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

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None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Preface

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Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

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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Technical Expert Panel

In designing the review questions and methodology at the outset of this report, the EPC consulted several technical and content experts, reflecting a variety of viewpoints relevant to this topic. Technical experts consulted are expected to have divergent and possibly conflicting opinions. This diversity is helpful in achieving a well-rounded report. The study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts 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 conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who participated in developing this report will be added for the final version.

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

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The list of Peer Reviewers who participated in reviewing this report will be added for the final version.

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 – January 2014, Cochrane Central Register of Controlled Trials, through December 2013, Cochrane Database of Systematic Reviews, through December 2013, Health Technology Assessment, through 4th Quarter, 2013, National Health Sciences Economic Evaluation Database, through 4th Quarter, 2013, and Database of Abstracts of Reviews of Effects, through 4th Quarter, 2013), references 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 0.58 to 0.77 and specificity from 0.72 to 0.89, for positive likelihood ratios from 2.18 to 6.10 and negative likelihood ratios from 0.21 to 0.48 (strength of evidence [SOE]: moderate for quantitative nuclear matrix protein 22 [NMP22] and qualitative bladder tumor antigen [BTA], 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 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], RR 0.63, 95% CI 0.50 to 0.79, SOE: moderate; for mitomycin C [MMC], doxorubicin, and epirubicin, RR 0.66 to 0.80). 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 specific 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 vesical therapy, BCG was associated with a higher rate of local and systemic adverse events (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). 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 is associated with a high rate of adverse events. More research is needed to define optimal doses and regimens of intravesical therapy.

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Executive Summary

Background

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 72,570 new cases of bladder cancer in the United States in 2013, and about 15,210 deaths due to bladder cancer.[1] Bladder cancer occurs primarily in men older than 60 and roughly twice as frequently in white compared to 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 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 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 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 percent).[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 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.

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.

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, and the 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 [MMC], apaziquone, paclitaxel, gemcitabine, thiotepa, valrubicin, doxorubicin, epirubicin), bacillus Calmette-Guérin (BCG), or interferon

immunotherapy.[10] Clinical trials of are underway in the United States for electromotive drug administration (EMDA) to enhance the effectiveness of intravesical chemotherapy.

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 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 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, 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., 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?

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?

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, 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 ethnicity?

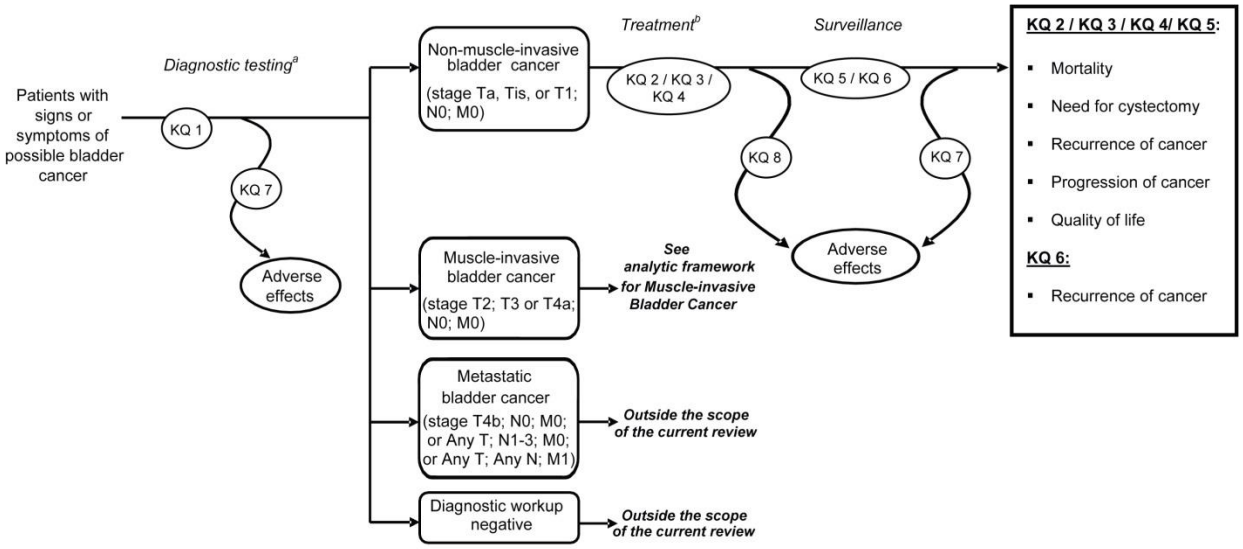
Key Question 6. For initial diagnosis or surveillance of patients treated for non-muscle-invasive bladder cancer, what is the effectiveness of blue light or other methods of augmented cystoscopy compared with standard cystoscopy for recurrence rates, progression of bladder cancer, mortality, or other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



