	NR	A: BCG Glaxo strain (1.2 x 10^9 CFU) B: BCG Pasteur strain (1.2 x 10^9 CFU) Six weekly instillations, followed by either monthly instillations if there was a complete response or 6-weeks if there was a partial or no response.
Niijima, 1983 RCT (Also Akaza, 1987) Medium	Japan Multicenter Study years: April 1980 - 1985	Histologically proven superficial bladder cancer (primary or recurrent). Stages Ta or T1; Grade not specified. Absence of tumor after TURBT.	Tis superficial cancer; other therapies, such as chemotherapy, immunotherapy, and/or radiotherapy within 3 or 4 weeks before initiation of study; severe cardiovascular, renal, hepatic or hematopoietic disturbances; simultaneous presence of another cancer.	A: Doxorubicin, 30 mg (in 30 mL saline). B: Doxorubicin, 20 mg (in 40 mL saline). C: Mitomycin C: 20 mg (in 40 mL saline). D: No adjuvant treatment. TURBT alone. For A, B, and C: First instillation within 1 week of TURBT. Twice weekly X 4 weeks (Total: 8 doses)
Nomata, 2002 RCT Medium	Japan Multicenter 1995-1998	Ta or T1/G1 or G2 transitional cell carcinoma of the bladder, ECOG performance status 0 or 1, age 20 to 80 years, post TURBT with no evidence of residual cancer based on cytological evaluation of voided urine	Prior treatment with anthracycline, uncontrollable UTI, prior muscle invasive transitional cell carcinoma, concurrent malignancy, pregnant	A. Epirubicin 30 mg/30 mL saline 19 times over 1 year (once weekly for 4 weeks, then every 2 weeks for 4 months) B. Epirubicin 30 mg/30 mL saline 12 times over 5 months (once weekly for 4 weeks, then every 2 weeks for 4 months, then once per month for 7 months)

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Mukherjee, 1992 RCT High Kaisary, 1987	Duration: Mean 60 months Method: Cystoscopy 3 months after final instillation, and then according to clinical criteria	Screened: NR Randomized: 21 Postrandomization exclusions: NR Lost to followup: 0 Total analyzed: 12 vs. 9	Age: NR Male: 17/21 Smoking status: NR Recurrent bladder cancer: 21/21 Stage: All T1 or less Functional status: NR
Niijima, 1983 RCT (Also Akaza, 1987) Medium	Duration: 5 years, maximum; Mean/Median NR Method: Cystoscopy and urinary cytology studies at 12-week intervals during the observation period.	Screened: NR Randomized: 707 (192 vs. 176 vs. 185 vs. 154) Postrandomization exclusions: NR Lost to followup: NR Total Analyzed: 575* Per Group Analyzed: (149 vs. 148 vs. 139 vs. 139) * Nonevaluated patients due to protocol violations, cessation of instillation, adverse effects, or other reasons. Not quantified overall or by group.	A vs. B vs. C vs. D Age (years), average: 62.3 vs. 62.9 vs. 62.9 vs. 62.9 Male: 82.6% vs. 75.7% vs. 74.8% vs. 74.1% Race: NR Smoking status: NR Recurrent bladder cancer: 29.5% vs. 31.1% vs. 33.8% vs. 35.3% Stage: NR Grade: NR Functional Status: NR Size > 3 cm: 14.8% vs. 74.3% vs. 12.2% vs. 5.0% Proportion with single tumor: 64.4% vs. 63.5% vs. 48.2% vs. 60.4%
Nomata, 2002 RCT Medium	Duration, median: 18.1 months Method: Cystoscopy every 3 months	Screened: NR Randomized: 138 Postrandomization exclusions: 13 (9 vs. 4) did not meet inclusion criteria Loss to followup: 25% (11/44) vs. 21% (12/58) Analyzed: 125 (55 vs. 70)	Age: NR Male: 80% vs. 86% Race: NR Smoking status: NR Primary: 78% vs. 77% Recurrent: 16% vs. 21% Ta: 51% vs. 60% T1: 45% vs. 37% Tx: 36% vs. 2.9% G1: 49% vs. 53% G2: 51% vs. 47%

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Mukherjee, 1992 RCT High Kaisary, 1987	At 5-year followup the Pasteur strain group was 1.12 times more likely to be free of disease than the Glaxo group, not statistically significant. At 5 years: Complete response: 5/12 vs. 4/9 Failures: 7/12 vs. 5/9	
Niijima, 1983 RCT (Also Akaza, 1987) Medium	A vs. B vs. C vs. D Recurrence-free survival rate at 540 days: 56.6% vs. 52.0% vs. 42.4% vs. 38.5%, generalized Wilcoxon test: A vs. D, $p < 0.05$ B vs. D, $p < 0.05$ C vs. D, $p < 0.10$ Recurrence-free survival at 1800 days,* generalized Wilcoxon test: B > D, $p < 0.05$ C > D, $p < 0.05$ NR for other treatment group comparisons. * from Akaza, 1987	Primary tumor: Recurrence-free survival rate at 1 year (A vs. B vs. C vs. D): 73.1% vs. 76.6% vs. 84.0% vs. 70% Recurrence-free survival at 1800 days, generalized Wilcoxon test: B > D, $p < 0.05$ C > D, $p < 0.01$ Comparisons NR for other treatment group comparisons. Recurrent tumor: Recurrence-free survival at 1800 days, generalized Wilcoxon test: A > D; B > D; C > D; differences reported as nonsignificant, no p - values reported.
Nomata, 2002 RCT Medium	Percent recurrence-free at 3 years: 48.5% vs. 55.1% (p>0.05)	Percent recurrence-free at 3 years, G2 bladder cancers: 54% (15/28) vs. 61% (20/33)

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Mukherjee, 1992 RCT High Kaisary, 1987		Most patients complained of hematuria and dysuria	NR	
Niijima, 1983 RCT (Also Akaza, 1987) Medium	NR	A vs. B vs. C (NR for group D) Pollakiuria: 33.8% vs. 28.3% vs. 33.1% Dysuria: 36.9% vs. 27.5% vs. 27.4% Hematuria: 20.0% vs. 11.6% vs. 9.7% Pyuria: 23.8% vs. 19.6% vs. 8.9% "No significant systemic side effects"	Ministry of Health and Welfare of Japan	
Nomata, 2002 RCT Medium		Urinary frequency (grade 1-3): 33% (18/55) vs. 20% (11/55) Dysuria (grade 1-3): 31% (17/55) vs. 21% (15/70) Gross hematuria (grade 1-3): 42% (23/55) vs. 36% (25/70)	NR	Reports 59.8% recurrence-free survival for patients with G2 bladder cancer in group B, but doesn't correspond with sample size (33 patients)

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Oddens, 2013 RCT Medium Brausi, 2014 (adverse events)	Europe Multicenter 1997-2005	Solitary T1G3 or multiple Ta-T1, G1-3 urothelial carcinoma of the bladder	Solitary tumors except T1G3, >10 tumors, CIS, ≥T2, age >83, WHO performance status 3 or 4, previous BCG, intravesical therapy in last 3 months	A: BCG (OncoTICE strain) 5 x 10^8 CFU at 1/3 dose, 15 instillations (started within 14 days after TURBT, one weekly for 6 weeks, then 3 weekly instillations at months 3 ,6, and 12) B: BCG full dose, 15 instillations (started within 14 days after TURBT, one weekly for 6 weeks, then 3 weekly instillations at months 3 ,6, and 12) C: BCG at 1/3 dose, 27 instillations (started within 14 days after TURBT, one weekly for 6 weeks, then 3 weekly instillations at months 3 ,6,12, 18, 24, 30, and 36) D: BCG full dose, 27 instillations (started within 14 days after TURBT, one weekly for 6 weeks, then 3 weekly instillations at months 3 ,6,12, 18, 24, 30, and 36)

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Oddens, 2013 RCT Medium Brausi, 2014 (adverse events)	Duration, median: 7.1 years Method: Cystoscopy and cytology every 3 months for 3 years, then every 6 months	Screened: NR Randomized: 1805 (450 vs. 453 vs. 450 vs. 452) Postrandomization exclusions:525 (132 vs. 135 vs. 131 vs. 127) Loss to followup: NR Analyzed: 1355 (341 vs. 339 vs. 337 vs. 338)	Age (median): 68 vs. 67 vs. 69 vs. 67 years Male: 81% vs. 83% vs. 81% vs. 80% Race: NR Smoking status: NR Primary: 61% vs. 62% vs. 58% vs. 53% Recurrent: 38% vs. 37% vs. 42% Vs. 46% WHO performance status 2 (excluded >2): 2.3% vs. 1.5% vs. 1.5% vs. 1.8% Unifocal: 15% vs. 14% vs. 13% vs. 11% Ta: 59% vs. 61% vs. 68% vs. 63% T1: 40% vs. 38% vs. 32% vs. 35% G1: 25% vs. 28% vs. 33% vs. 29% G2: 48% vs. 45% vs. 44% Vs. 41% G3: 28% vs. 27% vs. 23% vs. 29% EORTC recurrence score ≤9 (intermediate risk): 69% vs. 71% Vs. 67% Vs. 64% EORTC recurrence score 10-17 (high risk): 22% vs. 22% vs. 27% Vs. 28% EORTC progression score ≤6 (intermediate risk): 27% vs. 30% vs. 32% Vs. 21% EORTC progression score 7-13 (high risk): 51% vs. 52% vs. 53% vs. 60% EORTC progression score 14-23 (high risk): 13% vs. 12% vs. 8.9% vs. 11% Simplified risk group intermediate risk: 56% vs. 56% vs. 65% vs. 56^ Simplified risk group high risk (T1 and/or G3): 44% vs. 43% vs. 35% vs. 43%

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Oddens, 2013 RCT Medium Brausi, 2014 (adverse events)	Recurrence: 49% (168/341) vs. 43% (145/339) vs. 43% (145/337) vs. 39% (131/338) Percent recurrence-free at 5 years: 54% vs. 59% vs. 63% vs. 64% (unable to reject null hypothesis of inferiority of 1/3 dose or 1 year of treatment; >10% decrease was only observed for A vs. D, HR 0.75, 95% CI 0.59 to 0.94); 59% vs. 62% for A or C (1/3 dose) vs. B or D (full dose) (p=0.09); 57% for A or B (1 year maintenance) vs. 63% for C or D (3 years maintenance) (p=0.06) Progression to ≥T2: 7.6% (26/341) vs. 9.1% (31/339) vs. 8.9% (30/337) vs. 6.5% (22/338) Distant metastasis: 4.4% (15/341) vs. 4.7% (16/339) vs. 5.3% (18/337) vs. 5.3% (18/338) Mortality: 24% (83/341) vs. 26% (88/339) vs. 30% (101/337) vs. 29% (97/338) Bladder cancer mortality: 3.8% (13/341) vs. 5.9% (20/339) vs. 5.0% (17/337) vs. 5.3% (18/338)	1/3 dose (A or C) vs. full dose (B or D) No differences in recurrence-free rates, time to progression, or overall duration of survival when stratified by simplified risk group 3 years (C or D) vs. 1 year (A or B) maintenance, recurrence-free rate Intermediate-risk, 1/3 dose (C vs. A): HR 1.35, 95% CI 1.03 to 1.79 Intermediate-risk, full dose (D vs. B): HR 0.88, 95% CI 0.64 to 1.21 High-risk, 1/3 dose (C vs. A): HR 1.01, 95% CI 0.69 to 1.47 High risk, full dose (D vs. B): HR 1.61, 95% CI 1.13 to 2.30 Time to progression or overall duration of survival: No differences

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Oddens, 2013 RCT Medium Brausi, 2014 (adverse events)		Discontinuation due to systemic or local side effects within first year: 7.2% (24/334) vs. 7.0% (23/329) vs. 5.3% (17/323) vs. 5.5% (18/330) Discontinuation due to systemic or local side effects after the first year: 0% (0/334) vs. 0% (0/329) vs. 2.8% (9/323) vs. 3.6% (12/330) No differences for A or C vs. B or D, or A or B vs. C or D Bacterial cystitis: 21% (71/334) vs. 21% (69/329) vs. 28% (90/323) vs. 23% (77/330) Chemical cystitis: 28% (94/334) vs. 33% (109/329) vs. 39% (127/323) vs. 39% (130/330) Frequency: 19% (63/334) vs. 23% (76/329) vs. 27% (87/323) vs. 26% (84/330) Gross hematuria: 22% (73/334) vs. 24% (78/329) vs. 24% (77/323) vs. 21% (70/330) Any local side effect: 58% (195/334) vs. 62% (205/329) vs. 67% (217/323) vs. 63% (209/330) Fever: 5.1% (17/334) vs. 8.8% (29/329) vs. 8.4% (27/323) vs. 10% (33/330) General malaise: 13% (42/334) vs. 16% (51/329) vs. 15% (49/323) vs. 19% (62/330) Any systemic side effect: 28% (92/334) vs. 30% (100/329) vs. 31% (100/323) vs. 34% (111/330)	National Cancer Institute and from the Kankerbestrijding/KQF through the EORTC Charitable Trust	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Ojea, 2007 RCT Medium	Spain Multicenter 1995-1998	Intermediate risk with stages TaG2 and T1G1-2 superficial bladder tumors without carcinoma in situ	TaG1 tumors; concurrent or previous muscle-invasive disease; concurrent or previous tumor in upper urinary tract or prostatic urethra, intravesical treatment with MMC or BCG during previous 6 months; another malignancy except basal cell carcinoma of skin; previous pelvic irradiation	14-21 days after transurethral resection with histological confirmation of bladder cancer, patients received 6 weekly instillations then another 6 instillations one every 2 weeks; if a recurrence was diagnosed a further TURBT was performed and the treatment continued A. BCG 27 mg (Connaught strain) B. BCG 13.5 mg (Connaught strain) C. Mitomycin C: 30 mg
Okamura, 1998 RCT Medium	Japan Multicenter 1991-1993	Ta-T1 papillary bladder cancer resectable by TURBT, ECOG performance status 0 or 1, age <85 years; primary or recurrent bladder cancer if recurrence-free interval >1 year	Treatment with mitomycin C within 56 weeks, prior T2-T4 bladder cancer, concurrent cancer, pregnant, WBC <4000/mm3, platelets <100,000/mm3, Cr ≥2.0 mg/dL, Karnofsky performance score <50	A: Epirubicin 40 mg/40 mL saline 17 times (within 24 hours of TURBT, during first week, once weekly for 4 weeks, then once monthly for 11 months) B: Epirubicin 40 mg/40 mL saline 6 times (within 24 hours of TURBT, during first week, then once weekly for 4 weeks)

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Ojea, 2007 RCT Medium	Duration, median: 57 months vs. 61 months vs. 53 months Method: Cystoscopy every 3 months during first year and then every 4 months for the next 4 years	Screened: NR Randomized: 430 Postrandomization exclusion: 33 patients did not complete treatment and were withdrawn from study but were followed for recurrence and other end points Loss to followup: NR Analyzed: 397 (125 vs135 vs. 137)	Age (mean): 65 vs. 65 vs. 64 Male: 88% vs. 86% vs. 87% Race: NR Smoking: NR Stage: 16% vs. 14% vs. 9% TaG2 22% vs. 23% vs. 23% T1G1
Okamura, 1998 RCT Medium	Duration, median: 29.6 months Method: Cystoscopy and cytology at 4 weeks, then every 3 months	Screened: NR Randomized: 148 (74 vs. 74) Postrandomization exclusions: 10 (5 vs. 5) Loss to followup: NR Analyzed: 138 (69 vs. 69)	Age (mean): 64 vs. 61 years Male: 78% vs. 81% Race: NR Smoking status: NR Primary: 77% vs. 80% Recurrent: 23% vs. 20% Ta: 87% vs. 91% T1: 7.2% vs. 8.7% Tis: 5.8% vs. 0% G1: 55% vs. 43% G2: 39% vs. 48% G3: 5.8% vs. 8.7% Size ≥3 cm: 13% vs. 13% Single tumor: 65% vs. 70%

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Ojea, 2007 RCT Medium	A vs. B Recurrence: 27% (38/142) vs. 36% (50/139), RR 0.74 (95% CI 0.52 to 1.06) Disease-free interval (B vs. A): HR 1.35, (95% CI 0.89 to 2.06), adjusted HR 1.49 (95% CI 0.97 to 2.28) Recurrence rate: 0.58 vs. 0.74 per 100 patient-months Progression: 10% (14/142) vs. 13% (18/139), RR 0.76 (95% CI 0.39 to 1.47) Time to progression (B vs. A): HR 1.16 (95% CI 0.57 to 2.34) All-cause mortality: 9.2% (13/142) vs. 12% (17/139), RR 0.75 (95% CI 0.38 to 1.48) Bladder cancer death: 2.1% (3/142) vs. 3.6% (5/139), RR 0.59 (95% CI 0.14 to 2.41) Cancer-specific survival time (B vs. A): HR 1.60 (95% CI 0.38 to 6.72)	
Okamura, 1998 RCT Medium	Percent recurrence-free at 3 years: 75.1% vs. 77.2% (p=0.62) Time to first recurrence (mean, months): 36.0 vs. 36.9 % disease progression at 3 years: 2.9% (2/69) vs. 1.4% (1/69)	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Ojea, 2007 RCT Medium		A vs. B Withdrawals due to AE: NR Local toxicity 65% vs. 64% Systemic toxicity: 11% vs. 11%	NR	
Okamura, 1998 RCT Medium		Dysuria: 7.2% overall Gross hematuria: 0.7% overall Withdrawal due to adverse events: 1.4% (2/138) Local toxicity: No difference between groups	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Pagano, 1995 RCT High Bassi, 1992 Abstract of interim results	Italy Single center 1990	Multiple papillary tumors (Ta-T1) and CIS	NR	6-week course of intravesical therapy: A. Pasteur strain BCG 75 mg B. Pasteur strain BCG 150 mg
Palou, 2001 RCT Medium	Spain, England Number of centers: unclear 1989-1995	Primary or relapsing stage Ta or T1 grade 3 superficial bladder tumors with or without associated CIS or isolated CIS or associated with grade 2 superficial bladder tumors, responded to induction therapy with BCG	Invasive bladder tumors, bladder radiotherapy, intolerance to the first course of BCG instillations	Initial treatment with 6 weekly instillations of BCG 81 mg (Connaught strain); if relapse then 6 additional weekly instillations; if disease free then randomized to: A. BCG 81 mg (Connaught) 6 weekly instillations every 6 months for 2 years B. No further treatment After randomization, high grade superficial relapse treated with new course of BCG instillations; low grade relapses treated with MMC or BCG
Rentsch, 2014 RCT Medium	Switzerland Single center 1998-2010	High risk NMIBC (any high-grade tumor, any low-grade tumor with more than two recurrences within 2 years, or carcinoma in situ)	Prior intravesical BCG therapy	A: BCG Connaught (6.6-19.2 x 10^8 CFU) B: BCG Tice (2-8 x 10^8 CFU) Six weekly intravesical instillations