[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® [BTA], Alere NMP22®, BladderChek® [NMP22], UroVysion® [FISH] and ImmunoCyt™ [immunocytology]) or available in the United States and classified as a Laboratory Developed Test by the FDA (CxBladder™)
[b] Chemotherapeutic and immunotherapeutic agents of interest include: mitomycin (MMC); apaziquone; paclitaxel; gemcitabine; thiotepa; epirubicin; valrubicin; doxorubicin; bacillus Calmette-Guérin (BCG); and interferon.

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")[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 – January 2014), Cochrane Central Register of Controlled Trials (through December 2013), Cochrane Database of Systematic Reviews (through December 2013), Health Technology Assessment (through 4th Quarter, 2013), National Health Sciences Economic Evaluation Database (through 4th Quarter, 2013), and Database of Abstracts of Reviews of Effects (through 4th Quarter, 2013) to capture both published and grey literature. 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. Scientific information packets (SIPs) 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, settings, and study designs (PICOTS). 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 was 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., gross or microscopic hematuria, irritative voiding symptoms) or undergoing surveillance following treatment for bladder cancer. For Key Questions related to treatment, we included adults with non-muscle-invasive bladder cancer (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 U.S. Food and Drug Administration (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 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 (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 controlled trials (RCTs) and cohort studies with concurrent controls, when RCTs 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.

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, sex, stage of disease and functional status), results, adverse events, withdrawals due to adverse events, and sources of funding. We calculated relative risks and associated 95 percent 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, 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, 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.[17] These criteria were applied in conjunction with the approaches recommended in the AHRQ Methods Guide.[12] for medical interventions and 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 moderate 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 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, 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, and 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.[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 (LR+) and negative likelihood ratio (LR-) 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 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,[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 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 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 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.

Results

Database searches resulted in 3,740 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 of various urinary biomarkers compared with other urinary biomarkers

For this Key Question, we included 43 studies (in 44 publications) that evaluated the diagnostic accuracy of urinary biomarkers for diagnosis of bladder cancer:

- Quantitative nuclear matrix protein 22 (NMP22): Sensitivity was 0.70 (95% CI 0.62 to 0.77) and specificity 0.81 (95% CI 0.75 to 0.87), based on 15 studies, for a positive likelihood ratio of 3.75 (95% CI 2.73 to 5.16) and negative likelihood ratio of 0.37 (95% CI 0.28 to 0.48) (SOE: moderate)
  - For evaluation of symptoms: Sensitivity was 0.68 (95% CI 0.56 to 0.78; eight studies) and specificity 0.86 (95% CI 0.79 to 0.91; six studies).
  - For surveillance: Sensitivity was 0.62 (95% CI 0.50 to 0.72; seven studies) and specificity 0.78 (95% CI 0.68 to 0.86; five 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 0.57 to 0.72, 17 studies) and specificity 0.80 (95% CI 0.75 to 0.84, 17 studies), for a positive likelihood ratio of 3.26 (95% CI 2.61 to 4.08) and negative likelihood ratio of 0.44 (95% CI 0.36 to 0.54 (SOE: moderate).
  - For evaluation of symptoms: Sensitivity was 0.78 (95% CI 0.67 to 0.86; six studies), and specificity 0.86 (95% CI 0.80 to 0.91; four studies).

    - For surveillance: Sensitivity was 0.62 (95% CI 0.55 to 0.69; seven studies) and specificity 0.84 (95% CI 0.76 to 0.89; five studies).
- Quantitative BTA: Sensitivity was 0.66 (95% CI 0.53 to 0.77) and specificity 0.72 (95% CI 0.59 to 0.83), based on three studies, for a positive likelihood ratio of 2.38 (95% CI 1.69 to 3.35) and negative likelihood ratio of 0.47 (95% CI 0.36 to 0.62) (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 0.57 (95% CI 0.42 to 0.71) and specificity 0.79 (95% CI 0.68 to 0.88), based on one study.
- FISH: Sensitivity was 0.69 (95% CI 0.53 to 0.82) and specificity 0.89 (95% CI 0.73 to 0.96), based on six studies, for a positive likelihood ratio of 6.10 (95% CI 2.37 to 15.7) and negative likelihood ratio of 0.35 (95% CI 0.21 to 0.56) (SOE: low).
    - For evaluation of symptoms: Sensitivity was 0.86 (95% CI 0.68 to 0.96) in one study (specificity was not reported).
    - For surveillance: Sensitivity was 0.59 (95% CI 0.44 to 0.72; five studies) and specificity was 0.81 (95% CI 0.61 to 0.92; four studies).
- ImmunoCyt: Sensitivity was 0.77 (95% CI 0.57 to 0.90) and specificity 0.77 (95% CI 0.71 to 0.82), based on four studies, for a positive likelihood ratio of 5.59 (95% 3.32 to 9.40) and negative likelihood ratio of 0.47 (95% CI 0.32 to 0.69) (SOE: low).
    - For evaluation of symptoms: Sensitivity was 0.92 (95% CI 0.83 to 0.96) and specificity was 0.77 (95% CI 0.69 to 0.84), based on two studies.
    - For surveillance: Sensitivity was 0.82 (95% CI 0.76 to 0.88) and specificity was 0.74 (95% CI 0.67 to 0.80), based on three 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 versus qualitative BTA in sensitivity (0.72, 95% CI 0.67 to 0.77 vs. 0.71, 95% CI 0.65 to 0.76, for a difference of 0.01, 95% CI -0.05 to 0.08) or specificity (0.78, 95% CI 0.65 to 0.87 vs. 0.78, 95% CI 0.65 to 0.87, for a difference of 0.002, 95% CI -0.05 to 0.08), based on five studies (SOE: moderate).
    - Evidence for other head-to-head comparisons of urinary biomarkers was too sparse to draw reliable conclusions regarding diagnostic accuracy (SOE: insufficient).
    - Ten studies found sensitivity of various urinary biomarkers plus cytology associated with higher sensitivity than the urinary biomarker alone (0.84, 95% CI 0.76 to 0.90 vs. 0.69, 95% CI 0.58 to 0.78, for a difference of 0.15, 95% CI 0.09 to 0.21), with no difference in specificity (SOE: moderate)

Key Question 1a. Diagnostic accuracy according to patient characteristics or the nature of the presenting signs or symptoms

For this Key Question, we included 28 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 (eight studies) and

qualitative BTA (14 studies). Sensitivity for CIS tumors was intermediate between Ta and T1 (SOE: high).

- Effects of tumor grade: Across urinary biomarkers, sensitivity increased with higher tumor grade. Evidence was most robust for quantitative NMP22 (eight studies) and qualitative BTA (15 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).

Key Question 2. Does use of a formal risk-adapted assessment approach to treatment decisions decrease mortality or improve other outcomes compared with treatment not guided by an assessed risk-adapted 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. For patients 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 compared with TURBT alone?

For this Key Question, we included 36 studies (in 45 publications) that evaluated intravesical therapy versus no intravesical therapy:

- **BCG** was associated with decreased risk of bladder cancer recurrence (5 trials, RR 0.63, 95% CI 0.50 to 0.79, I^2=40%) and progression (6 trials, RR 0.50, 95% CI 0.32 to 0.77, I^2=69%) versus no intravesical therapy, but there was no difference in risk of all-cause (3 trials, RR 0.90, 95% CI 0.72 to 1.11, I^2=0%) and the effect on bladder cancer-specific mortality was not statistically significant (3 trials, RR 0.68, 95% CI 0.37 to 1.24, I^2=0%). (SOE: low for all-cause and bladder cancer mortality; SOE: moderate for recurrence and progression)
- **MMC** was associated with decreased risk of bladder cancer recurrence versus no intravesical therapy (6 trials, RR 0.68, 95% CI 0.53 to 0.88, I2=75%), 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 (4 trials, RR 0.71, 95% CI 0.39 to 1.29, I^2=0%) were not statistically significant (SOE: moderate for recurrence, low for progression, and low for all-cause and bladder cancer-specific mortality).
- **Doxorubicin** was associated with decreased risk of bladder cancer recurrence versus no intravesical therapy (8 trials, RR 0.80, 95% CI 0.74 to 0.88, I^2 = 42%), no difference in risk of bladder cancer progression (5 trials, RR 1.03, 95% CI 0.72 to 1.46, I^2 = 0.0%), and no clear effects on all-cause mortality (2 trials) or bladder-cancer specific mortality (1 trial) (SOE: moderate for recurrence and low for progression, all-cause mortality, and bladder-cancer specific mortality).