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Pagano, 1995 RCT High Bassi, 1992 Abstract of interim results	Duration: NR Method: NR	Screened: NR Randomized: NR Postrandomization exclusions: None reported Loss to followup: None reported Analyzed: 183 (90 vs. 93)	NR
Palou, 2001 RCT Medium	Duration: Median followup 78 months Method: Alternating cytology and cystoscopy every 3 months for 2 years and then cytology and cystoscopy every 6 months	Screened: NR Randomized: 131 Post-randomization exclusions: None reported Loss to followup: None reported Analyzed: 126 (65 vs. 61)	Age (mean) 65 vs. 63 Male: 98% vs. 92% Race: NR Smoking: NR Stage: Ta: 22 (34%) vs. 19 (31%) T1: 31 (48%) vs. 34 (56%) Solitary CIS: 12 (18%) vs. 8 (13%)
Rentsch, 2014 RCT Medium	Duration: Median followup: 47.6 vs. 51.4 months Method: Cystoscopy and cytology at 3- month intervals for the first 3 years, then at 6-moth intervals for the following 2 years. Urography or CT scan at 1 and 3 years after BCG.	Screened: 179 Randomized: 142 Postrandomization exclusions: 7 Lost to followup: 2 vs. 2 Total analyzed: 71 vs. 60	Age (median): 72 vs. 72 years Race: NR Male: 86% vs. 83% Smoking status: NR Recurrent bladder cancer: 69% vs. 72% no prior TURBT Stage: Ta: 27/71 (38%) vs. 19/60 (32%) T1: 41/71 (58%) vs. 32/60 (53%) Tis: 3/71 (4%) vs. 9/60 (15%) Functional status: NR

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Pagano, 1995 RCT High Bassi, 1992 Abstract of interim results	Disease free survival Ta: no difference between doses (p=0.55) Disease free survival CIS: favors the low dose group (p<0.001) Disease free survival T1: number of patients enrolled to date does not allow a statistical conclusion (p=0.07)	
Palou, 2001 RCT Medium	Tumor-free: 53 vs. 46 Superficial relapse: 10 (15%) vs. 16 (26%), p=0.07 Progression: 3 vs. 2 Mortality: 11 vs. 8 Died of bladder cancer: 3 vs. 2	
Rentsch, 2014 RCT Medium	A vs. B 5- year recurrence-free survival: 74% (95% CI 39.1-63.3 months) vs. 48% (95% CI 35.5-65.1 months), p=0.0108 5- year progression-free survival: 94.1% (95% CI 87.8-100%) vs. 87.9 (95% CI 76.5-100), p=0.3442 Overall survival: 84.9% (95% CI 75.5-95.5) vs. 93.6 (95% CI 85.2-100), p=0.2652 Disease-specific survival: 93% (95% CI 86.5-100) vs. 100% (100-100), no p-value reported	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Pagano, 1995 RCT High Bassi, 1992 Abstract of interim results		Withdrawals due to AE: NR Fever: 18 vs. 33, p<0.05 Cystitis: 32 vs. 57, p<0.05 Macroscopic hematuria: 13 vs. 26, p<0.05	NR	Only interim results
Palou, 2001 RCT Medium		Discontinued instillations due to side effects: 32 in BCG maintenance group; number in control group NR	NR	
Rentsch, 2014 RCT Medium		Side effects caused by BCG: 20/71 vs. 25/60, p=0.09	Swiss Naational Science Foundation	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Rubben, 1988 RCT Medium	Germany Single center 1979-1981	Primary or recurrent NMIBC, any grade	Bimanual palpable tumor after TURBT, previous radiotherapy, intravesical chemotherapy within 6 months, other malignancy	A: Doxorubicin 50 mg/50 mL saline, 13 instillations (2 hours prior to TURBT, then twice weekly for 6 weeks) B: Doxorubicin 50 mg/50 mL saline, 28 instillations (2 hours prior to TURBT, then twice weekly for 6 weeks, twice monthly for 4.5 months, once monthly for 6 months) C: No intravesical therapy
Saika, 2010 RCT Medium	Japan Multicenter Study years: April 1995 - January 2001	Transitional cell carcinoma of the bladder (primary or recurrent). Stages Ta or T1; Grade G1, G2, or G3. Age $\geq$ 20 years.	Concurrent or previous CIS; Concurrent or previous urinary tract cancer; Concurrent or previous muscle invasive disease; Lethal disease.	A. Epirubicin, 20 mg (in 40 mL physiological saline). Two intravesical infusions, one immediately after (< 1 hour) TURBT and one in the early morning of the following day, retained in bladder for 1 hour. B. Epirubicin, 50 mg (in 100 mL physiological saline). Same procedure as A. C. No adjuvant therapy. TURBT only.

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Rubben, 1988 RCT Medium	Duration: Mean, median NR Method: Cystoscopy and cytology every 3 months for 2 years, then every 6 months	Screened: NR Randomized: 268 (91 vs. 88 vs. 89) Postrandomization exclusions: NR Loss to followup: NR Analyzed: 220 (79 vs. 59 vs. 82)	Age (mean): 64 vs. 64 vs. 68 years Male: 79% vs. 79% vs. 77% Race: NR Smoking status: NR Primary: 75% vs. 67% vs. 74% Recurrent: 25% vs. 33% vs. 26% Ta: 84% vs. 81% vs. 77% T1: 16% vs. 19% vs. 23% G1: 60% vs. 65% vs. 59% G2: 36% vs. 28% vs. 34% G3: 7.0% vs. 4.0% vs. 7.2% >3 cm: 19% vs. 15% vs. 24% Solitary: 69% vs. 66% vs. 82%
Saika, 2010 RCT Medium	Duration, median: Overall: 44 months; A vs. B vs. C: 44 vs. 46 vs. 42 Method: Cystoscopy every 3 months for 2 years and every 6 months thereafter.	Screened: NR Randomized: 303 Postrandomization exclusions: 21 Eligible: 257 (83 vs. 90 vs. 84) Lost to followup: 17 Total analyzed: 240 (79 vs. 84 vs. 77)	A vs. B vs. C Median age, years: 69 vs. 69 vs. 71 Male: 81% vs. 89% vs. 88% Race: NR Recurrent bladder cancer: 40% vs. 43% vs. 40% Stage Ta: 54% vs. 60% vs. 64% Stage T1: 46% vs. 40% vs. 36% Grade G1: 25% vs. 33% vs. 31% Grade G2: 59% vs. 47% vs. 52% Grade G3: 14% vs. 20% vs. 17% Functional status: NR

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Rubben, 1988 RCT Medium	All-cause mortality: 6.7% vs. 1.8% vs. 13.3% (p>0.35) Bladder cancer mortality: 5.3% vs. 1.8% vs. 7.2% (p>0.35) Recurrence rate: 2.5 vs. 2.3 vs. 2.7 per 100 patient-months (p>0.35) Progression: 16% vs. 11% vs. 12% (p>0.35) Time to recurrence (months): 19 vs. 22 vs. 19 (p>0.1)	Recurrence rate (per 100 patient-months) (p>0.05 in all subgroups) Primary: 2.5 vs. 2.4 vs. 2.3 Recurrent: 2.6 vs. 2.8 vs. 3.9 Solitary: 1.8 vs. 3.0 vs. 2.0 Multiple: 3.6 vs. 3.6 vs. 4.6 <3 cm: 1.9 vs. 3.4 vs. 2.9 >3 cm: 2.7 vs. 2.9 vs. 2.6 Tis negative: 2.3 vs. 3.1 vs. 2.2 Tis positive: 3.2 vs. 3.2 vs. 4.4
Saika, 2010 RCT Medium	A vs. B Median recurrence-free survival, months: 24 vs. 38 (p>0.05) Progression: 0.0% (0/83) vs. 1.1% (1/90), RR 0.36 (95% CI 0.01 to 8.74)	NR

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Rubben, 1988 RCT Medium		Systemic side effects: None observed Local side effects resulting in incomplete treatment: 11% vs. 33% vs. 11%	NR	
Saika, 2010 RCT Medium	NR	A vs. B Bladder Grade 1 irritabilities (e.g., micturition pain and/or frequency): 22.9% vs. 35.6%; p=0.106 Grade 1 anemia: 2.4% (2/83) vs.2.2% (2/90) Grade 1 serum transaminases elevation: 1.2% (1/83) vs. 3.3% (3/90) Grade 1 leukopenia: 0.0% (0/83) vs.1.1% (1/90)	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Schwaibold, 1997 RCT Medium	Germany Single center 1983-1987	Ta, T1, or Tis transitional cell carcinoma of the bladder	Unable to perform instillation due to age, immobility, or lack of cooperation	A: Mitomycin C 20 mg/20 mL saline, 42 instillations (every 2 weeks for 1 year, every 4 weeks for 1 year, every 3 months for 1 year) B: Mitomycin C 20 mg/20 mL saline, 42 instillation (every week for 8 weeks, every 4 weeks for 44 weeks and 2 additional years) C: Mitomycin C 20 mg/20 mL saline, 20 instillations (every week for 20 weeks) D: Doxorubicin 50 mg/50 mL saline, 42 instillations (same schedule as A)
Sengiku, 2013 RCT Medium	Japan Single center 2004-2012	Stage Ta/T1 or Tis, multiple tumors and recurrence-free period of 3 months or less		At least 2 weeks after removing as much of visible lesion as possible by TURBT, patients received weekly up to 8 times: A. BCG 80 mg (Tokyo strain) in 40 mL saline B. BCG 81 mg (Connaught strain) in 40 mL saline

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Schwaibold, 1997 RCT Medium	Duration, median: 57 months Method: Cystoscopy every 3 months	Screened: NR Randomized: 477 Postrandomization exclusions: 29 Loss to followup: 29 Analyzed: 419 (209 vs. 96 vs. 75 vs. 39)	Age (median): 72 vs. 71 vs. 69 vs. 73 Male: 82% vs. 77% vs. 77% vs. 74% Race: NR Smoking status: NR Primary: 68% vs. 75% vs. 75% vs. 56% Recurrent: 32% vs. 25% vs. 25% vs. 44% Ta: 74% vs. 78% vs. 76% vs. 59% T1: 23% vs. 20% vs. 21% vs. 33% Tis: 3.3% vs. 2.1% vs. 2.7% vs. 7.7% G1: 47% vs. 58% vs. 52% vs. 44% G2: 57% vs. 35% vs. 37% vs. 38% G3: 1.9% vs. 4.2% vs. 8.0% vs. 10% Solitary: NR Tumor size: NR
Sengiku, 2013 RCT Medium	Method: Cystoscopy and urine cytology every 3 months for first 2 years and every 3-6 months thereafter	Screened: NR Randomized: 178 Postrandomizations exclusions (for efficacy): 49 with a history of intravesical BCG therapy or concurrent upper urinary tract tumor or discontinued BCG therapy before 6 doses were excluded Loss to followup: none reported Analyzed: 129: (66 vs. 63)	Age (mean): 70 vs. 71 Male: 89% vs. 76% Race: NR Smoking: NR Stage: 45% vs. 43% Ta 33% vs. 33% T1 21% vs. 24% Tis Grade: 61% vs. 57% High 39% vs. 43% Low 26% vs. 8% CIS

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Schwaibold, 1997 RCT Medium	A vs. B vs. C vs. D Recurrence: 24% (51/209) vs. 18% (17/96) vs. 20% (15/75) vs. 31% (12/39) (p=0.21 for overall treatment effect in Cox proportional hazards model adjusted for number of prior recurrences, and grade/Tis); RR for B vs. A 0.53, 95% CI 0.29 to 0.96) Progression: 12% (24/209) vs. 5.2% (5/96) vs. 6.7% (5/75) vs. 18% (7/39) (p=0.01 for overall treatment effect in Cox proportional hazards model adjusted for number of prior recurrences, grade/Tis, recurrent cancer); RR for B vs. A 0.06, 95% CI 0.01 to 0.51	Recurrence Primary: 15% (21/142) vs. 12% (9/72) vs. 12% (7/56) vs. 27% (6/22) Recurrent: 45% (30/67) vs. 33% (8/24) vs. 42% (8/19) vs. 35% (6/17) Progression Primary: 4.9% (7/142) vs. 4.2% (3/72) vs. 5.4% (3/56) vs. 18% (4/22) Recurrent: 25% (17/67) vs. 4.2% (1/24) vs. 10% (2/19) vs. 18% (3/17), RR for B vs. A 5.1, 95% CI 1.2 to 23 Recurrence rate (per 100 patient-months) Primary: 2.11 vs. 1.52 vs. 1.00 vs. 0.80 Recurrent: 0.54 vs. 0.49 vs. 0.27 vs. 0.91
Sengiku, 2013 RCT Medium	Percent recurrence-free: 73% vs. 69% at 2 years, 62% vs. 56% at 5 years (p=0.75)	Percent recurrence-free Ta/T1 without CIS (n=78): 77.6% vs. 62.6% at 2 years, 69.0% vs. 42.6% at 5 years (p=0.22) Complete response (negative urine cytology and random biopsies) Ta/T1 with CIS (n=51): 90% (28/31) vs. 85% (17/20) (p=0.90)

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Schwaibold, 1997 RCT Medium		NR	NR	Reported RR for recurrence, B vs. A, appears much lower than expected based on crude rates, even if adjusted
Sengiku, 2013 RCT Medium		Withdrawals due to AE: 7 (8%) vs. 9 (10%) Fever AE or complication events: 12 vs. 10 Cystitis AE or complication events: 33 vs. 28 Hematuria AE or complication events: 8 vs. 12	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Serretta, 2010 RCT Medium	Italy Multicenter 2002-2003	Multiple and recurrent Ta tumors; recurrent, single or multiple T1 tumors	Single and primary Ta/T1 G1/G2 tumors, concomitant or previous Tis and/or T1G3, lesions >3 cm, previous BCG, previous doxorubicin or epirubicin, other intravesical therapy in last 12 months, previous radiotherapy and/or systemic chemotherapy	A: Epirubicin 80 mg/50 mL saline, 16 instillations (within 6 hours of TURBT, then once weekly for 5 weeks, once weekly for 10 months) B: Epirubicin 80 mg/50 mL saline, 6 instillations (within 6 hours of TURBT, then once weekly for 5 weeks)
Tolley, 1996 RCT Medium	United Kingdom Multicenter Study years: March 1984 - December 1986	Patients with newly diagnosed stage Ta or T1 transitional cell carcinoma of the bladder; Grades 1 -3.	CIS alone	A: Mitomycin C 40 mg (in 40 mL water), single instillation within 24 hours of TURBT; retained for 60 minutes. B: Mitomycin C 40 mg (in 40 mL water), instillation within 24 hours of TURBT; retained for 60 minutes. Additional instillations (same dose) every 3 months x 1 year (total 5 instillations). C: No adjuvant treatment. TURBT alone.

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Serretta, 2010 RCT Medium	Duration, median: 48 months Method: Cystoscopy and cytology every 3 months for 2 years, then 6 months from years 3 to 5	Screened: 577 Randomized: 482 (245 vs. 237) Postrandomization exclusions: NR Loss to followup: 87 (43 vs. 44) Analyzed: 395 (185 vs. 210)	Age (median): 69 vs. 68 years Male: 89% vs. 84% Race: NR Smoking status: NR Primary: 62% vs. 58% Recurrent: 38% vs. 42% Single: 34% vs. 34% Multiple: 66% vs. 66^ TaG1-2: 37% Vs. 35% T1G1: 24% vs. 21% T1G2: 39% vs. 44%
Tolley, 1996 RCT Medium	Duration, median: (A and B, NR for C): 7 years Method: Cystoscopy every 3 months for a year, then every 6 months for a year, annually thereafter.	Screened: 502 Randomized: 452 Postrandomization exclusions: NR Lost to followup: 5* (2 vs. 1 vs. 2) Total analyzed: 452 (149 vs. 146 vs. 157) * reportedly with no followup data, but included in ITT analyses	A vs. B vs. C Age 24-50: 13% vs. 9% vs. 9% Age 51-60: 24% vs. 23% vs. 29% Age 61-70: 36% vs. 37% vs. 34% Age 71-80: 23% vs. 30% vs. 25% Age 81-100: 4% vs. 1% vs. 3% Male: NR Race: NR Stage Ta: 50% vs. 52% vs. 56% Stage T1: 48% vs. 50% vs. 43% Grade 1: 37% vs. 34% vs. 45% Grade 2: 52% vs. 55% vs. 46% Grade 3: 10% vs. 10% vs. 8%

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Serretta, 2010 RCT Medium	Percent recurrence-free at 3 months: 98.4% (182/185) vs. 94.8% (199/210) (p=0.06) Percent recurrence-free at 6 months: 95.1% (174/183) vs. 87.3% (157/180) (p=0.004) Percent recurrence-free at 12 months: 86.7% (143/165) vs. 79.1% (136/172) (p=0.03) Percent recurrence-free at 18 months: 77.8% (105/135) vs. 68.1% (98/144) (p=0.03) Percent recurrence-free at 24 months: 70.2% (87/124) vs. 63.0% (85/135) (p=0.11) Percent recurrence-free at 36 months: 62.1% (72/116) vs. 54.4% (69/127) (p=0.11) Percent recurrence-free at 48 months: 50.5% (48/95) vs. 45.9% (51/111) (p=0.26) Time to recurrence (median, months): 17 vs. 12 (p=0.10) Progression to muscle-invasive: 2.9% (7/245) vs. 1.3% (3/237)	Percent recurrence-free at 12 months Primary: 91.4% vs. 82.6% (p=0.03) Recurrent: 82.3% vs. 77.1% (p=0.67) Single: 87.1% vs. 83.9% (p=0.45) Multiple: 88.3% vs. 78.4% (p=0.08) Ta: 88.8% vs. 81.6% (p=0.10) T1: 87.4% vs. 79.7% (p=0.28) G1: 92.6 vs. 78.3% (p=0.05) G2: 84.9% vs. 81.6% (p=0.41)
Tolley, 1996 RCT Medium	**A vs. B** Recurrence at 24 months: 42% vs. 31% (p=0.14) Recurrence-free interval, group comparisons, HR 0.74 (95% CI 0.51 to 1.06) Progression-free interval, group comparisons, HR 0.97 (95% CI 0.46 to 2.06) All-cause mortality: 33.6% (50/149) vs. 42.5% (62/146), RR 0.79 (95% CI 0.59 to 1.1) Bladder cancer mortality: 5.4% (8/149) vs. 5.5% (8/146), RR 0.98 (95% CI 0.38 to 2.5)	NR

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Serretta, 2010 RCT Medium		Serious adverse events: 0.2% overall Chemical cystitis with discontinuation of treatments: 0.4% overall Fever: 2.2% overall Dysuria and urgency resulting in treatment interruption: 7.1% overall Hematuria: 2.9% overall Treatment postponement: 15.7% overall	NR	
Tolley, 1996 RCT Medium	NR	A vs. B (none reported for C) Dysuria and frequency: 0% (0/149) vs. 6.2% (9/146), RR 0.05 (95% CI 0.003 to 0.88) Delayed healing of biopsy site: 0.7% (1/149) vs. 4.1% (6/146) Chemical cystitis was NR as a side effect by any patient in either group.	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Turkeri, 2010 RCT Medium	Turkey Multicenter 2002-2004	Primary bladder tumor, ≤3 lesions, Ta (G2 or G3) or T1 (G1 or G2)	Tis, incomplete TURBT, tumor in the urethra or upper urinary tract, other malignancy, >80 years of age, WHO performance score >2; instillation >18 hours after TURBT	A: Epirubicin 100 mg within 6 hours after TURBT B: Epirubicin 100 mg within 6 hours and 12-hours after TURBT
Ueda, 1992 RCT Medium	Japan Multicenter 1984-1986	Ta and T1 transitional cell carcinoma of bladder	Incomplete resection with recurrence within first month	A: Doxorubicin 30 mg/30 mL saline, 19 instillations (immediately and 2 days after TURBT, then weekly for 2 weeks, every 2 weeks for 14 weeks, monthly for 8 months) B: Doxorubicin 30 mg/30 mL saline, 19 instillations (immediately and 2 days after TURBT, then weekly for 2 weeks, every 2 weeks for 14 weeks, monthly for 8 months) plus 5-fluorouracil 200 mg/day starting at 1 week C: Doxorubicin 30 mg/30 mL saline, 17 instillations (starting 7 days after TURBT weekly for 2 weeks, every 2 weeks for 14 weeks, monthly for 8 months) D: Doxorubicin 30 mg/30 mL saline, 17 instillations (starting 7 days after TURBT weekly for 2 weeks, every 2 weeks for 14 weeks, monthly for 8 months) plus 5-fluorouracil 200 mg/day starting at 1 week

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Turkeri, 2010 RCT Medium	Duration, mean: 16.9 months Method: Cystoscopy every 3 months for 1 year, then every 6 months during years 2 and 3, then once yearly	Screened: NR Randomized: 299 Postrandomization exclusions: NR Loss to followup: NR Analyzed: 143 (68 vs. 75)	Mean age: 59 vs. 62 years Male: NR Race: NR Smoking status: NR Primary: 85% vs. 79% Recurrent: 15% vs. 21% Ta: 54% vs. 52% T1: 46% vs. 48% G1: 19% vs. 17% G2: 78% vs. 80% G3: 2.9% vs. 2.7%
Ueda, 1992 RCT Medium	Duration, mean: 31 months Method: Cystoscopy at 4 weeks then every 3 months	Screened: NR Randomized: 275 (68 vs. 67 vs. 70 vs. 70) Postrandomization exclusions: 51 (18 vs. 12 vs. 12 vs. 9) Loss to followup: 37 (10 vs. 11 vs. 5 vs. 11) Analyzed: 187 (40 vs. 44 vs. 53 vs. 50)	Mean age: 64 vs. 66 vs. 63 vs. 60 years Male: 72% vs. 82% vs. 83% vs. 78% Race: NR Smoking status: NR Primary: 70% vs. 77% vs. 75% vs. 70% Recurrent: 30% vs. 23% vs. 25% vs. 30% Ta: 55% vs. 50% vs. 47% vs. 68% T1: 40% vs. 34% vs. 40% vs. 28% Tx: 5.0% vs. 16% vs. 13% vs. 4.0% G1: 35% Vs. 34% vs. 23% vs. 42% G2: 55% vs. 52% vs. 62% Vs. 40% G3: 10% vs. 14% vs. 9.4% vs. 18% >3 cm: 7.5% vs. 9.1% vs. 5.7% vs. 14% Solitary: 52% vs. 48% vs. 57% vs. 48%

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Turkeri, 2010 RCT Medium	Recurrence rates: 14.7% vs. 21.3%, adjusted HR 0.67 (95% CI 0.30 to 1.51) (adjusted for grade, stage, solitary vs. multiple, age <70 vs. ≥70 years) Progression: 1.5% (1/68) vs. 4.0% (3/75), RR 0.37 (95% CI 0.04 to 3.45) Recurrence-free survival (months): 10.3 vs. 10.5 months (p=0.47, log-rank) Disease-free survival (months): 14.9 vs. 15.5 months	
Ueda, 1992 RCT Medium	Percent recurrence-free at 36 months: 79.4% vs. 73.7% vs. 67.6% vs. 63.1% (NS); 76.4% vs. 65.4% for A + B vs. C +D (p>0.05)	Higher recurrence-free rate in early therapy groups (A + B) vs. delayed therapy groups (C + D) for primary tumors, Ta, <1 cm, G1, multiple tumors, G2

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Turkeri, 2010 RCT Medium		NR	NR	
Ueda, 1992 RCT Medium		Bladder irritation: 48% (24/50) vs. 55% (30/55) vs. 26% (15/58) vs. 26% (16/61) Bladder irritation resulting in withdrawal: 8% (4/50) vs. 5% (3/55) vs. 2% (1/58) vs. 3% (2/61) Hematuria and bladder calculi: 0 vs. 0 vs. 0 vs. 2% (1/61)	NR	

Author, Year Study Design Risk of Bias	Setting (country, single/multi-sites) Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)
Ueda, 1992 RCT Medium	The Netherlands Multicenter 1987-1990	Histologically proven papillary pTa-pT1 transitional cell transitional cell carcinoma of the bladder with or without CIS	Previous local or systemic cancer therapy or radiotherapy	A. MMC 30mg in 50mL saline once a week for 4 weeks and thereafter once a month for 5 months. If a superficial recurrence or persistent CIS after 6 months, 3 additional monthly instillations given B. BCG-Tice C. BCG RIVM BCG 5X108 bacilli in 50mL saline, administered once a week for 6 weeks. At the time of first superficial recurrence or persistent CIS at 3 or 6 months, a second 6 week course with BCG instillations was given after complete TURBT or biopsy.
Witjes, 1993 RCT Medium The Dutch Cooperative Trial Witjes, 1996	The Netherlands Multicenter 1987-1990	Histologically proven papillary pTa-pT1 transitional cell transitional cell carcinoma of the bladder with or without CIS	Previous local or systemic cancer therapy or radiotherapy	A. MMC 30mg in 50mL saline once a week for 4 weeks and thereafter once a month for 5 months. If a superficial recurrence or persistent CIS after 6 months, 3 additional monthly instillations given B. BCG-Tice C. BCG RIVM BCG 5X108 bacilli in 50mL saline, administered once a week for 6 weeks. At the time of first superficial recurrence or persistent CIS at 3 or 6 months, a second 6 week course with BCG instillations was given after complete TURBT or biopsy.

Author, Year Study Design Risk of Bias	Duration of Followup and Followup Method	Number of Treatment and Control Subjects (screened, randomized, postrandomization exclusions, lost to followup, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, smoking status, recurrent bladder cancer, stage of disease, functional status)
Ueda, 1992 RCT Medium	Duration, median: 32 months Method: Cystoscopy every 3 months for 2 years, every 4 months in years 3 and 4 and every 6 months thereafter	Screened: NR Randomized: 469 (156 vs. 154 vs. 159) postrandomization exclusions: 17 (ineligible) Loss to followup: None reported although 15 patients excluded for "different reasons" Analyzed: 437 (148 vs. 140 vs. 149)	Age (mean): 66 vs. 66 vs. 66 years Male: 80% vs. 86% vs. 87% Race: NR Smoking status: NR G1: 16% vs. 20% vs. 22% pTaG2: 37% vs. 34% vs. 36% G3: 4% vs. 4% vs. 3% CIS: 8% vs. 16% vs. 10%
Witjes, 1993 RCT Medium The Dutch Cooperative Trial Witjes, 1996	Duration, median: 32 months Method: Cystoscopy every 3 months for 2 years, every 4 months in years 3 and 4 and every 6 months thereafter	Screened: NR Randomized: 469 (156 vs. 154 vs. 159) Post-randomization exclusions: 17 (ineligible) Loss to followup: None reported although 15 patients excluded for "different reasons" Analyzed: 437 (148 vs. 140 vs. 149)	Age (mean): 66 vs. 66 vs. 66 Male: 80% vs. 86% vs. 87% Race: NR Smoking status: NR G1: 24 (16%) vs. 28 (20%) vs. 32 (22%) pTaG2: 55 (37%) vs. 48 (34%) vs. 54 (36%) G3: 4 (4%) vs. 5 (4%) vs. 4 (3%) CIS: 12 (8%) vs. 23 (16%) vs. 15 (10%)

Author, Year Study Design Risk of Bias	Results	Results: According to Tumor Characteristics (KQ3 b)
Ueda, 1992 RCT Medium	B vs. C % Recurrence-free, all papillary tumors 1 yr: 68% vs. 69% 2 yr: 54% vs. 62% 5 yr: 36% vs. 54% (log-rank, p=0.07) Recurrence: 64% (75/117) vs. 46% (62/134), RR 1.39 (95% CI 1.10 to 1.74) Progression: 5% (7) vs. 6% (8)	B vs. C % Disease-free, G3 papillary tumors 1 yr: 55% vs. 64% 2 yr: 46% vs. 50% Complete response (negative cystoscopy, cytology, and biopsies), CIS: 70% (16/23) vs. 47% (7/16), RR 1.59 (95% CI 0.86 to 2.95)
Witjes, 1993 RCT Medium The Dutch Cooperative Trial Witjes, 1996	% Disease-free, all papillary tumors 1 year: 76% vs. 68% vs. 69% 2 year: 65% vs. 54% vs. 62% % Disease-free, grade 3 papillary tumors 1 year: 79% vs. 55% vs. 64% 2 year: 0 vs. 46% vs. 50% Complete response in patients with CIS (N=50) 5 (42%) vs. 16 (70%) vs. 7 (47%), p=0.20 5 year followup: % Disease-free (all papillary tumors): 57% vs. 36% vs. 54% Response rate (CIS): 8 (67%) vs.17 (74%) vs. 9 (60%) Recurrence: 58/136 (43%) vs. 75/117 (64%) vs. 62/134 (46%)	

Author, Year Study Design Risk of Bias	Results: According to Patient Characteristics (KQ3 e)	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Ueda, 1992 RCT Medium		B vs. C Drug-induced cystitis: 30% (42/140) vs. 32% (48/149) Drug-induced cystitis requiring treatment delay or discontinuation: 1.4% (2/140) vs. 2.0% (3/149) Systemic side-effects: 27% (38/140) vs. 18% (27/149) Systemic side-effects requiring treatment delay or discontinuation: 4.3% (6/140) vs. 2.0% (3/149) Withdrawals due to AE: 14 (total across 3 arms) Intercurrent death=10 (total across 3 arms)		
Witjes, 1993 RCT Medium The Dutch Cooperative Trial Witjes, 1996		Drug-induced cystitis: 26 (18%) vs. 42 (30%) vs. 48 (32%), p=0.009 Systemic side-effects: 6 (4%) vs. 38 (27%) vs. 27 (18%) Sepsis: 0 vs. 1 vs. 0 Withdrawals due to AE: 14 (total) Intercurrent death=10 (total)	NR	

Please see Appendix C. Included Studies for full study references.

Table E5. Key Question 4: Included randomized controlled trials

Author, Year Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Cystoscopic Followup Method
Harland, 2007 RCT Medium	United Kingdom Multicenter 1991-2003	Diagnosed with pT1G3 NX M0 tumor or tumors of the bladder in the previous 6 months; muscle from base of tumor was histologically clear; all visible tumors resected transurethrally	Prior therapy with intravesical chemotherapy or BCG (other than a single adjuvant treatment)	Group 1: Patients with single tumors and no carcinoma *in situ* A: Observation, no treatments given other than TURBT before 3 month cystoscopy (n=38) B: Radiation therapy, 60 Gy in 30 fractions during 6 weeks (n=39) Group 2: Patients with multiple tumors or carcinoma *in situ* C: Radiation therapy, 60 Gy in 30 fractions during 6 weeks (n=65) D: Intravesical therapy, clinician preference for either Mitomycin C, 40 mg in 40 mL water, weekly for 6 weeks OR BCG approximately 109 viable organisms in 50 mL normal saline, weekly for 6 weeks A second course of 6 BCG instillations could be given if followup biopsy was positive. After initial treatment period clinicians were free to treat patients as they thought appropriate	Duration: Median followup in survivors: 44 months Method: Cystoscopy at 3, 6,9 and 12 months after randomization, then at least annually
Mulders, 1994 Retrospective Cohort High	The Netherlands 1983-1988	T1G3 tumors	Not Reported	A: TURBT only B: TURBT + intravesical therapy with 30mg Mitomycin C in 50 mL saline once per week for one month and then once per month for a total of 6 months OR BCG given once per week for 6 consecutive weeks C: TURBT + external beam radiation therapy with 44 Gy on the pelvic region and 66 Gy boost on the bladder region	Duration (Median): 4 years Method: Not reported

Author, Year Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Comments
Harland, 2007 RCT Medium	Screened: Not reported Randomized: 210 (38 vs. 38 vs. 65 vs. 68) Post-randomization exclusions: 6, pT2 at diagnosis Lost to followup: 7 Analyzed: 204 (38 vs. 38 vs. 64 vs. 64)	Age (median): 70 vs. 69 vs. 70 vs. 68 years Male: 84% vs. 92% vs. 84% vs. 81% Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Largest Tumor Diameter <2cm: 56% vs. 53% vs. 69% vs. 72% Functional status:	A,B,D vs. C: Hazard Ratio (95% CI) Progression-free interval: 1.0 (0.65-1.74) Progression-free survival: 1.35 (0.92-1.98) Overall survival: 1.32 (0.86-2.04) Recurrence-free interval: 0.77 (0.54-1.10) Recurrence-free survival: 0.94 (0.67-1.30)	A vs. D vs. B,C: Urinary frequency: 4/38 vs. 1/6 vs. 8/102 Cystitis: 1/38 vs. 0 vs. 2/102	Not Reported	
Mulders, 1994 Retrospective Cohort High	Screened: 155 Randomized: Not applicable, non randomized study Post-randomization exclusions: Not applicable, non randomized study Lost to followup: Not reported Analyzed: 121 (48 vs. 51 vs. 17)	Age (years): ≥ 70: 51%; <70: 49% Male: 86% Race: Not reported Smoker: Not reported Recurrent bladder cancer: 0 Single tumor only: 61% Functional status: Not reported	Median time to first recurrence (months): 11 vs. 19 vs. 25; P<0.05 for A vs. B,C; B vs. C not significantly different Recurrence during followup: 75% vs. 55% vs. 35%; P<0.05 for A vs. B,C; B vs. C not significantly different	Not Reported	Not Reported	

Please see Appendix C. Included Studies for full study references.