- **Epirubicin** was associated with decreased risk of bladder cancer recurrence (9 trials, RR 0.66, 95% CI 0.56 to 0.77, I^2 = 54%) (SOE: moderate) but the effect on bladder cancer progression was not statistically significant (8 trials, RR 0.72, 95% CI 0.44 to 1.17, I^2 = 26%) (SOE: low).
- **Gemcitabine.** One trial found no difference between 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** (IFN-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** (IFN-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 in two trials (RR 0.34, 95% CI 0.16 to 0.72 and RR 0.58, 95% CI 0.37 to 0.93) (SOE: low).

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

For this Key Question, we included 47 studies in 57 publications:

BCG Versus MMC

- There were no differences between BCG versus MMC in risk of bladder cancer recurrence (9 trials, RR 0.97, 95% CI 0.78 to 1.16, I^2=68%), but BCG was associated with decreased risk in the subgroup of trials that evaluated maintenance regimens (5 trials, RR 0.77, 95% CI 0.68 to 0.88, 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 0.6 and RR 0.75, 95% CI 0.6 to 0.88), but there were no difference in risk of all-cause mortality (2 trials, RR 0.40, 95% CI 0.1 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, 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

- One trial found BCG associated with reduced risk of bladder cancer recurrence versus thiotepa (RR 0.38, 95% CI 0.19 to 0.76) but the difference in risk of progression was not statistically significant (RR 0.42, 95 5CI 0.19 to 0.76). (SOE: low for recurrence and progression).

MMC Versus Doxorubicin

- There was no difference between MMC versus doxorubicin in risk of bladder cancer recurrence (4 trials, RR 1.02, 95% CI 0.86 to 1.21, I^2=30%), but MMC was associated with decreased risk of bladder cancer progression (3 trials, RR 0.48, 95% CI 0.26 to 0.90, I^2 = 53%) (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

- MMC was associated with no difference 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) versus interferon-alpha (SOE: low).

MMC Versus Interferon-gamma

- MMC was associated with increased risk of bladder cancer recurrence versus IFN-gamma in one trial (RR 1.61, 95% CI 0.97 to 2.67) (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 IFN-alpha in one trial (RR 0.67, 95% CI 0.49 to 0.91) (SOE: low).

Key Question 3b. Does the comparative effectiveness differ according to tumor characteristics?

For this Key Question, we included 27 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 policy (SOE: low for stage, grade, tumor multiplicity, primary versus recurrent, and DNA ploidy).

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

- No trial evaluated how estimates of effectiveness of intravesical therapy vary in subgroups defined by patient characteristics such as age, sex, ethnicity, performance status, and co-morbidities. (SOE: insufficient)

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?

For this Key Question, we included 41 (in 44 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 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 (SOE: low).
- Two trials found more prolonged courses of BCG associated with decreased risk of bladder cancer recurrence versus induction therapy in patients with higher-risk NMIBC (RR 0.54, 95% CI 0.31 to 0.95), but increased risk of adverse events (SOE: low).

- One trial of patients with solitary T1G3 or multiple Ta-T1/G1-G3 tumors found no difference between 1 versus 3 years of BCG maintenance therapy in risk of recurrence, progression, mortality, or adverse events (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 nonoptimized 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 (two 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

- Three 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 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 patients treated with TURBT, what is the effectiveness of external beam radiation therapy for decreasing mortality or improving other outcomes compared with intravesical chemotherapy/immunotherapy alone or cystectomy?

One randomized trial (rated moderate risk of bias) compared external beam radiation therapy versus no radiation therapy in patients with NMIBC:

- 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).

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)?

- 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?

- 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)?

- No evidence (SOE: insufficient).