Table E6. Key Question 6: Included randomized controlled trials

Author, Year Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Cystoscopic Followup Method
Babjuk, 2005 High	Czech Republic Single center 2001-2003	Patients with suspected primary or recurrent superficial urinary bladder cancers	History of surgical or instillation intravesical therapy within the previous 3 months	A: White light and 5-ALA fluorescent cystoscopy with TURBT (n=60) B: White light cystoscopy with TURBT (n=62) All patients with G1 or G2 tumors received adjuvant intravesical therapy; all patients with G3 tumors received intravesical BCG	Duration: 24 months Method: followup with white light cystoscopy
Dragoescu, 2011 Medium	Romania Single center 2009	Patients with NMIBC	Not stated	A: White light and HAL fluorescent cystoscopy with TURBT B: White light cystoscopy with TURBT All patients received postoperative intravesical epirubicin (Farmorubicin) and additional therapy based on risk group	Duration: 12 months, followup Method: cystoscopy method not reported

Author, Year Risk of Bias	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results
Babjuk, 2005 High	Screened: Not reported Randomized: 128 (64 vs. 64) Post-randomization exclusions: None reported Lost to followup: None reported Analyzed for recurrence (NMIBC): 122 (60 vs. 62)	Age (mean): 68 vs. 70 years Male: 72% vs. 63% Race: Not reported Smoker: Not reported Recurrent bladder cancer: 67% vs. 55% Stage: 63% vs. 60% Ta, 37% vs. 40% T1 Grade: 50% vs. 53% G1, 40% vs. 35% G2, 10% vs. 11% G3	A vs. B Recurrence at 10-15 weeks: 8% (5/60) vs. 37% (23/62) Recurrence-free (n=60 and 62): 66% vs. 39% at 12 months, 40% vs. 28% at 24 months Median time to recurrence: 14 vs. 4 months (p=0.008, log-rank test) Recurrence-free, multiple tumors (n=45 and 38): 62% vs. 32% at 12 months, 39% vs. 13% at 24 months (p=0.001, log-rank test) Recurrence-free, solitary tumors (n=15 and 24): 80% vs. 52% at 12 months, 46% vs. 48% at 24 months (p=0.47, log-rank test) Recurrence-free, primary tumors (n=20 and 28): 85% vs. 46% at 12 months, 39% vs. 34% at 24 months (p=0.13, log-rank test) Recurrence-free, recurrent tumors (n=40 and 34): 57% vs. 33% at 12 months, 40% vs. 23% at 24 months (p=0.02, log-rank test) Progression through 15 months: 8.3% (5/60) vs. 8.1% (5/62)
Dragoescu, 2011 Medium	Screened: Not reported Randomized: 57 (27 vs. 35) Post-randomization exclusions: None reported Lost to followup: None reported Analyzed for recurrence (NMIBC): 44 (22 vs. 22)	Age (mean): 59 vs. 62 years Male: 78% Race: Not reported Smoker: 73% vs. 64% Recurrent bladder cancer: Not reported Stage: 22% vs. 18% Ta, 78% vs. 82% T1 Grade: 32% vs. 27% G1, 55% vs. 64% G2, 14% vs. 9.1% G3	A vs. B Recurrence at 3 months: 4.6% (1/22) vs. 14% (3/22) Recurrence at 6 months: 9.1% (2/22) vs. 23% (5/22) Recurrence at 12 months: 18% (4/22) vs. 45% (10/22), HR 0.33 (95% CI 0.11 to 0.98)

Author, Year Risk of Bias	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Comments
Babjuk, 2005 High	Not reported	Czech Health Ministry	
Dragoescu, 2011 Medium	Not reported	National Exploratory Research Project Program	

Author, Year Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Cystoscopic Followup Method
Filbeck, 2002 (also Denzinger 2007a, Denzinger 2007b) Medium	Germany Single center 1997-2000	Patients suspected of having bladder cancer on preoperative endoscopy	Not stated	A: White light and 5-ALA fluorescent cystoscopy with TURBT (n=88) B: White light cystoscopy with TURBT (n=103) All patients received intravesical prophylaxis based on AUA guidelines according to number of tumors, stage, and grade	Duration: Mean 21 months, followup Method: cystoscopy method not reported

Author, Year Risk of Bias	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results
Filbeck, 2002 (also Denzinger 2007a, Denzinger 2007b) Medium	Screened: Not reported Randomized: 301 (151 vs. 150) Post-randomization exclusions: None reported Loss to followup: 4 (2 vs. 2) Analyzed for recurrence (NMIBC): 191 (88 vs. 103)	Age (median): 68 vs. 70 years Sex: Not reported Race: Not reported Smoker: Not reported Recurrent bladder cancer: 31% vs. 18% (p=0.06) Stage: 42% vs. 41% pTaG1, 31% vs. 28% pTaG2, 2.3% vs. 1.0% pTaG3, 7.9% vs. 13% pT1G2, 11.4% vs. 11.7% pT1G3, 5.7% vs. 4.9% CIS Risk group: 35% vs. 48% low, 46% vs. 34% intermediate, 19% vs. 18% high	A vs. B Residual tumor at 6 weeks, overall: 4.5% (4/88) vs. 25% (26/103), RR 0.18 (95% CI 0.07 to 0.47) Residual tumor at 6 weeks, pTa: 3.0% (2/66) vs. 18% (13/73), p=0.006 Residual tumor at 6 weeks, pT1: 12% (2/17) vs. 36% (9/25), p=0.15 Residual tumor at 6 weeks, pTis: 0.0% (0/5) vs. 80% (4/5), p=0.05 Recurrence free (n=88 and 103): 90% vs. 74% at 12 months, 90% vs. 66% at 24 months (p=0.004, log-rank test); adjusted HR 0.33 (95% CI 0.16 to 0.67) (adjusted for prophylaxis and prognostic group) Recurrence free, low risk (n=31 and 50): 92% vs. 88% at 12 months, 92% vs. 78% at 24 months (p=0.25, log-rank test) Recurrence free, intermediate risk (n=40 and 35): 89% vs. 65% at 12 months and 89% vs. 61% at 24 months (p=0.02, log rank test) Recurrence free, high risk (n=17 and 18): 87% vs. 54% at 12 months, 87% vs. 40% at 24 months (p=0.05, log-rank test) Recurrence at complete followup (median 83 vs. 86 months): 16% (18/88) vs. 44% (43/103) Recurrence free: 88% vs. 73% at 2 years, 84% VS. 64% at 4 years, 79% vs. 54% at 6 years, 71% vs. 45% at 8 years; HR 0.36 (95% CI 0.21 to 0.63) Recurrence free, low risk: 98% vs. 84% at 2 years, 95% vs. 72% at 4 years, 81% vs. 45% at 8 years (p=0.003, log-rank test) Recurrence free, intermediate risk: 86% vs. 60% at 2 years, 83% vs. 51% at 4 years, 71% vs. 42% at 8 years (p=0.02, log-rank test) Recurrence free, high risk: 85% vs. 58% at 2 years, 75% vs. 46% at 4 years, 60% vs. 43% at 8 years (p=0.04, log-rank test) Patients with T1 high grade lesions on initial cystoscopy (multifocal, concomitant CIS, >3 cm, n=21 and 25) Residual tumor at 6 weeks: 12% vs. 41% (p<0.001) Recurrent at complete followup (median 7.5 vs. 7.3 years): 14% (3/21) vs. 44% (11/25) Recurrence free: 91% vs. 69% at 4 years, 80% vs. 52% at 8 years (p=0.02, log-rank test)

Author, Year Risk of Bias	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Comments
Filbeck, 2002 (also Denzinger 2007a, Denzinger 2007b) Medium	Not reported	Not reported	

Author, Year Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Cystoscopic Followup Method
Filbeck, 2002 (also Denzinger 2007a, Denzinger 2007b) Medium Continued					
Geavlete, 2010 Medium	Romania Single center 2007-2009	Patients suspected of having bladder cancer based on positive urinary cytology and ultrasonographic suspicion of bladder tumor	Massive hematuria, moderate to severe leukocyturia, previous intravesical instillations within 3 months, imaging suggesting upper tract disease	A: White light and HAL fluorescent cystoscopy with TURBT (n=223) B: White light cystoscopy (n=223) All patients received single, immediate postoperative mitomycin-C instillation	Duration: 6 weeks Method: followup with white light cystoscopy

Author, Year Risk of Bias	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results
Filbeck, 2002 (also Denzinger 2007a, Denzinger 2007b) Medium Continued			Progression to muscle invasive disease: 19% (4/21) vs. 12% (3/25), p=0.23; unadjusted HR 0.77 (95% CI 0.19 to 1.4), adjusted HR 0.89 (0.15 to 1.72) (adjusted for multifocality, concomitant CIS, tumor size, sex) Median time to progression: 36 vs. 31 months Bladder cancer-specific survival after cystectomy: No difference (data not reported)
Geavlete, 2010 Medium	Screened: Not reported Randomized: 466 (223 vs. 223) Post-randomization exclusions: None reported Lost to followup: None reported Analyzed for recurrence (CIS, pTaG3, pT1): 136 (72 vs. 64)	Age (mean): 64 years (overall) Male: 73% (overall) Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage: 10% vs. 8.1% CIS, 51% vs. 47% pTa, 17% vs. 17% pT1, 14% vs. 15% MIBC Grade (for Ta and T1 tumors): 40% vs. 40% G1, 41% vs. 41% G2, 19% vs. 19% G3	A vs. B Recurrence at 6 weeks: 11% (8/72) vs. 31% (20/64), p=0.0001 Recurrence at 6 weeks, high grade tumors: 17% (5/29) vs. 37% (10/27), p=0.018 Recurrence at 6 weeks, solitary papillary tumors < 3 cm: 9.1% (1/11) vs. 20% (2/10), p>0.05 Recurrence at 6 weeks, solitary papillary tumors >3 cm or multiple: 16% (6/38) vs. 36% (13/36), p=0.005 Arm A (blue light), fluorescence cystoscopy vs. standard cystoscopy, detection rates CIS: 96% (22/23) vs. 74% (17/23), p=0.009 pTa: 94% (107/114) vs. 83% (95/114), p=0.001 pT1: 100% (39/39) vs. 97% (38/39), p=0.0001 (???) Any NMIBC: 96% (168/176) vs. 85% (150/176), p=0.0001

Author, Year Risk of Bias	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Comments
Filbeck, 2002 (also Denzinger 2007a, Denzinger 2007b) Medium Continued			
Geavlete, 2010 Medium	Not reported	Not reported	

Author, Year Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Cystoscopic Followup Method
Geavlete, 2011 Medium	Romania Single center Study years not reported	Patients suspected of having bladder cancer based on positive urinary cytology and ultrasonographic suspicion of bladder tumor	Massive hematuria, moderate to severe leukocyturia, previous intravesical instillations within 3 months, imaging suggesting upper tract disease, previously cystoscopically diagnosed bladder tumor	A: White light and HAL fluorescent cystoscopy with TURBT (n=125) B: White light cystoscopy and TURBT (n=114) All patients received single, immediate postoperative mitomycin-C instillation	Duration: 2 years Method: followup with white light cystoscopy

Author, Year Risk of Bias	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results
Geavlete, 2011 Medium	Screened: Not reported Randomized: 362 (181 vs. 181) Post-randomization exclusions: None reported Lost to followup: 30 (17 vs. 13) Analyzed for recurrence (NMIBC): 239 (125 vs. 114)	Age (mean): 67 years (overall) Male: 74% (overall) Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage: 11% vs. 8.3% CIS, 45% vs. 41% pTa, 19% vs. 18% pT1 Grade: Not reported	A vs. B Recurrence at 3 months, overall (primary or other): 7.2% (9/125) vs. 16% (18/114), p=0.003 Recurrence at 3 months, primary site: 7.9% (9/114) vs. 5.6% (7/125), p=0.22 Recurrence at 6 months: 12% (15/125) vs. 22% (25/114), p=0.003 Recurrence at 12 months: 22% (27/125) vs. 32% (37/114), p=0.005 Recurrence at 24 months, overall: 31% (39/125) vs. 46% (52/114), p=0.001 Recurrence at 24 months, primary NMIBC: 24% (18/74) vs. 37% (26/70), p=0.014 Recurrence at 24 months, recurrent NMIBC: 41% (21/51) vs. 59% (26/44), p=0.007 Recurrence at 24 months, single tumor NMIBC: 23% (10/43) vs. 35% (18/51), p=0.06 Recurrence at 24 months, multiple tumor NMIBC: 35% (29/82) vs. 54% (34/63), p=0.001 Progression rates: 2.4% (3/125) vs. 4.4% (5/114) at 1 year (p=0.20), 4% (5/125) vs. 7% (8/114) at 2 years (p=0.12) Arm A (blue light), fluorescent cystoscopy vs. white light cystoscopy, detection rates CIS: 95% (20/21) vs. 71% (15/21), p=0.008 pTa: 95% (81/85) vs. 87% (74/85), p<0.001 pT1: 97% (35/36) vs. 92% (33/36), p=0.16 Any NMIBC: 96% (136/142) vs. 86% (122/142), p<0.001

Author, Year Risk of Bias	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Comments
Geavlete, 2011 Medium	"No complications related to HAL instillation"	Not reported	

Author, Year Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Cystoscopic Followup Method
Hermann, 2011 Medium	Denmark Two centers Study years not reported	Patients >18 years of age suspected of having Ta/T1 bladder cancer based on cystoscopy	Porphyria, gross hematuria, known allergy to HAL	A: White light and HAL fluorescent cystoscopy with TURBT (n=59) B: White light cystoscopy (n=74) No patient received intravesical therapy immediately after TURBT, 3 patients in each arm had previously received mitomycin and 21 patients BCG (10 in arm A and 11 in arm B)	Duration: 12 months Method: followup with white light cystoscopy
Karaolides, 2012 Medium	Greece Single center 2008-2010	Patients with suspected bladder cancer	Upper urinary tract urothelial or bladder cancer with recurrence within the last 12 months or intravesical chemotherapy or immunotherapy within the last 3 months	A: White light and HAL fluorescent cystoscopy with TURBT (n=41) B: White light cystoscopy with TURBT (n-45) Patients with moderate and high risk tumors received epirubicin 6 weeks after TURBT, or BCG	Duration: 18 months Method: followup with white light cystoscopy

Author, Year Risk of Bias	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results
Hermann, 2011 Medium	Screened: Not reported Randomized: 233 (115 vs. 118) Underwent allocated procedure: 219 (102 vs. 117) Post-randomization exclusions: 14 (14 vs. 1) Lost to followup: 25 (17 vs. 9) Analyzed for recurrence (Ta or nonsurgical T1): 133 (59 vs. 74)	Age (mean): 71 vs. 69 years Male: 75% Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage and grade: 84% vs. 90% Ta low grade, 12% vs. 6% Ta high grade, 0% T1 low grade, 2% vs. 4% T1 high grade	A vs. B Recurrence at 4 months: 17% (10/59) vs. 31% (23/74) Recurrence through 12 months: 31% (18/59) vs. 47% (35/74), p=0.05
Karaolides, 2012 Medium	Screened: 140 Randomized: 102 (49 vs. 53) Received allocated procedure: 88 (42 vs. 46) Post-randomization exclusions: None reported Lost to followup: 2 (1 vs. 1) Analyzed for recurrence (NMIBC): 86 (41 vs. 45)	Age (mean): 66 vs. 64 years Male: 80% vs. 89% Race: Not reported Smoker: Not reported Recurrent bladder cancer: 29% vs. 24% Tumor stage and grade: 12% vs. 6.7% CIS, 22% vs. 31% high grade, 63% vs. 60% low grade, 2.4% vs. 2.2% low malignant potential	A vs. B Recurrence through complete followup (median 18 vs. 14 months): 17% (7/41) vs. 40% (18/45), p=0.02 Recurrence at 3 months: 2.4% (1/41) vs. 13% (6/45), p<0.001 Recurrence free: 91% vs. 56% at 12 months, 82% Vs. 51% at 18 months (p=0.006, log-rank test) Recurrence free, solitary tumors: 93% vs. 77% at 12 months, 74% vs. 77% at 18 months (p=0.35, log-rank test) Recurrence free, multifocal tumors: 89% vs. 27% at 12 months, 90% vs. 14% at 18 months (p<0.001) Recurrence free, primary tumors: 90% vs. 62% at 12 months, 77% vs. 55% at 18 months (p=0.02, log-rank test) Recurrence free, recurrent tumors: 92% vs. 42% at 12 months, 92% vs. 42% at 18 months (p=0.02, log-rank test) Recurrence free, low-grade tumors and low malignant potential lesions: 94% vs. 63% at 12 months, 89% vs. 63% at 18 months (p=0.02, log-rank test) Recurrence free, CIS and high-grade tumors: 84% vs. 43% at 12 months, 73% vs. 34% at 18 months (p=0.01, log-rank test) Progression to MIBC: 0% (0/41) vs. 4.4% (2/45)

Author, Year Risk of Bias	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Comments
Hermann, 2011 Medium	A vs. B False-positives: 25% (25/102) (false-positives for fluorescent cystoscopy performed after white light cystoscopy) vs. 16% (19/117)	Photocure, Juchum and Boemske Foundations	
Karaolides, 2012 Medium	Not reported	None reported	

Author, Year Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Cystoscopic Followup Method
Kriegmair, 2002 High	Austria Multicenter 1997-1998	Patients suspected of having primary bladder cancer or tumor recurrence	Not stated	A: White light and 5-ALA fluorescent cystoscopy with TURBT (n=52) B: White light cystoscopy with TURBT (n=49) Additional treatments not reported	Duration: 10 to 14 days Method: NR
Naselli, 2012 Italy Medium	Italy Two centers 2009-2010	Patients with overt or suspected bladder cancer	Not stated	A: Narrow band imaging cystoscopy and TURBT (n=76) B: White light cystoscopy and TURBT (n=72) Additional treatments not reported	Duration: 1 year Method: followup with white light cystoscopy
O'Brien, 2013 Medium	UK Single center 2005-2010	Patients with suspected new NMIBC	Suspected MIBC, porphyria, pregnancy, sensitivity to 5-ALA based intravesical photosensitizers	A: HAL fluorescent cystoscopy with TURBT (n=86) B: White light cystoscopy with TURBT (n=82) All patients received single shot intravesical mitomycin, BCG for grade tumors or CIS	Duration: 12 months Method: NR

Author, Year Risk of Bias	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results
Kriegmair, 2002 High	Screened: Not reported Randomized: 165 (83 vs. 82) Post-randomization exclusions: None reported Lost to followup: 13 (6 vs. 7) Analyzed for recurrence (bladder cancer present): 101 (52 vs. 49)	Age (mean): 69 vs. 70 years Male: 82% vs. 70% Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage: 4.6% vs. 6.2% CIS, 55% vs. 47% Ta, 18% vs. 20% T1, 7.7% vs. 16% T2 Grade: 32% vs. 12% G1, 32% vs. 42% G2, 9.2% vs. 12% G3	A vs. B Recurrence free at 10 to 14 days: 67% (35/52) vs. 46% (23/49), p<0.014 (per-protocol, patients with bladder cancer on initial cystoscopy); 62% (40/65) vs. 41% (26/64), p<0.031 (including patients without bladder cancer on initial cystoscopy or did not undergo repeat cystoscopy for other reasons)
Naselli, 2012 Italy Medium	Screened: 223 Randomized: 188 (95 vs. 93) Post-randomization exclusions: None reported Lost to followup: 7 (3 vs. 4) Analyzed for recurrence (Ta, T1, or CIS): 148 (76 vs. 72)	Age (mean): 71 vs. 72 years Male: 16% vs. 24% Race: Not reported Smoker: Not reported Recurrent bladder cancer: 49% vs. 39% Stage: 76% vs. 72% Ta or CIS, 24% vs. 28% T1 Grade: 51% vs. 57% low, 49% vs. 43% high (including CIS)	A vs. B Recurrence at 3 months: 3.9% (3/76) vs. 17% (12/72), unadjusted RR 0.24 (95% CI 0.07 to 0.81), adjusted RR 0.26 (95% CI 0.07 to 0.75) Recurrence through 1 year: 32% (24/76) vs. 51% (37/72), unadjusted RR 0.62 (95% CI 0.41 to 0.92), adjusted RR 0.57 (95% CI 0.38 to 0.85); OR adjusted for age, year of enrollment, sex, clinical status, multifocal tumor, grading, staging and adjuvant therapy regimen
O'Brien, 2013 Medium	Screened: Not reported Randomized: 249 (129 vs. 129) Post-randomization exclusions: None reported Lost to followup: 6 (3 vs. 3) Analyzed for recurrence (Ta or T1): 168 (86 vs. 82)	Age (mean): 68 vs. 68 years Male: 74% vs. 73% Race: Not reported Smoker: Not reported Recurrent bladder cancer: 0% Stage and grade: 57% vs. 50% G1pTa or G2 (low grade) pTa/pT1; 17% vs. 13% G2 (high grade) pTa or G3pTa; 25% vs. 36% G2 (high grade) pTa or G3pT1; 14% vs. 26% secondary CIS	A vs. B Recurrence at 3 months: 20% (17/86) vs. 17% (14/82), p=0.7 Recurrence at 3 months, low-grade: 19% (9/48) vs. 9% (4/46) Recurrence at 3 months, high-grade: 21% (8/38) vs. 28% (10/36) Recurrence at 3 months, unifocal: 15% (8/52) vs. 17% (10/60) Recurrence at 3 months, multifocal: 26% (9/34) vs. 18% (4/22) Recurrence through 12 months: 31% (27/86) vs. 35% (29/82); adjusted HR 0.72 (P=0.36) (adjusted for age, focality, tumor grade and stage and postoperative mitomycin c) Recurrence through 12 months, low-grade: 15/48 (31%) vs. 13/46 (28%) Recurrence through 12 months, high-grade: 12/38 (32%) vs. 16/36 (44%) Recurrence through 12 months, unifocal: 13/52 (25%) vs. 20/60 (33%) Recurrence through 12 months, multifocal: 14/34 (41%) vs. 9/22 (41%) Mortality: 5.4% (7/129) vs. 0.8% (1/120)

Author, Year Risk of Bias	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Comments
Kriegmair, 2002 High	Not reported	Not reported	
Naselli, 2012 Italy Medium	A vs. B False-positive findings: 21% (26/124) vs. 28% (46/164), RR 0.75 (95% CI 0.47 to 1.2)	None	
O'Brien, 2013 Medium	"No adverse reactions to HAL"	Guy's and Saint Thomas' Hospitals	

Author, Year Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Cystoscopic Followup Method
Riedl, 2001 (also Daniltchenko, 2005) Medium	Germany Two centers 1998-2000	Patients with superficial bladder cancer	MIBC	A: 5-ALA fluorescent cystoscopy with TURBT (n=51) B: White light cystoscopy with TURBT (n=51) Mitomycin for pTa and pT1G1-2, BCG for pT1G3, CIS, and failed mitomycin	Duration: 60 months (median 42 vs. 39 months) Method: followup ALA fluorescent cystoscopy at 6 weeks
Schumacher, 2010 Medium	Sweden Multicenter 2002-2005	Patients >19 years of age with suspected NMIBC (primary or recurrent) based on at least one cystoscopy	WHO general health status score >2 (Eastern Cooperative Oncology Group), porphyria or hypersensitivity to porphyrins, renal and/or hepatic impairment, malignancies other than basalioma, planned or existing pregnancy, or simultaneous participation in other trials	A: White light and 5-ALA fluorescent cystoscopy with TURBT (n=141) B: White light cystoscopy with TURBT (n=138) Patients received BCG for CIS, pTaG3, and pT1G2-3 starting 4 weeks after TURBT	Duration: 12 months Method: followup with white light cystoscopy

Author, Year Risk of Bias	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results
Riedl, 2001 (also Daniltchenko, 2005) Medium	Screened: Not reported Randomized: 115 Lost to followup: None reported Analyzed for recurrence (NMIBC): 102 (51 vs. 51)	Age (mean): 70 vs. 67 years Male: 71% vs. 73% Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage: 78% vs. 78% Ta, 22% vs. 22% T1 Grade: 18% vs. 14% G1, 69% vs. 76% G2, 14% vs. 9.8% G3	A vs. B Residual tumor at 6 weeks: 16% (8/51) vs. 41% (21/51), p=0.003) Recurrence, through end of followup: 59% (30/51) vs. 75% (38/51) Median time to first recurrence (months): 12 vs. 5, p=0.015 Progression: 7.8% (4/51) vs. 18% (9/51), p=0.04 Secondary transurethral resections (per year): 0.92 vs. 1.17
Schumacher, 2010 Medium	Screened: Not reported Randomized: 300 (153 vs. 147) Post-randomization exclusions: None reported Lost to followup: None reported Analyzed for recurrence (NMIBC): 279 (141 vs. 138)	Age (mean): 70 vs. 69 years Male: 73% vs. 75% Race: Not reported Smoker: Not reported Recurrent bladder cancer: 52% vs. 50% Stage and grade: 0.7% vs. 4.3% CIS, 55% vs. 48% pTaG1-2, 12% vs. 10% pTaG3 or pT1G1-2, 4.3% vs. 5.1% pT1G3, 0.7% vs. 3.6% pT2	A vs. B Recurrence-free at 12 months (n=141 and 138): 55% vs. 56% for all patients (p=0.69, log-rank test), 50% vs. 53% for patients with histologically verified tumor (n=119 and 119) on initial TURBT (p=0.98, log-rank test) Recurrence-free at 12 months, low risk tumor (n=68 and 76): 49% vs. 50% (p=0.51, log-rank test) Recurrence-free at 12 months, high risk tumor (n=51 and 43): 53% vs. 58% (p=0.35, log-rank test) Progression free at 12 months (n=136 and 130): 91% vs. 89% (p=0.11, log-rank test) Mortality: 3.5% (5/141) v. 2.9% (4/138)

Author, Year Risk of Bias	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Comments
Riedl, 2001 (also Daniltchenko, 2005) Medium	Not reported	Not reported	
Schumacher, 2010 Medium	A vs. B Adverse events: 28% vs. 18% Renal and genitourinary adverse events: 13% vs. 10%	Meda GmbH	

Author, Year Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Cystoscopic Followup Method
Stenzl, 2010 (also Grossman 2012) USA, Canada, and Europe RCT High	USA, Canada, and Europe Multicenter Study years not reported	Patients with suspected Ta or T1 bladder cancer, at increased risk for recurrence based on presence of multifocal tumors or recurrence within 12 months	Gross hematuria, porphyria, received BCG or multiple instillation chemotherapy in the 3 months before initial TURBT	A: White light cystoscopy following instillation of HAL, followed by second randomization: a: Fluorescent cystoscopy and TURBT (n=271) b: TURBT without fluorescent cystoscopy (excluded from recurrence analysis, n unclear) B: White light cystoscopy and TURBT (n=280) Intravesical BCG for high grade T1 or CIS	Duration: 9 months Method: followup with white light cystoscopy

Author, Year Risk of Bias	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results
Stenzl, 2010 (also Grossman 2012) USA, Canada, and Europe RCT High	Screened: 814 Randomized: 779 (395 vs. 384) Post-randomization exclusions: Unclear (some patients in HAL arm randomized out of study per protocol) Lost to followup: Unclear, 149 (71 vs. 78) did not complete study per protocol Analyzed for recurrence (Ta or T1): 551 (271 vs. 280)	Age (mean): 68 vs. 70 years Male: 78% vs. 79% White race: 92% vs. 96% Smoker: Not reported Recurrent bladder cancer: 63% vs. 56% Stage: 72% vs. not reported Ta, 17% vs. not reported T1, 11% vs. not reported CIS Grade: Not reported	A vs. B Recurrence through 9 months: 47% (128/271) vs. 56% (157/280) (p=0.03, log-rank test; ITT, includes 45 and 55 imputed recurrences due to lack of histological confirmation or lack of followup); 36% (72/200) vs. 46% (92/202) (p=0.03, log-rank test, per-protocol analysis) Recurrence through 9 months, initial cancer: 42% (42/101) vs. 49% (60/123), p=0.31 Recurrence through 9 months, recurrent cancer: 51% (86/170) vs. 62% (97/157), p=0.04 Recurrence through 9 months, TaG1 or TaG2: 45% (99/218) vs. 55% (113/204), p=0.02 Recurrence through 9 months, TaG3, Ta + CIS, T1, T1 + CIS: 55% (40/73) vs. 57% (47/83), p=0.48 Progression to muscle invasion through 9 months: 1.8% (5/271) vs. 1.8% (5/280) Recurrence-free through long-term followup (median 53 vs. 55 months): 38% (97/255) vs. 32% (83/261), p=0.14 Median time to recurrence: 16 vs. 9.4 months (p=0.04) Progression to muscle invasion through long-term followup: 2.4% (6/255) vs. 6.1% (16/261), p=0.16 Cystectomy through long-term followup: 4.8% (13/271) vs. 7.9% (22/280), p=0.16 Arm A, additional tumors detected with fluorescent cystoscopy, as a proportion of total tumors

Author, Year Risk of Bias	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Comments
Stenzl, 2010 (also Grossman 2012) USA, Canada, and Europe RCT High	A vs. B Mortality: 1.4% (5/365) vs. 1.4% (5/361) at 9 months, 14% (39/271) vs. 16% (44/280) at median 53 to 55 months Bladder cancer mortality at long-term followup: 2.2% (6/271) vs. 2.9% (8/280) known bladder cancer deaths; 7.0% (19/271) vs. 8.6% (24/280) assuming deaths with incomplete information due to bladder cancer Any adverse event: 48% (202/365) vs. 51% (193/361) Renal or urinary adverse event: 31% vs. 32% Serious adverse event: 9.3% (39/365) vs. 8.4% (32/361) False-positives: 10% (91/933) vs. 12% (120/988)	Photocure ASA	

Author, Year Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Cystoscopic Followup Method
Stenzl, 2011 Medium	Italy Two centers 2009-2010	Patients >19 years of age with suspected NMIBC based on at least 1 imaging procedure	WHO general health status score >2 (Eastern Cooperative Oncology Group), porphyria or hypersensitivity to porphyrins, renal and/or hepatic impairment, malignancies other than basalioma, planned or existing pregnancy, or simultaneous participation in other trials, or mental disorders	A: White light and fluorescent cystoscopy with TURBT following instillation of 5-ALA (n=183) B: White light and fluorescent cystoscopy with TURBT following instillation of placebo (n=176) CIS, pTaG3, or pT1G2-3 received BCG 4 weeks after TURBT	Duration: 12 months Method: followup with white light cystoscopy

Author, Year Risk of Bias	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results
Stenzl, 2011 Medium	Screened: Not reported Randomized: 381 (192 vs. 189) Post-randomization exclusions: 11 (5 vs. 6) Lost to followup: None reported Analyzed for recurrence (NMIBC): 370 (183 vs. 176)	Age (mean): 66 years (overall) Male: 72% (overall) Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage and grade: 33% vs. 28% pTaG1, 19% vs. 20% pTaG2, 1.1% vs. 0% pTaG3, 1.1% vs. 0.6% pT1G1, 8.7% vs. 8.5% pT1G2, 10% vs. 31% pT1G3, 5.5% vs. 4.5% pT2, 1.6% vs. 1.7% isolated CIS	A vs. B Recurrent tumor at 2 to 4 weeks, pTaG2-3 or T2 (with no indication for cystectomy): 65% (24/37) vs. 47% (17/36) Recurrence-free at 12 months (n=183 and 176): 64% vs. 73% (p=0.22); similar results in analyses stratified by high vs. low risk tumor, study center Progression-free at 12 months (n=183 and 176): 89% vs. 89% (p=0.91) Arm A (5-ALA), fluorescence cystoscopy vs. standard cystoscopy, detection rates CIS: 100% (49/49) vs. 65% (32/49) pTaG1: 96% (112/117) vs. 84% (98/117) pTaG2: 91% (64/70) vs. 81% (57/70) pTaG3: 100% (2/2) vs. 100% (2/2) pT1G1: 50% (1/2) vs. 50% (1/2) pT1G2: 86% (19/22) vs. 96% (21/22) pT1G3: 100% (31/31) vs. 87% (27/31) pT2: 90% (18/20) vs. 85% (17/20)

Author, Year Risk of Bias	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Comments
Stenzl, 2011 Medium	A vs. B Adverse events: 33% (60/183) vs. 34% (60/176) Serious adverse events: 2.2% (4/183) vs. 1.1% (2/176) Fatal adverse events: 1.1% (2/183) vs. 1.1% (2/176)	Medac GmbH	

Please see Appendix C. Included Studies for full study references.

Appendix F. Risk of Bias

Table F1. Assessment of risk of bias of biomarker studies

Author, Year	Random or Consecutive Sample	Avoidance of Case-control Design	Avoidance of Inappropriate Exclusions	Index Test Performed In All Patients	Index Test Results Interpreted Without Knowledge of Reference Standard	Use of Prespecified Threshold or Definition for a Positive Test
Cha, 2012 Germany	Yes	Yes	Yes	No	Yes	Yes
Chahal, 2001 UK	Yes	Yes	Yes	Yes	Yes	No
Feil, 2003 Germany	Yes	Yes	Yes	No	Unclear	Yes
Friedrich, 2002 Germany	Unclear	Yes	Yes	Yes	Unclear	Yes
Giannopoulos, 2001 Greece	Unclear	Yes	Yes	Yes	Unclear	No
Gibanel, 2002 Spain	Unclear	Yes	Yes	Yes	Unclear	No
Grossman, 2005 United States Lotan, 2009	Yes	Yes	Yes	No	Yes	Yes
Grossman, 2006 United States	Yes	Yes	Yes	Yes	Yes	Yes
Gudjonsson, 2008 Sweden	Unclear	Yes	Yes	Yes	Yes	Yes
Gupta, 2009 India	Yes	Yes	No	Yes	Yes	Yes
Gutierrez Banos, 2001 Spain	Unclear	Yes	No	Yes	Yes	Yes
Halling, 2002 USA	Unclear	Yes	Yes	Unclear	Unclear	Yes
Horstmann, 2009 Germany	Unclear	Yes	Yes	Yes	Unclear	Yes
Ianari, 1997 Italy	Unclear	Yes	Yes	Yes	Unclear	Yes
Irani, 1999 France	Unclear	Yes	Yes	Yes	Yes	Yes

Author, Year	Reference Standard Interpreted Independently from the Test Under Evaluation	Appropriate Interval Between Index Test and Reference Standard	Same Reference Standard Applied to All Patients	Were all patients included in the analysis?	Overall Risk of Bias (Low, Medium, High)
Cha, 2012 Germany	Unclear	Yes	Yes	No	Medium
Chahal, 2001 UK	Yes	Yes	Yes	Yes	Medium
Feil, 2003 Germany	Unclear	Yes	Yes	No	Medium
Friedrich, 2002 Germany	Unclear	Yes	Yes	Yes	Medium
Giannopoulos, 2001 Greece	Unclear	Yes	Yes	Yes	Medium
Gibanel, 2002 Spain	Unclear	Yes	Yes	Yes	Medium
Grossman, 2005 United States Lotan, 2009	Yes	Yes	Yes	Yes	Low
Grossman, 2006 United States	Yes	Yes	Yes	Yes	Low
Gudjonsson, 2008 Sweden	Unclear	Yes	Yes	Yes	Medium
Gupta, 2009 India	Yes	Yes	Yes	Yes	Medium
Gutierrez Banos, 2001 Spain	Unclear	Yes	Yes	Yes	Medium
Halling, 2002 USA	Unclear	Yes	Yes	No	High
Horstmann, 2009 Germany	Unclear	Unclear	Yes	Yes	Medium
Ianari, 1997 Italy	Unclear	Yes	Yes	Yes	Medium
Irani, 1999 France	Unclear	Yes	Yes	Yes	Medium