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

- No evidence (SOE: insufficient).

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

- 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?

For this Key Question, 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 (three trials, RR 1.27, 95% CI 0.56 to 2.87, 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, eight trials, RR 0.56, 95% CI 0.34 to 0.94, I^2=72%), intermediate-term (3 months to <1 year, four trials, RR 0.71, 95% CI 0.53 to 0.95, I^2=26%), and long-term followup (≥1 year, 11 trials, RR 0.80, 95% CI 0.67 to 0.94, I^2=58%), 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 (six trials, RR 0.83, 95% CI 0.53 to 1.28, 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).

Key Question 7. Comparative adverse effects of various tests for diagnosis and post-treatment surveillance of bladder cancer

We included 7 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 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).

Key Question 8. Comparative adverse effects of various treatments, including intravesical chemotherapeutic or immunotherapeutic agents and TURBT

For this Key Question, we included 53 studies (in 63 publications) of BCG versus other intravesical therapies that reported harms:

Intravesical Therapy Versus No Intravesical Therapy

- Four trials of BCG versus no intravesical therapy reported chemical 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 (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 and 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%), chemical 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 chemical 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 chemical cystitis (1 trial, RR 1.30, 95% CI 0.88 to 1.93) (SOE: low for local adverse events and chemical 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), chemical 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 and dysuria; low for chemical 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), chemical 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, chemical 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 four 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 IFN-alpha in risk of dysuria or fever (SOE: low).

Key Question 8a. How do adverse effects of treatment vary by patient characteristics?

- No study evaluated how harms of treatment vary in subgroups defined by patient characteristics such as age, sex, 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 0.70 (95% CI 0.62 to 0.77) and specificity 0.81 (95% CI 0.75 to 0.87), based on 15 studies, for a positive likelihood ratio of 3.75 (95% CI 2.73 to 5.16) and negative likelihood ratio of 0.37 (95% CI 0.28 to 0.48)
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 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)
Qualitative BTA: Sensitivity and specificity	Moderate	Sensitivity was 0.64 (95% CI 0.57 to 0.72, 17 studies) and specificity 0.80 (95% CI 0.75 to 0.84, 17 studies), for a positive likelihood ratio of 3.26 (95% CI 2.61 to 4.08) and negative likelihood ratio of 0.44 (95% CI 0.36 to 0.54)
Quantitative BTA: Sensitivity and specificity	Low	Sensitivity was 0.66 (95% CI 0.53 to 0.77) and specificity 0.72 (95% CI 0.59 to 0.83), based on three studies, for a positive likelihood ratio of 2.38 (95% CI 1.69 to 3.35) and negative likelihood ratio of 0.47 (95% CI 0.36 to 0.62)
FISH: Sensitivity and specificity	Low	Sensitivity was 0.69 (95% CI 0.53 to 0.82) and specificity 0.89 (95% CI 0.73 to 0.96), based on six studies, for a positive likelihood ratio of 6.10 (95% CI 2.37 to 15.7) and negative likelihood ratio of 0.35 (95% CI 0.21 to 0.56)
Immunocyt: Sensitivity and specificity	Low	Sensitivity was 0.77 (95% CI 0.57 to 0.90) and specificity 0.77 (95% CI 0.71 to 0.82), based on four studies, for a positive likelihood ratio of 5.59 (95% 3.32 to 9.40) and negative likelihood ratio of 0.47 (95% CI 0.32 to 0.69)
CxBladder: Sensitivity and specificity	Low	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)