Author, Year	Random or Consecutive Sample	Avoidance of Case-control Design	Avoidance of Inappropriate Exclusions	Index Test Performed In All Patients	Index Test Results Interpreted Without Knowledge of Reference Standard	Use of Prespecified Threshold or Definition for a Positive Test
Junker, 2006 Germany	Unclear	Yes	Yes	No	Unclear	Yes
Karnwal, 2010 USA	Yes	Yes	Yes	Yes	Yes	Unclear
Leyh, 1997 Germany, UK, and France	Unclear	Yes	Yes	Yes	Unclear	Yes
Leyh, 1997 Germany and France	Unclear	Yes	Yes	Yes	Unclear	Yes
Leyh, 1999 Europe	Unclear	Yes	Unclear	No	Unclear	Yes
Lodde, 2003 Italy	Yes	Yes	Yes	No	Unclear	Yes
Messing, 2005 USA	Unclear	Yes	Yes	No	Yes	Yes
Mian, 1999 Italy	Yes	Yes	Yes	No	Unclear	Yes
Mian, 2000 Italy and Austria	Unclear	Yes	Yes	Yes	Unclear	Yes
Nasuti, 1999 USA	Unclear	Yes	Yes	Yes	Unclear	Yes
Olsson, 2001 Sweden	Unclear	Yes	Yes	No	Unclear	Yes
O'Sullivan, 2012 New Zealand	Yes	Yes	No	Yes	Unclear	Unclear
Paoluzzi, 1999 Italy	Unclear	Yes	Yes	Unclear	Unclear	Yes
Piaton, 2003 and Pfister, 2003 France	Yes	Yes	Yes	Yes	Unclear	Yes
Placer, 2002 Spain	Yes	Yes	Yes	No	Unclear	Yes
Pode, 1999 Israel	Unclear	Yes	Yes	Yes	Unclear	Yes
Ponsky, 2001 USA	Unclear	Yes	Yes	Yes	Unclear	Yes

Author, Year	Reference Standard Interpreted Independently from the Test Under Evaluation	Appropriate Interval Between Index Test and Reference Standard	Same Reference Standard Applied to All Patients	Were all patients included in the analysis?	Overall Risk of Bias (Low, Medium, High)
Junker, 2006 Germany	Unclear	Unclear	Yes	No	Medium
Karnwal, 2010 USA	Unclear	Yes	Yes	Yes	Medium
Leyh, 1997 Germany, UK, and France	Yes	Yes	Yes	Yes	Medium
Leyh, 1997 Germany and France	Yes	Yes	Yes	Yes	Medium
Leyh, 1999 Europe	Yes	Yes	Yes	No	High
Lodde, 2003 Italy	Unclear	Yes	Yes	Yes	Medium
Messing, 2005 USA	Unclear	Yes	Yes	Yes	Medium
Mian, 1999 Italy	Unclear	Yes	Yes	Yes	Medium
Mian, 2000 Italy and Austria	Unclear	Yes	Yes	Yes	Medium
Nasuti, 1999 USA	Unclear	Yes	Yes	Yes	Medium
Olsson, 2001 Sweden	Unclear	Yes	Yes	No	Medium
O'Sullivan, 2012 New Zealand	Unclear	Yes	Yes	Yes	Medium
Paoluzzi, 1999 Italy	Unclear	Yes	Yes	Yes	Medium
Piaton, 2003 and Pfister, 2003 France	Yes	Yes	Yes	Yes	Medium
Placer, 2002 Spain	Unclear	Yes	Yes	Yes	Medium
Pode, 1999 Israel	Unclear	Yes	Yes	Yes	Medium
Ponsky, 2001 USA	Unclear	Yes	Yes	Yes	Medium

Author, Year	Random or Consecutive Sample	Avoidance of Case-control Design	Avoidance of Inappropriate Exclusions	Index Test Performed In All Patients	Index Test Results Interpreted Without Knowledge of Reference Standard	Use of Prespecified Threshold or Definition for a Positive Test
Quek, 2002 Singapore	Unclear	Yes	Yes	Yes	Unclear	Yes
Raitanen, 2001a and 2001b Finland	Yes	Yes	Yes	Yes	Unclear	Yes
Saad, 2002 UK	Unclear	Yes	Yes	Yes	Unclear	Yes
Sanchez-Carbayo, 2001 Spain	Unclear	Yes	Yes	Yes	Unclear	Yes
Sarosdy, 2002 USA	Unclear	Yes	Yes	Yes	Yes	Yes
Sawczuk, 2000 USA	Unclear	Yes	Yes	Yes	Unclear	Yes
Schamhart, 1998 the Netherlands	Unclear	Yes	Yes	Yes	Yes	Yes
Schmitz-Drager, 2007a Germany	Yes	Yes	Yes	No	Unclear	Yes
Schmitz-Drager, 2007b Germany	Yes	Yes	Yes	No	Unclear	Yes
Serretta, 1998 Italy	Unclear	Yes	Yes	Yes	Unclear	Yes
Serretta, 2000 Italy	Unclear	Yes	No	No	Unclear	Yes
Shariat, 2006 USA, Europe, Japan, Canada	Unclear	Yes	Yes	Yes	Unclear	Yes
Sharma, 1999 USA	Unclear	Yes	Yes	Yes	Unclear	Yes
Song, 2010 South Korea	Unclear	Yes	Yes	Yes	Yes	Yes
Sullivan, 2009 USA	Unclear	Yes	Yes	No	Unclear	Yes
Tetu, 2005 Canada	Yes	Yes	Yes	No	Unclear	Yes
Thomas, 1999 Europe	Unclear	Yes	Yes	Yes	Unclear	Yes
Toma, 2004 Germany	Unclear	Yes	Unclear	Unclear	Unclear	Yes

Author, Year	Reference Standard Interpreted Independently from the Test Under Evaluation	Appropriate Interval Between Index Test and Reference Standard	Same Reference Standard Applied to All Patients	Were all patients included in the analysis?	Overall Risk of Bias (Low, Medium, High)
Quek, 2002 Singapore	Unclear	Yes	Yes	Yes	Medium
Raitanen, 2001a and 2001b Finland	Unclear	Yes	Yes	No	Medium
Saad, 2002 UK	Unclear	Yes	Yes	Yes	Medium
Sanchez-Carbayo, 2001 Spain	Unclear	Yes	Yes	Yes	Medium
Sarosdy, 2002 USA	Yes	Yes	Yes	Yes	Medium
Sawczuk, 2000 USA	Unclear	Yes	Yes	Yes	Medium
Schamhart, 1998 the Netherlands	Unclear	Yes	Yes	No	Medium
Schmitz-Drager, 2007a Germany	Unclear	Unclear	Yes	Yes	Medium
Schmitz-Drager, 2007b Germany	Unclear	Unclear	Yes	Yes	Medium
Serretta, 1998 Italy	Unclear	Yes	Yes	Yes	Medium
Serretta, 2000 Italy	Unclear	Unclear	Yes	No	High
Shariat, 2006 USA, Europe, Japan, Canada	Unclear	Yes	Yes	Yes	Medium
Sharma, 1999 USA	Unclear	Yes	Yes	Yes	Medium
Song, 2010 South Korea	Unclear	Unclear	Yes	Yes	Medium
Sullivan, 2009 USA	Unclear	Unclear	No	No	Medium
Tetu, 2005 Canada	Unclear	Unclear	Yes	No	Medium
Thomas, 1999 Europe	Unclear	Yes	Yes	Yes	Medium
Toma, 2004 Germany	Unclear	Unclear	Yes	Unclear	Medium

Author, Year	Random or Consecutive Sample	Avoidance of Case-control Design	Avoidance of Inappropriate Exclusions	Index Test Performed In All Patients	Index Test Results Interpreted Without Knowledge of Reference Standard	Use of Prespecified Threshold or Definition for a Positive Test
United Kingdom and Eire Bladder Tumour Antigen Study Group, 1997 UK	Unclear	Yes	Yes	Yes	Unclear	Yes
van Der Poel, 1998 the Netherlands	Unclear	Yes	Yes	Yes	Unclear	Yes
Varella-Garcia, 2004	Unclear	Yes	Yes	Yes	Yes	Yes
Vriesema, 2001 the Netherlands	Unclear	Yes	Yes	No	Unclear	Yes
Wiener, 1998 Austria	Unclear	Yes	Yes	Yes	Unclear	Yes
Witjes, 1998 the Netherlands	Unclear	Yes	Yes	Yes	Unclear	Yes
Zippe, 1999 USA	Unclear	Yes	Yes	Yes	Unclear	Yes

Author, Year	Reference Standard Interpreted Independently from the Test Under Evaluation	Appropriate Interval Between Index Test and Reference Standard	Same Reference Standard Applied to All Patients	Were all patients included in the analysis?	Overall Risk of Bias (Low, Medium, High)
United Kingdom and Eire Bladder Tumour Antigen Study Group, 1997 UK	Unclear	Yes	Yes	Yes	Medium
van Der Poel, 1998 the Netherlands	Unclear	Yes	Yes	Yes	Medium
Varella-Garcia, 2004	Yes	Yes	Yes	Yes	Medium
Vriesema, 2001 the Netherlands	Unclear	Unclear	Yes	No	Medium
Wiener, 1998 Austria	Unclear	Unclear	Yes	Yes	Medium
Witjes, 1998 the Netherlands	Unclear	Yes	Yes	Yes	Medium
Zippe, 1999 USA	Yes	Yes	Yes	Yes	Medium

Please see Appendix C. Included Studies for full study references.

Table F2. Assessment of risk of bias of randomized controlled trials

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline? (age, sex, race, smoking status-if available, bladder cancer stage)	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?
Abrams, 1981	No	No	Yes	Yes	Unclear	Unclear
Addeo, 2010	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Akaza, 1987 Study One (followup of Niijima, 1983)	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Akaza, 1987 Study Two	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Akaza, 1992	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Ali-El-Dein, 1997 (Brit J Urol)	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Ali-El-Dein, 1997 (J Urol)	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Ali-El-Dein, 1999	Unclear	Unclear	No: differences in single vs multiple tumors	Yes	Unclear	Unclear
Au, 2001	Unclear	Yes	Yes	Yes	No	No
Babjuk, 2005	Unclear	Unclear	Yes	Yes	No	No
Badalament,1987	Yes	Unclear	Yes	Yes	Unclear	No
Berrum-Svennung, 2008	Yes	Unclear	Yes	Yes	Yes	No
Bilen, 2000	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Boccardo, 1994	Yes	Unclear	Yes	Yes	Unclear	Unclear
Böhle, 2009	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Bouffioux, 1995	Unclear	Yes	Unclear	Yes	Unclear	Unclear

Author, Year	Patient Masked?	Attrition Reported?	Overall loss to followup <20%? Differential attrition <10%?	Intention-to-Treat Analysis (analyzed by groups they were assigned to)	Postrandomization Exclusions	Outcomes Prespecified	Risk of Bias
Abrams, 1981	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	High
Addeo, 2010	Unclear	Yes	Overall: Yes Differential: Unclear	Yes	Unclear	Yes	Medium
Akaza, 1987 Study One (followup of Niijima, 1983)	Unclear	Yes	Overall: Yes Differential: No	Yes	Unclear	Yes	Medium
Akaza, 1987 Study Two	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Unclear	Yes	Medium
Akaza, 1992	Unclear	Yes	Overall: No Differential: No	Yes	Unclear	Yes	High
Ali-El-Dein, 1997 (Brit J Urol)	Unclear	No	Overall: Yes Differential: Unclear	Yes	No	Yes	Medium
Ali-El-Dein, 1997 (J Urol)	Unclear	No	Overall: Unclear Differential: Unclear	Yes	No	Yes	Medium
Ali-El-Dein, 1999	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Yes: 11% not available for evaluation for reasons not reported	Yes	Medium
Au, 2001	No	Yes	Overall: Yes Differential: Yes	Yes	Yes	Yes	Medium
Babjuk, 2005	No	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	High
Badalament, 1987	No	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Berrum-Svennung, 2008	Yes	Yes	Overall: Yes Differential: Unclear	Yes	Yes, but mainly due to incorrect inclusion	Yes	Medium
Bilen, 2000	Unclear	All analyzed	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Boccardo, 1994	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Böhle, 2009	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Yes	Yes	Medium
Bouffioux, 1995	Unclear	Yes	Overall: No Differential: Unclear	Yes	Yes	Yes	Medium

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline? (age, sex, race, smoking status-if available, bladder cancer stage)	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?
Brosman, 1982	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Burnand, 1976	Yes	Unclear	Unclear	Yes	Unclear	No
Cai, 2008	Unclear	Yes	Yes	Yes	Unclear: double blind; statistician masked	Unclear: double blind
Cheng, 2005 (Clin Urol)	Unclear	Unclear	No, control group with more solitary tumors	Yes	Unclear	Unclear
Cheng, 2005 (Int. Journal of Urol.)	Unclear	Unclear	Some differences in distribution of tumor grade	Yes	Unclear	Unclear
Cho, 2009	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Colombo, 2012	Unclear	Unclear	Yes	Yes	Unclear	Unclear
De Nunzio, 2011	Unclear	Unclear	Yes	Yes	Unclear	Unclear
De Reijke, 2005	Unclear	Unclear	Yes	Yes	Unclear	Unclear
DeBruyne, 1988 Witjes, 1998a DeBruyne, 1992	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Di Lorenzo, 2010	Yes	Yes	Yes	Yes	No	Unclear
Di Stasi, 2003	Yes	Yes	Yes	Yes	Unclear	Unclear
Dragoescu, 2011	Unclear	Unclear	Yes	Yes	No	No
Ducheck, 2010 Hemdan, 2014	Yes	Yes	Yes	Yes	Unclear	Unclear
Ersoy, 2013	No	Unclear	No	Yes	Unclear	Unclear
Eto, 1994	Unclear	Yes	Yes (except age)	Yes	Unclear	Unclear
Fellows, 1994	Yes	Unclear	Yes	Yes	Unclear	Unclear
Flamm, 1990	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Flanigan, 1986	Unclear	Unclear	Unclear	Yes	Unclear	Unclear

Author, Year	Patient Masked?	Attrition Reported?	Overall loss to followup <20%? Differential attrition <10%?	Intention-to-Treat Analysis (analyzed by groups they were assigned to)	Postrandomization Exclusions	Outcomes Prespecified	Risk of Bias
Brosman, 1982	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Burnand, 1976	Unclear	No	Unclear	Yes	No	Unclear	Medium
Cai, 2008	Unclear: double blind	Yes	Overall: Yes Differential: Yes	Yes	No	Unclear	Medium
Cheng, 2005 (Clin Urol)	Unclear	No	Overall: Yes Differential: Unclear	Yes	No	Yes	Medium
Cheng, 2005 (Int. Journal of Urol.)	Unclear	All analyzed	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Cho, 2009	Unclear	all analyzed	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Colombo, 2012	No	No	Overall: Unclear Differential: Unclear	Yes	Unclear	Yes	Medium
De Nunzio, 2011	Unclear	Yes	Overall: Yes Differential: Unclear	Yes	No	Yes	Medium
De Reijke, 2005	Unclear	All analyzed	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
DeBruyne, 1988 Witjes, 1998a DeBruyne, 1992	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Di Lorenzo, 2010	No	All analyzed	Overall: Yes Differential: Yes	Yes	No	Yes	Low
Di Stasi, 2003	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Low
Dragoescu, 2011	No	Yes	Yes	Yes	Unclear	Unclear	Medium
Ducheck, 2010 Hemdan, 2014	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Low
Ersoy, 2013	Unclear	No	Overall: Yes Differential: Unclear	Yes	Unclear	Yes	High
Eto, 1994	Unclear	Yes	Overall: Yes Differential: Unclear	Yes	Unclear	Yes	Medium
Fellows, 1994	Unclear	Yes	Yes	Yes	Yes	Yes	Medium
Flamm, 1990	Unclear	No	Overall: Yes Differential: Unclear	Yes	Yes, 9% not evaluable	Yes	Medium
Flanigan, 1986	Unclear	Yes	Overall: Yes Differential: Yes	No	No	Yes	Medium

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline? (age, sex, race, smoking status-if available, bladder cancer stage)	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?
Filbeck, 2002 Burger, 2008 Denginger, 2007a Denzinger, 2007b	Unclear	Unclear	No	Yes	No	No
Friedrich, 2007	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Fukui, 1992	Unclear	Unclear	Yes	Yes	Unclear	No
Gardmark, 2005	Unclear	Yes	Unclear	Yes	Unclear	Unclear
Geavlete, 2010	Unclear	Yes	Yes	Yes	Yes	No
Geavlete, 2011	Unclear	Yes	Yes	Yes	Yes	No
Giannakopoulos, 1998	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Giannopoulos, 2003	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Glashan, 1990	Yes	Unclear	Unclear	Yes	Unclear	Yes
Gontero, 2013	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Gruenwald, 1997	Yes	Unclear	Yes	Yes	Unclear	Unclear
Gudjónsson, 2009	Unclear	No	Yes	Yes	Unclear	Unclear
Gulpinar, 2012	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Gustafson, 1991	Unclear	Unclear	Yes	No	Unclear	Unclear
Harland, 2007	Unclear	No	Yes	Yes	Unclear	No
Hendricksen, 2008	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Hermann, 2011	Unclear	Unclear	Yes	Yes	No	No

Author, Year	Patient Masked?	Attrition Reported?	Overall loss to followup <20%? Differential attrition <10%?	Intention-to-Treat Analysis (analyzed by groups they were assigned to)	Postrandomization Exclusions	Outcomes Prespecified	Risk of Bias
Filbeck, 2002 Burger, 2008 Denginger, 2007a Denzinger, 2007b	No	Yes	Yes	Yes	No	Yes	Medium
Friedrich, 2007	Unclear	Yes	Overall: Yes Differential: Unclear	Yes	No	Yes	Medium
Fukui, 1992	No	No	Unclear	Yes	Unclear	Unclear	High
Gardmark, 2005	No	No	Unclear	Yes	Unclear	Yes	High
Geavlete, 2010	No	Yes	Yes	Yes	No	Yes	Medium
Geavlete, 2011	No	Yes	Yes	Yes	No	Yes	Medium
Giannakopoulos, 1998	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Giannopoulos, 2003	Unclear	No	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Glashan, 1990	Yes	Yes	Yes	Yes	No	Yes	Medium
Gontero, 2013	Unclear	Yes	Overall: Yes Differential: Yes	No; analyzed all individual who completed maintenance course for QOL	Yes	Yes	Medium
Gruenwald, 1997	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Gudjónsson, 2009	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Gulpinar, 2012	Unclear	No	Overall: Unclear Differential: Unclear	Yes	No	Yes	Medium
Gustafson, 1991	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Harland, 2007	No	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Hendricksen, 2008	Unclear	No	Overall: Unclear Differential: Unclear	Yes	Yes	Yes	Medium
Hermann, 2011	No	Yes	Yes	Yes	Yes	Yes	Medium

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline? (age, sex, race, smoking status-if available, bladder cancer stage)	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?
Herr, 1995 Herr, 1988 Herr, 1997 Cookson, 1997 Pinsky, 1985	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Hinotsu, 2006	Yes	Yes	Yes	Yes	Unclear	Unclear
Hinotsu, 2011	Yes (minimization method)	Yes (minimization method)	Yes	Yes	Unclear	Unclear
Hirao, 1992	Unclear	Unclear	No (grade)	Yes	Unclear	Unclear
Hoeltl, 1991	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Huland, 1990	Unclear	Unclear	No (age, grade)	Yes	Unclear	Unclear
Igawa, 1996	Unclear	Unclear	No % solitary tumors	No	Unclear	Unclear
Inamoto, 2013	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Irie, 2003	No (sequential)	No	Yes	Yes	Unclear	Unclear
Jarvinen, 2012 Rintala, 1996 Rintala, 1995	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Jauhiainen, 1987	No	No	Unclear	Yes	Unclear	Unclear
Jimenez-Cruz, 1997	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Kaasinen, 2000	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Kaasinen, 2003	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Karaolides, 2012	Unclear	Unclear	Yes	Yes	No	No
Kim, 1989	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Koga, 2004	Unclear	Yes	Yes	Yes	Unclear	Unclear

Author, Year	Patient Masked?	Attrition Reported?	Overall loss to followup <20%? Differential attrition <10%?	Intention-to-Treat Analysis (analyzed by groups they were assigned to)	Postrandomization Exclusions	Outcomes Prespecified	Risk of Bias
Herr, 1995 Herr, 1988 Herr, 1997 Cookson, 1997 Pinsky, 1985	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Hinotsu, 2006	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Low
Hinotsu, 2011	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Yes	Yes	Medium
Hirao, 1992	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Unclear	Yes	Medium
Hoeltl, 1991	Unclear	Yes	Overall: No Differential: Unclear	Yes	Yes	Yes	Medium
Huland, 1990	No	Yes	Overall: Yes Differential: Unclear	Yes	Yes	Yes	Medium
Igawa, 1996	Unclear	Yes	Overall: Yes Differential: Unclear	Yes	Unclear	Yes	Medium
Inamoto, 2013	Unclear	Yes	Yes	Yes	No	Yes	Medium
Irie, 2003	Unclear	No	Overall: Unclear Differential: Unclear	Yes	Unclear	Yes	Low
Jarvinen, 2012 Rintala, 1996 Rintala, 1995	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Jauhiainen, 1987	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	High
Jimenez-Cruz, 1997	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Yes, could not get interferon for 12 patients	Yes	Medium
Kaasinen, 2000	Unclear	Yes	Overall: Yes Differential: Yes	No 13% not eligible for randomization violations	Yes	Yes	Medium
Kaasinen, 2003	Unclear	Yes	Overall: Yes Differential: Unclear	Yes	Yes	Yes	Medium
Karaolides, 2012	No	Yes	Yes	Yes	No	Yes	Medium
Kim, 1989	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Koga, 2004	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Yes	Yes	Medium

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline? (age, sex, race, smoking status-if available, bladder cancer stage)	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?
Koga, 2010	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Koontz, 1981 (prophylaxis)	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Koontz, 1981 (treatment)	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Krege, 1996	Yes(randomization by random permuted block design?)	Unclear	Yes	Yes	Unclear	Unclear
Kriegmair, 2002	Unclear	Unclear	Yes	Yes	No	No
Kuroda, 2004	Unclear	Yes	Yes	Yes	Unclear	Unclear
Kurth, 1997 Kurth, 1984	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Lamm, 1991	Yes	Yes	Yes	Yes	Unclear	Unclear
Lamm, 1995	Yes (dynamic balancing algorithm)	Unclear	Yes	Yes	Unclear	Unclear
Lamm, 2000 Lerner, 2007	Yes	Unclear	Yes, although specific grade and stage of tumor not reported by group	Yes	Unclear	Unclear
Liu, 2006	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Lundholm, 1996 Malmstrom, 1999 Gardmark, 2007	Unclear	Yes	Unclear as only tumor information provided which showed no differences	Yes	Unclear	Unclear

Author, Year	Patient Masked?	Attrition Reported?	Overall loss to followup <20%? Differential attrition <10%?	Intention-to-Treat Analysis (analyzed by groups they were assigned to)	Postrandomization Exclusions	Outcomes Prespecified	Risk of Bias
Koga, 2010	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Koontz, 1981 (prophylaxis)	Unclear	No	Overall: Unclear Differential: Unclear	Yes	Yes	Yes	Medium
Koontz, 1981 (treatment)	Unclear	No	Overall: Unclear Differential: Unclear	Yes	No	Yes	Medium
Krege, 1996	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Kriegmair, 2002	No	Yes	Overall: No Differential: Yes	Yes	No	Yes	High
Kuroda, 2004	Unclear	No	Overall: Unclear Differential: Unclear	Yes	Unclear	Yes	Medium
Kurth, 1997 Kurth, 1984	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Yes	Yes	Medium
Lamm, 1991	Unclear	All analyzed	Overall: Yes Differential: Yes	Unclear	Yes; 9% randomized not eligible and not analyzed	Yes	Medium
Lamm, 1995	Unclear	Yes	Overall: Yes Differential: Unclear as 16% not evaluable but	Yes	No	Yes	Medium
Lamm, 2000 Lerner, 2007	Unclear	All analyzed	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Liu, 2006	Unclear	No	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Lundholm, 1996 Malmstrom, 1999 Gardmark, 2007	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline? (age, sex, race, smoking status-if available, bladder cancer stage)	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?
Malmström, 2002	Unclear	Unclear	Yes	Yes	Yes	Unclear
Mangiarotti, 2008	Unclear	Unclear	No, Tumor Stage differed	Yes	Unclear	Unclear
Martinez-Pineiro, 1990	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Martinez-Pineiro, 2002	Unclear	Yes	Yes	Yes	Unclear	Unclear
Martinez-Pineiro, 2005	Unclear	Yes	Yes	Yes	Unclear	Unclear
Masters, 1999	Unclear	Yes	Yes	Yes	Unclear	Unclear
Matsumura, 1992	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Melekos, 1990	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Melekos, 1992	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Melekos, 1993	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Melekos, 1996	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Mitsumori, 2004	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Mohsen, 2010	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Morales, 1992	No (sequential)	No	Unclear	Yes	Unclear	Unclear

Author, Year	Patient Masked?	Attrition Reported?	Overall loss to followup <20%? Differential attrition <10%?	Intention-to-Treat Analysis (analyzed by groups they were assigned to)	Postrandomization Exclusions	Outcomes Prespecified	Risk of Bias
Malmström, 2002	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Mangiarotti, 2008	Unclear	All analyzed	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Martinez-Pineiro, 1990	Unclear	Yes	Overall: Yes Differential: Unclear	No, excluded patients lost to followup	No	Unclear	Medium
Martinez-Pineiro, 2002	Unclear	No	Overall: Unclear Differential: Unclear	Yes	No	Yes	Medium
Martinez-Pineiro, 2005	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Masters, 1999	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Matsumura, 1992	Unclear	Yes	Overall: Yes Differential: Unclear	Yes	Yes	Unclear	Medium
Melekos, 1990	Unclear	all analyzed	Overall: Yes Differential: Yes	Yes	No	Unclear	Medium
Melekos, 1992	Unclear	Yes	Overall: Yes Differential: Unclear	No-19% not evaluated	Unclear	Yes	Medium
Melekos, 1993	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Yes: 15% excluded due to protocol violation, loss to followup, or	Yes	Medium
Melekos, 1996	Unclear	All analyzed	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Mitsumori, 2004	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Yes	Yes	Medium
Mohsen, 2010	Unclear	No	Overall: Unclear Differential: Unclear	Unclear	Unclear	Yes	Medium
Morales, 1992	Unclear	No	Overall: Unclear Differential: Unclear	Yes	No	Yes	High

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline? (age, sex, race, smoking status-if available, bladder cancer stage)	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?
MRC Research Council, 1994 and 1985	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Mukherjee, 1992 Kaisary, 1987	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Naselli, 2012	Yes	Unclear	Yes	Yes	No (pathologist blinded but followup cystoscopies not)	No
Nepple, 2010	Yes	Yes	Baseline characteristics by group not reported	Yes	Unclear	Unclear
Niijima, 1983 Akaza,1987	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Nomata, 2002	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Obata, 1994	Unclear	Unclear	No	Yes	Unclear	Unclear
O'Brien, 2013	Unclear	Yes	Yes	Yes	No	No
Oddens, 2013	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Ojea, 2007	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Okamura, 1998	Unclear	Unclear	Yes	Yes	Unclear	No
Okamura, 2002	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Oosterlinck, 1993	Unclear	Unclear	No (grade) Unclear (age, sex)	Yes	Unclear	Unclear
Oosterlinck, 2011	Unclear	Unclear	No: gender and performance status differences	Yes	Unclear	Unclear
Pagano, 1991 Pagano, 1990	Unclear	Unclear	Unclear, baseline characteristics not given	Yes	Unclear	Unclear
Pagano, 1995 Bassi, 1992	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Palou, 2001	Unclear	Unclear	Yes	Yes	Unclear	Unclear

Author, Year	Patient Masked?	Attrition Reported?	Overall loss to followup <20%? Differential attrition <10%?	Intention-to-Treat Analysis (analyzed by groups they were assigned to)	Postrandomization Exclusions	Outcomes Prespecified	Risk of Bias
MRC Research Council, 1994 and 1985	Unclear	Yes	Yes	Yes	Yes	Unclear	Medium
Mukherjee, 1992 Kaisary, 1987	Unclear	No	Unclear	Yes	Yes	Yes	High
Naselli, 2012	No	Yes	Overall: Yes	Yes	No	Yes	Medium
Nepple, 2010	Unclear	all analyzed	Differential: Yes	Yes	No	Yes	Medium
Niijima, 1983 Akaza,1987	Unclear	Yes	Overall: No Differential: Unclear	Yes	Unclear	Yes	Medium
Nomata, 2002	Unclear	Yes	Overall: No Differential: Yes	Yes	Yes	Yes	Medium
Obata, 1994	Unclear	Yes	Overall: Yes Differential: Unclear	No	Yes	Yes	Medium
O'Brien, 2013	No	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Oddens, 2013	Unclear	No	Overall: Unclear Differential: Unclear	Yes	Yes	Yes	Medium
Ojea, 2007	Unclear	No	Overall: Unclear Differential: Unclear	Yes	No	Yes	Medium
Okamura, 1998	No	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Okamura, 2002	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Yes- 10 patients not included	Yes	Medium
Oosterlinck, 1993	Unclear	Yes	Overall: Yes Differential: Unclear	Yes	Yes	Yes	Medium
Oosterlinck, 2011	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Yes	Yes	Medium
Pagano, 1991 Pagano, 1990	Unclear	No	Overall: Unclear Differential: Unclear	Unclear	Unclear	Yes	High
Pagano, 1995 Bassi, 1992	Unclear	No	Overall: Unclear Differential: Unclear	Yes	Unclear	Yes	High
Palou, 2001	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline? (age, sex, race, smoking status-if available, bladder cancer stage)	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?
Porena, 2010	Yes	Unclear	Yes	Yes	No	No
Portillo, 1997	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Rajala, 1999	Unclear	Unclear	No (grade)	Yes	Yes	Unclear
Rajala, 2002	Unclear	Unclear	Yes	Yes	No	No
Rentsch, 2014	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Riedl, 2001 Daniltchenko, 2005	Unclear	Unclear	Yes	Yes	No	No
Rintala, 1991 Jarvinen, 2009	No, based on date of birth	Unclear	No, difference in recurrence rate before therapy	Yes	Unclear	Unclear
Rubben, 1988	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Saika, 2010	Yes	Yes	Yes	Yes	Unclear	Unclear
Schulman, 1978	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Schumacher, 2010	Unclear	Yes	Yes	Yes	Yes	No
Schwaibold, 1997	Unclear	Unclear	No	Yes	Unclear	Unclear
Sekine, 2001	Unclear	Unclear	Unclear	Yes	Unclear	No
Sengiku, 2013	Yes	Yes	Yes	Yes	Unclear	Unclear
Serretta, 2010	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Shuin, 1994	Unclear	Unclear	No (single vs. multiple tumors)	Yes	Unclear	Unclear
Solsona, 1999	Unclear	Unclear	Yes	Yes	Unclear	Unclear

Author, Year	Patient Masked?	Attrition Reported?	Overall loss to followup <20%? Differential attrition <10%?	Intention-to-Treat Analysis (analyzed by groups they were assigned to)	Postrandomization Exclusions	Outcomes Prespecified	Risk of Bias
Porena, 2010	No	No	Overall: Unclear Differential: Unclear	Unclear	Unclear	Yes	Medium
Portillo, 1997	Unclear	Yes	Overall: Yes Differential: Yes	No-13% not evaluated	Unclear	Yes	Medium
Rajala, 1999	Unclear	No	Overall: Yes Differential: Yes	Yes	Yes	Unclear	Medium
Rajala, 2002	No	Yes	Overall: Yes Differential: Unclear	Yes	Yes	Yes	Medium
Rentsch, 2014	Unclear	Yes	Yes Yes	Yes	No	Yes	Medium
Riedl, 2001 Daniltchenko, 2005	No	Yes	Yes	Yes	No	Yes	Medium
Rintala, 1991 Jarvinen, 2009	Unclear	All analyzed	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Rubben, 1988	Unclear	No	Overall: Unclear Differential: Unclear	Yes	Unclear	Yes	Medium
Saika, 2010	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Yes	Yes	Medium
Schulman, 1978	Unclear	Yes	Overall: No Differential: Unclear	Yes	Unclear	Yes	Medium
Schumacher, 2010	No	Yes	No	Yes	No	Yes	Medium
Schwaibold, 1997	Unclear	Yes	Overall: No Differential: No	Yes	Yes	Yes	Medium
Sekine, 2001	No	No	Unclear	Yes	Unclear	Yes	Medium
Sengiku, 2013	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Yes	Yes	Medium
Serretta, 2010	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Unclear	Yes	Medium
Shuin, 1994	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Unclear	High
Solsona, 1999	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Yes	Yes	Medium

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline? (age, sex, race, smoking status-if available, bladder cancer stage)	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?
Stavropoulos, 2002	Unclear	Unclear	No (Ta vs. T1)	Yes	Unclear	Unclear
Stenzl, 2010 Grossman, 2012 Mostafid, 2009	Unclear	Yes	Yes	Yes	No (pathologist blinded but followup cystoscopies not)	No
Stenzl, 2011 Penkoff, 2007	Unclear	Unclear	Yes	Yes	Yes	Yes
Tolley, 1996 Tolley, 1988	Unclear	Yes	Yes	Yes	Unclear	Unclear
Tsushima, 1987	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Turkeri, 2010	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Ueda, 1992	Unclear	Unclear	No	Yes	Unclear	Unclear
Van Der Meljden, 2001 Sylvester, 2010	Unclear	Yes	Yes	Yes	Unclear	Unclear
Van Gils-Gielen, 1995	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Witjes, 1993 Witjes, 1996 Vegt, 1995	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Witjes, 1998b	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Zincke, 1985	Unclear	Unclear	Yes	Yes	Unclear	Unclear

Appendix F2. Assessment of Risk of Bias of Randomized Controlled Trials

Author, Year	Patient Masked?	Attrition Reported?	Overall loss to followup <20%? Differential attrition <10%?	Intention-to-Treat Analysis (analyzed by groups they were assigned to)	Postrandomization Exclusions	Outcomes Prespecified	Risk of Bias
Stavropoulos, 2002	Unclear	Yes	Overall: Yes Differential: Yes	No, did not evaluate 10%	No	Yes	Medium
Stenzl, 2010 Grossman, 2012 Mostafid, 2009	No	Yes	No	Yes	No	Yes	High
Stenzl, 2011 Penkoff, 2007	Yes	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Tolley, 1996 Tolley, 1988	Unclear	Yes	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Tsushima, 1987	Unclear	Yes	Overall: Yes Differential: Unclear	Yes	No	Yes	Medium
Turkeri, 2010	Unclear	No	Overall: Unclear Differential: Unclear	Unclear	Unclear	Yes	Medium
Ueda, 1992	Unclear	Yes	Overall: Yes Differential: Yes	Yes	Yes	Yes	Medium
Van Der Meljden, 2001 Sylvester, 2010	Unclear	No	Overall: Yes Differential: Yes	Yes	No	Yes	Medium
Van Gils-Gielen, 1995	Unclear	Yes	Yes/Yes	Yes	No	Yes	Medium
Witjes, 1993 Witjes, 1996 Vegt, 1995	Unclear	Unclear	Overall: Yes Differential: Unclear	Yes	No	Yes	Medium
Witjes, 1998b	Unclear	All analyzed	Overall: Yes Differential: Yes	Yes	No	Unclear	Medium
Zincke, 1985	Unclear	Yes	No	Yes	Yes	Yes	Medium

Please see Appendix C. Included Studies for full study references.