Key Question Outcome	Strength of Evidence Grade	Conclusion
Quantitative NMP22 versus qualitative BTA: Sensitivity and specificity	Moderate	Based on 5 studies, there was no difference between quantitative NMP22 versus qualitative BTA in sensitivity (0.72, 95% CI 0.67 to 0.77 vs. 0.71, 95% CI 0.65 to 0.76, for a difference of 0.01, 95% CI -0.05 to 0.08) or specificity (0.78, 95% CI 0.65 to 0.87 vs. 0.78, 95% CI 0.65 to 0.87, for a difference of 0.002, 95% CI -0.05 to 0.08)
Other head-to-head urinary biomarkers	Insufficient	comparisons of urinary biomarkers was too sparse to draw reliable conclusions regarding diagnostic accuracy
Various urinary biomarkers plus cytology versus the urinary biomarker alone: Sensitivity and specificity	Moderate	Ten studies found sensitivity of various urinary biomarkers plus cytology associated with higher sensitivity than the urinary biomarker alone (0.84, 95% CI 0.76 to 0.90 vs. 0.69, 95% CI 0.58 to 0.78, for a difference of 0.15, 95% CI 0.09 to 0.21), with no difference in specificity
a. 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?		
Effects of tumor stage: Sensitivity	High	Across urinary biomarkers, sensitivity increased with higher tumor stage. Evidence was most robust for quantitative NMP22 (eight studies) and qualitative BTA (14 studies). Sensitivity for CIS tumors was intermediate between Ta and T1
Effects of tumor grade: Sensitivity	High	Across urinary biomarkers, sensitivity increased with higher tumor grade. Evidence was most robust for quantitative NMP22 (eight studies) and qualitative BTA (15 studies)
Effects of tumor size: Sensitivity	Low	Two studies found sensitivity was higher for larger (>1 cm or >2 cm) 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
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	Insufficient	No studies

Key Question Outcome	Strength of Evidence Grade	Conclusion
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	Low	There was no difference in risk of all-cause mortality vs. no intravesical therapy (3 trials, RR 0.90, 95% CI 0.72 to 1.11, I^2=0%)
Bladder cancer-specific mortality	Low	The effect on bladder cancer-specific mortality was not statistically significant (3 trials, RR 0.68, 95% CI 0.37 to 1.24,I^2=0%) vs. no intravesical therapy
Recurrence	Moderate	BCG was associated with decreased risk of bladder cancer recurrence (5 trials, RR 0.63, 95% CI 0.50 to 0.79, I^2=40%)
Progression	Moderate	BCG was associated with decreased risk of bladder cancer progression (6 trials, RR 0.50, 95% CI 0.32 to 0.77, I^2=69%) versus no intravesical therapy
MMC vs. no intravesical therapy		
All-cause mortality	Low	There was no difference in risk of all cause-mortality (1 trial, HR 1.17, 95% CI 0.89 to 1.53) vs. no intravesical therapy
Bladder cancer-specific mortality	Low	The effects on bladder cancer-specific mortality were not statistically significant (1 trial, HR 0.71, 95% CI 0.34 to 1.46) vs. no intravesical therapy
Recurrence	Moderate	MMC was associated with decreased risk of bladder cancer recurrence vs. no intravesical therapy (6 trials, RR 0.68, 95% CI 0.53 to 0.88, I2=75%)
Progression	Low	The effects on bladder cancer progression were not statisticaly significant (4 trials, RR 0.71, 95% CI 0.39 to 1.29, 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
Bladder cancer-specific mortality	Low	Doxorubicin was associated with no clear effects on bladder cancer-specific mortality (1 trial) vs. no intravesical therapy
Recurrence	Moderate	Doxorubicin was associated with decreased risk of bladder cancer recurrence vs. no intravesical therapy (8 trials, RR 0.80, 95% CI 0.74 to 0.88, I^2 = 42%)
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 0.66, 95% CI 0.56 to 0.77, I^2 = 54%) vs. no intravesical therapy

Key Question Outcome	Strength of Evidence Grade	Conclusion
Progression	Low	Epirubicin was associated with a non statistically significant effect on bladder cancer progression (8 trials, RR 0.72, 95% CI 0.44 to 1.17, I^2 = 26%)
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 were very imprecise (RR 1.00, 95% CI 0.06 to 15.81)
Recurrence	Low	One trial found no difference between gemcitabine versus 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 (IFN-alpha) was associated with and no difference in risk of bladder-cancer specific mortality (1 trial, RR 1.00, 95% CI 0.15 to 6.75)
Recurrence	Low	Interferon-alpha was associated with a non statistically significant difference 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%)
Progression	Low	Interferon-alpha (IFN-alpha) was associated with decreased risk of bladder cancer progression (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 (IFN-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)
Progression	Low	Interferon-gamma (IFN-gamma) was associated with no difference in risk of bladder cancer progression (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 versus no intravesical therapy in two trials (RR 0.34, 95% CI 0.16 to 0.72 and RR 0.58, 95% CI 0.37 to 0.93)
a. What is the comparative effectiveness of various chemotherapeutic or immunotherapeutic agents, as monotherapy or in combination?		
BCG versus MMC		
All-cause mortality	Moderate	There was no difference in risk of all-cause (7 trials, RR 0.94, 95% CI 0.83 to 1.06, I^2=0%)
Bladder cancer- specific mortality	Moderate	There was no difference in risk of bladder cancer-specific mortality (5 trials, RR 0.77, 95% CI 0.54 to 1.10, I^2=0%
Recurrence	Low	There were no differences between BCG versus MMC in risk of bladder cancer recurrence (9 trials, RR 0.97, 95% CI 0.78 to 1.16, I^2=68%)
Progression	Moderate	There was no difference in risk of or progression (7 trials, RR 0.88, 95% CI 0.66 to 1.17, I^2=18%)
BCG vs. BCG plus MMC given sequentially		