Table F3. Assessment of risk of bias of cohort studies

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (age, sex, race, smoking status-if available, bladder cancer stage; e.g., by restriction or matching)?	Did the study maintain comparable groups through the study period?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Overall loss to followup <20%? Differential attrition <10%?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Risk of Bias
Mulders, 1994	Yes, all patients in registry	Yes	Yes	No	Not reported	Yes	No	No	Yes	High

Please see Appendix C. Included Studies for full study references.

Appendix G. Strength of Evidence

Table G1. Strength of evidence

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
1. What is the diagnostic accuracy of various urinary biomarkers compared with other urinary biomarkers or standard diagnostic methods (cystoscopy, cytology, and imaging) in 1) persons with signs or symptoms warranting evaluation for possible bladder cancer or 2) persons undergoing surveillance for previously treated bladder cancer?							
Quantitative NMP22: Sensitivity and specificity	19 studies of diagnostic accuracy	Moderate	Inconsistent	Direct	Precise	Not detected	Moderate
Qualitative NMP22: Sensitivity and specificity	4 studies of diagnostic accuracy	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
Qualitative BTA: Sensitivity and specificity	22 studies of diagnostic accuracy	Moderate	Inconsistent	Direct	Precise	Not detected	Moderate
Quantitative BTA: Sensitivity and specificity	4 studies of diagnostic accuracy	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
FISH: Sensitivity and specificity	11 studies of diagnostic accuracy	Moderate	Inconsistent	Direct	Imprecise	Not detected	Moderate
ImmunoCyt: Sensitivity and specificity	14 studies of diagnostic accuracy	Moderate	Inconsistent	Direct	Imprecise	Not detected	Moderate
CxBladder: Sensitivity and specificity	1 study of diagnostic accuracy	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Quantitative NMP22 versus qualitative BTA: Sensitivity and specificity	7 studies of diagnostic accuracy	Moderate	Consistent	Direct	Precise	Not detected	Moderate
ImmunoCyt versus FISH: Sensitivity and specificity	3 studies	Moderate	Consistent	Direct	Precise	Not detected	Low
Other head-to-head urinary biomarkers							Insufficient
Various urinary biomarkers plus cytology versus the urinary biomarker alone: Sensitivity and specificity	16 studies of diagnostic accuracy	Moderate	Consistent	Direct	Precise	Not detected	Moderate
KQ1a. Does the diagnostic accuracy differ according to patient characteristics (e.g., age, sex, ethnicity), or according to the nature of the presenting signs or symptoms?							

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
Effects of tumor stage: Sensitivity	Quantitative NMP22: 11 studies Qualitative BTA: 18 studies FISH: 8 studies ImmunoCyt: 10 studies	Moderate	Consistent	Direct	Precise	Not detected	High
Effects of tumor grade: Sensitivity	Quantitative NMP22: 12 studies Qualitative BTA: 18 studies ImmunoCyt: 10 studies FISH: 9 studies	Moderate	Consistent	Direct	Precise	Not detected	High
Effects of tumor size: Sensitivity	2 studies	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Effects of patient characteristics (age, sex, smoking status, and presence of other clinical conditions): sensitivity and specificity		Moderate	Consistent	Direct	Imprecise	Not detected	Low
2. For patients with non-muscle-invasive bladder cancer, does the use of a formal risk-adapted assessment approach to treatment decisions (e.g., Guidelines of the European Association of Urology or based on urinary biomarker tests) decrease mortality or improve other outcomes (e.g., recurrence, progression, need for cystectomy, quality of life) compared with treatment not guided by an assessed risk-adapted approach?							
Mortality, recurrence, progression, need for cystectomy, quality of life	No studies	-	-	-	-	-	Insufficient

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
3. For patients with non-muscle-invasive bladder cancer treated with transurethral resection of bladder tumor (TURBT), what is the effectiveness of various intravesical chemotherapeutic or immunotherapeutic agents for decreasing mortality or improving other outcomes (e.g., recurrence, progression, need for cystectomy, quality of life) compared with other agents, TURBT alone, or cystectomy?							
BCG vs. no intravesical therapy							
All-cause mortality	No studies	-	-	-	-	-	Insufficient
Bladder cancer-specific mortality	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Insufficient
Recurrence	3 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Low
Progression	4 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Low
MMC vs. no intravesical therapy							
All-cause mortality	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Bladder cancer-specific mortality	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Recurrence	8 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Moderate
Progression	5 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Doxorubicin vs. no intravesical therapy							
All cause mortality	2 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
Bladder cancer-specific mortality	1 RCTs	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Recurrence	10 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Moderate
Progression	5 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Epirubicin vs. no intravesical therapy							
Recurrence	9 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Moderate
Progression	8 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Low
Gemcitabine vs. no intravesical therapy							
All-cause mortality	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Insufficient
Bladder cancer-specific mortality	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Insufficient
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Insufficient
Interferon-alpha vs. no intravesical therapy							
Bladder cancer-specific mortality	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Recurrence	3 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Progression	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Interferon-gamma vs. no intravesical therapy							
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
Progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Thiotepa vs. no intravesical therapy							
Recurrence	4 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
3a. What is the comparative effectiveness of various chemotherapeutic or immunotherapeutic agents, as monotherapy or in combination?							
BCG versus MMC							
All-cause mortality	7 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Moderate
Bladder cancer- specific mortality	5 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Moderate
Recurrence	9 RCTs	Moderate	Inconsistent	Direct	Precise	Not detected	Low
Progression	7 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Moderate
BCG vs. BCG plus MMC given sequentially							
All-cause mortality	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Bladder cancer- specific mortality	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Recurrence	4 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
Progression	3 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
BCG plus MMC given sequentially vs. MMC							
All-cause mortality	2 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
Bladder cancer- specific mortality	2 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
Recurrence	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Progression	2 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
BCG vs. doxorubicin							
All-cause mortality	2 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
Recurrence	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
BCG vs. epirubicin							
All-cause mortality	3 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
Bladder cancer-specific mortality	3 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
Recurrence	5 RCTs	Moderate	Inconsistent	Direct	Precise	Not detected	Moderate
Progression	5 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
BCG vs. BCG plus epirubicin given sequentially							
Recurrence	3 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Progression	3 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
BCG vs. Epirubicin plus interferon							
Bladder cancer-specific mortality	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
BCG vs. gemcitabine							
All-cause mortality	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
Recurrence	3 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Insufficient
Progression	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Quality of life	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
BCG vs. BCG plus gemcitabine given sequentially							
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
BCG vs. interferon alpha-2a							
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
BCG vs. alternating BCG and interferon alpha-2b							
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
BCG vs. coadministration of BCG and interferon alpha-2b							
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
BCG vs. thiotepa							
Recurrence	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
MMC vs. doxorubicin							
Recurrence	6 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Progression	4 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
MMC vs. epirubicin							
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
MMC vs. gemcitabine							
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
MMC vs. interferon-alpha							
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
MMC vs. interferon-gamma							
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
MMC vs. thiotepa							
Recurrence	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Doxorubin vs. epirubicin							
Recurrence	3 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Doxorubicin vs. thiotepa							
Bladder cancer-specific mortality	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Insufficient
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
Progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Insufficient
Epirubicin vs. interferon-alpha							
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
3b. Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?	Varied depending on tumor characteristic	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
3c. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, ethnicity, performance status, or medical comorbidities?							
Age, sex, ethnicity, performance status, co-morbidities	No studies	-	-	-	-	-	Insufficient
Recurrence, gemcitabine vs. BCG after progression or recurrence on BCG	1RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Disease-free survival, MMC vs. gemcitabine maintenance	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
3d. Does the comparative effectiveness of various chemotherapeutic or immunotherapeutic agents differ according to dosing frequency, duration of treatment, and/or the timing of administration relative to TURBT?							
Standard vs. lower dose BCG: Recurrence, progression, mortality, adverse events	6 RCTs	Moderate	Inconsistent	Direct	Precise	Not detected	Low
Maintenance vs. induction BCG: Recurrence, progression, adverse events	2 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
BCG maintenance for 1 vs. 3 years: Recurrence, progression, mortality, adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
MMC single vs. 5 instillations: Recurrence, progression, mortality, adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
MMC induction vs. maintenance: Recurrence, adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
MMC maintenance therapy with increased frequency and number of instillations vs. fewer instillations: Recurrence, progression, adverse events	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
MMC optimized vs. nonoptimized administration: Recurrence, adverse events	2 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Low
Doxorubicin eight weeks vs. two years: Recurrence, progression, adverse events	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Doxorubicin induction vs. maintenance: Recurrence, progression, mortality, adverse events	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Doxorubicin prior to vs. after TURBT: Recurrence, adverse events	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Epirubicin higher vs. lower doses: recurrence, progression, adverse events	3 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Moderate
Epirubicin single vs. multiple instillations: Recurrence, progression, bladder cancer mortality, adverse events	3 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Moderate
Epirubicin maintenance vs. induction without maintenance: Recurrence, progression, adverse events	2 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Moderate
Epirubicin more versus less intensive therapy: Recurrence, adverse events	5 RCTs	Moderate	Inconsistent	Direct	Precise	Not detected	Low
Thiotepa 30 vs. 60 mg: Recurrence, adverse events	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Interferon alpha-2b, high vs. lower doses: recurrence, progression, resolution of bladder cancer marker lesions	3 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
MMC or doxorubicin on day of TURBT vs. 1 to 2 weeks after TURBT: Recurrence, progression, mortality, adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
MMC or doxorubicin maintenance vs. no maintenance: Recurrence, progression, mortality, adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
4. For patients with high risk non-muscle-invasive bladder cancer treated with TURBT, what is the effectiveness of external beam radiation therapy (either alone or with systemic chemotherapy/immunotherapy) for decreasing mortality or improving other outcomes compared with intravesical chemotherapy/immunotherapy alone or cystectomy?							

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
Mortality, recurrence, progression	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
5. In surveillance of patients treated for non-muscle-invasive bladder cancer, what is the effectiveness of various urinary biomarkers to decrease mortality or improve other outcomes compared with other urinary biomarkers or standard diagnostic methods (cystoscopy, cytology, and imaging)?	No Studies	-	-	-	-	-	Insufficient
a. Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?	No Studies	-	-	-	-	-	Insufficient
b. Does the comparative effectiveness differ according to the treatment used (i.e., specific chemotherapeutic or immunotherapeutic agents and/or TURBT)?	No Studies	-	-	-	-	-	Insufficient
c. Does the comparative effectiveness differ according to the length of surveillance intervals?	No Studies	-	-	-	-	-	Insufficient
d. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, or ethnicity?	No Studies	-	-	-	-	-	Insufficient
6. For initial diagnosis or surveillance of patients treated for non-muscle-invasive bladder cancer, what is the effectiveness of blue light or other methods of augmented cystoscopy compared with standard cystoscopy for recurrence rates, progression of bladder cancer, mortality, or other clinical outcomes?							
Fluorescent cystoscopy vs. white light cystoscopy							
Mortality	3 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Recurrence	13 RCTs	Moderate	Inconsistent	Direct	Precise	Suspected	Low
Progression	6 RCTs	Moderate	Consistent	Direct	Precise	Not detected	Moderate
Narrow band imaging vs. white light cystoscopy							
Recurrence	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
7. What are the comparative adverse effects of various tests for diagnosis and post-treatment surveillance of bladder cancer, including urinary biomarkers, cytology, and cystoscopy?							
Urinary biomarkers: Adverse clinical outcomes	No Studies	-	-	-	-	-	Insufficient
Fluorescent vs. white light cystoscopy: False positives	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
Fluorescent vs. white light cystoscopy: Renal and genitourinary adverse events	2 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
8. What are the comparative adverse effects of various treatments for non-muscle-invasive bladder cancer, including intravesical chemotherapeutic or immunotherapeutic agents and TURBT?							
BCG vs. no intravesical therapy: Local and systemic adverse events	4 RCTs (harms only reported for BCG arm)	High	Inconsistent	Direct	Imprecise	Not detected	Low
Non-BCG intravesical therapies vs. no intravesical therapy: Local and systemic adverse events	Varied depending on intravesical agent	High	Inconsistent	Direct	Imprecise	Not detected	Low for local adverse events, insufficient for systemic adverse events
BCG vs. MMC							
Local adverse events	2 to 6 RCTs	Moderate	Consistent	Direct	Imprecise (precise for cystitis and hematuria)	Not detected	Low (moderate for cystitis and hematuria)
Systemic adverse events	2 to 4 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
BCG vs. BCG plus MMC given sequentially							
Discontinuation of therapy	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
BCG plus MMC given sequentially vs. MMC							
Local adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Systemic adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Discontinuation of therapy	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
BCG vs. doxorubicin							

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
Local adverse events	1 to 3 RCTs	Moderate	Inconsistent or cannot determine	Direct	Imprecise	Not detected	Low (cystitis); insufficient (dysuria and hematuria)
BCG vs. epirubicin							
Local adverse events	1 to 4 RCTs	Moderate	Consistent or cannot determine	Direct	Imprecise	Not detected	Low
Discontinuation of therapy	2 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Insufficient
Systemic adverse events	4 RCTs	Moderate	Consistent	Direct	Imprecise	Not detected	Low
BCG vs. BCG plus epirubicin given sequentially							
Local adverse events	1 to 2 RCTs	Moderate	Consistent or cannot determine	Direct	Imprecise	Not detected	Low
Systemic adverse events	1 to 2 RCTs	Moderate	Consistent or cannot determine	Direct	Imprecise	Not detected	Low
Discontinuation of therapy							
BCG vs. gemcitabine							
Local adverse events	1 to 2 RCTs	Moderate	Consistent or cannot determine	Direct	Imprecise	Not detected	Low
Systemic adverse events	1 to 2 RCTs	Moderate	Consistent or cannot determine	Direct	Imprecise	Not detected	Low
BCG vs. BCG plus gemcitabine given sequentially							
Local adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
BCG vs. interferon alpha-2a							
Local adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Systemic adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
BCG vs. coadministration of BCG and interferon alpha-2b							
Systemic adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
BCG vs. thiotepa							
Local adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Systemic adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
MMC vs. doxorubicin							
Local adverse events	6 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not detected	Insufficient
MMC vs. epirubicin							
Local adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
MMC vs. interferon-alpha							
Local adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Systemic adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
MMC vs. gemcitabine							
Local adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Doxorubicin vs. epirubicin							
Local adverse events	1 to 3 RCTs	Moderate	Consistent or cannot determine	Direct	Imprecise	Not detected	Low
Doxorubicin vs. thiotepa							
Local adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Epirubicin vs. interferon-alpha							
Local adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
Systemic adverse events	1 RCT	Moderate	Cannot determine	Direct	Imprecise	Not detected	Low
8a. How do adverse effects of treatment vary by patient characteristics, such as age, sex, ethnicity, performance status, or medical comorbidities such as chronic kidney disease?	No studies	-	-	-	-	-	Insufficient

Appendix H. Abbreviations Used in the Appendixes

Abbreviation	Term
AE	Adverse event
5-ALA	5-Aminolevulinic acid
ALT	Alanine transaminase
AOR	Adjusted odds ratio
AST	Aspartate transaminase
AUA	American Urological Association
AUC	Area under the curve
AUROC	Area under the receiver operating curve
BCG	Bacillus Calmette-Guérin
BCG-RIVM	RIVM strain of bacillus Calmette- Guérin
BPH	Benign prostatic hypertrophy
BTA	Bladder tumor antigen
BTA stat	Bladder tumor antigen Polymedco rapid test
BTA TRAK	Bladder tumor antigen quantitative immunoassay
BUN	Blood urea nitrogen
CBC	Complete blood count
CFU	Colony Forming Unit
CI	Confidence interval
CIS	Carcinoma in situ
Cr	Serum creatinine level
CRR	Cumulative recurrence rate
CT scan	Computerized axial tomography
DNA	Deoxyribonucleic acid
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
FOCA	Fonds Cancer
FISH	Fluorescent in situ hybridization
G0	Grade 0
G1	Grade 1
G2	Grade 2
G3	Grade 3
G4	Grade 4
Gx	Grade unknown
GEM	Gemcitabine
HAL	Hexaminolevulinate
Hgb	Hemoglobin
HR	Hazard ratio
IA	Intra-arterial
IFN-a-2b	Interferon alpha 2b
INH	Isoniazid
IV	Intravenous
IQR	Interquartile range
ISUP	International Society of Urological Pathology
ITT	Intention-to-treat
KQ	Key question
LMP	Low malignant potential
MIBC	Muscle-invasive bladder cancer
MMC	Mitomycin C
MU	Million units
NA	Not applicable
NaCl	Sodium chloride

Abbreviation	Term
NMIBC	Non-muscle-invasive bladder cancer
NMP22	Nuclear matrix protein-22
NPV	Negative predictive value
NR	Not reported
NRCT	Nonrandomized controlled trial
NS	Not significant
OncoTICE BCG	OncoTICE strain of bacillus Calmette-Guérin
PBO	Placebo
PPD	Purified protein derivative
PPV	Positive predictive value
pT1	Tumor stage 1 determined by pathology
pT1b	Tumor stage 1b determined by pathology
pT2	Tumor stage 2 determined by pathology
pTis	Tumor in situ determined by pathology
RCT	Randomized controlled trial
RFS	Recurrence-free survival
RNA	Ribonucleic acid
RR	Risk ratio
SD	Standard deviation
SWOG	Southwest Oncology Group
T0	Tumor stage 0
T1	Tumor stage 1
T2	Tumor stage 2
T2a	Tumor stage 2a
T3	Tumor stage 3
T3a	Tumor stage 3a
T3b	Tumor stage 3b
T4	Tumor stage 4
TCC	Transitional cell carcinoma
Tis	Carcinoma in situ
TUC	Transurethral coagulation
TURBT	Transurethral resection of bladder tumor
Tx	Tumor stage unknown
UK	United Kingdom
UTI	Urinary tract infection
WBC	White blood cell
WHO	World Health Organization