Key Question Outcome	Strength of Evidence Grade	Conclusion
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		
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 versus doxorubicin (2 trials, RR 0.31, 95% CI 0.16 to 0.6 and RR 0.75, 95% CI 0.6 to 0.88), but there were no difference in risk of all-cause mortality (2 trials, RR 0.40, 95% CI 0.1 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)
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%)
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%)
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%)
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 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, though BCG was associated with decreased risk of bladder cancer recurrence (RR 0.66, 95% CI 0.51 to 0.85)
BCG vs. gemcitabine		

Key Question Outcome	Strength of Evidence Grade	Conclusion
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)
Recurrence	Insufficient	Evidence from three trials was insufficient to determine 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)
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)
Quality of life	Low	There were no differences in risk of quality of life (1 trial)
BCG 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)
BCG vs. alternating BCG and interferon alpha-2b		
Recurrence	Low	BCG was associated with reduced risk of bladder cancer recurrence (1 trial, RR 0.42, 95% CI 0.30 to 0.59)
BCG 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 .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, progression	Low	One trial found reduced risk of bladder cancer recurrence (RR 0.38, 95% CI 0.19 to 0.76) but the difference in risk of progression was not statistically significant (RR 0.42, 95 5CI 0.19 to 0.76)
MMC vs. doxorubicin		
Recurrence, progression	Low	There was no difference in risk of bladder cancer recurrence (4 trials, RR 1.02, 95% CI 0.86 to 1.21, I^2=30%), but MMC was associated with decreased risk of bladder cancer progression (3 trials, RR 0.48, 95% CI 0.26 to 0.90, I^2 = 53%)
MMC vs. epirubicin		
Recurrence	Low	There was no difference in risk of bladder cancer recurrence in one trial (RR 1.16, 95% CI 0.52 to 2.58)
MMC vs. gemcitabine		
Recurrence, progression	Low	In one 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		

Key Question Outcome	Strength of Evidence Grade	Conclusion
Recurrence, progression	Low	MMC was associated with no difference 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 one trial (RR 1.61, 95% CI 0.97 to 2.67)
Doxorubin 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 difficerence 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).
Progression, noncancer mortality, cancer-specific mortality	Insufficient	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.
Epirubicin vs. interferon-alpha		
Recurrence	Low	Epirubicin was associated with decreased risk of bladder cancer recurrence in one trial (RR 0.67, 95% CI 0.49 to 0.91)
b. 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 policy
c. 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	Insufficient	No studies
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?		
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, though there was some inconsistency between trials. Standard therapy was associated with increased risk of local and systemic adverse events versus lower dose BCG

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 associated with decreased risk of bladder cancer recurrence versus 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 T1G3 or multiple Ta-T1/G1-G3 tumors found no difference between 1 versus 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 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 vs. nonoptimized administration: Recurrence, adverse events	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
Doxorubicin eight weeks vs. two 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 week) or long (two 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 versus lower doses, with no differences in adverse events

Key Question Outcome	Strength of Evidence Grade	Conclusion
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
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 one trial of patients with higher-risk NMIBC. There were no differences in risk of local adverse events
Epirubicin more versus 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 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
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 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 versus no additional maintenance therapy. There were no clear differences in local or systemic adverse events
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 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

Key Question Outcome	Strength of Evidence Grade	Conclusion
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
a. Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?	Insufficient	No studies
b. Does the comparative effectiveness differ according to the treatment used (i.e., specific chemotherapeutic or immunotherapeutic agents and/or TURBT)?	Insufficient	No studies
c. Does the comparative effectiveness differ according to the length of surveillance intervals?	Insufficient	No studies
d. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, or ethnicity?	Insufficient	No studies
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 versus white light cystoscopy in risk of mortality (three trials, RR 1.27, 95% CI 0.56 to 2.87, I^2=41%)
Recurrence	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, eight trials, RR 0.56, 95% CI 0.34 to 0.94, I^2=72%), intermediate-term (3 months to <1 year, four trials, RR 0.71, 95% CI 0.53 to 0.95, I^2=26%), and long-term followup (≥1 year, 11 trials, RR 0.80, 95% CI 0.67 to 0.94, I^2=58%), but findings were inconsistent and potentially susceptible to performance bias (due to failure to blind the initial cystoscopy) and publication bias
Progression	Moderate	There was no difference between fluorescent versus white light cystoscopy in risk of progression to muscle invasive bladder cancer (six trials, RR 0.83, 95% CI 0.53 to 1.28, 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% 0.07 to 0.81) in one trial

Key Question Outcome	Strength of Evidence Grade	Conclusion
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 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
Fluorescent vs. white light cystoscopy: False positives	Low	There were no clear differences between fluorescent cystoscopy versus white light cystoscopy in risk of false-positives in two trials
Fluorescent vs. white light cystoscopy: Renal and genitourinary adverse events	Low	There were no clear differences between fluorescent cystoscopy versus white light cystoscopy in risk of renal and genitourinary adverse events in two trials
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 of reported chemical 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 for local adverse events, insufficient for systemic adverse events	Evidence on harms 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
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%), chemical 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
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%) versus MMC
BCG vs. BCG plus MMC given sequentially		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)
Discontinuation of therapy	Low	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%)
BCG plus MMC given sequentially vs. MMC		

Key Question Outcome	Strength of Evidence Grade	Conclusion
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 chemical cystitis (1 trial, RR 1.30, 95% CI 0.88 to 1.93)
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)
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 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
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)
Discontinuation of therapy	Insufficient	Results were mixed for discontinuation of intravesical therapy (2 trials, data not pooled)
Systemic adverse events	Low	BCG was associated with increased risk chemical 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 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%)
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), chemical 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%)
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)
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)

Key Question Outcome	Strength of Evidence Grade	Conclusion
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 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 1319)
Systemic adverse events	Low	There was no difference in risk of fever (1 trial, RR 4.82, 95% CI 0.25 to 94)
BCG 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), cystitis (1 trial, RR 18, 95% CI 1.11 to 306)
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 versus doxorubicin on risk of local adverse events, based on inconsistent results from four trials
MMC vs. epirubicin		
Local adverse events	Low	One small trial found no difference between MMC versus epirubicin 80 mg in risk of urinary symptoms
MMC vs. interferon-alpha		
Local adverse events	Low	One trial found MMC associated with greater risk of hematuria versus interferon-alpha (RR 2.00, 95% CI 1.09 to 3.65) and no difference in risk of dysuria or urinary frequency
Systemic adverse events	Low	One trial found MMC 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 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		

Key Question Outcome	Strength of Evidence Grade	Conclusion
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
Systemic adverse events	Low	One trial found no difference in risk of fever
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?		
Adverse effects	Insufficient	No studies

BCG, bacillus Calmette–Guérin; CI, confidence interval; IFN, interferon; MMC, mitomycin C; RR, relative risk; 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, though 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 for quantitative NMP22. 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 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[25] designed to minimize performance bias (by blinding the cystoscopist to instillation of photosensitizer versus 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. Versus 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, though limited evidence suggested that. 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, performance status, or comorbidities on estimates of effectiveness of intravesical therapies was not available.

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 differences between standard and lower doses of BCG 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 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 (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 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).[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 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.[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 associated decreased risk of bladder cancer recurrence versus no intravesical therapy,[35,36] 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.[37-39] Like our review, a prior systematic review 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.[40] Our findings are also consistent with prior systematic reviews that found BCG 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, 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 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, ethnicity, performance status, or co-morbidities.

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 pre-test 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 trade-offs between potential benefits, which 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	Post-Test Probability of HCC Following a Positive Test	Negative Likelihood Ratio	Post-Test Probability of HCC Following a Negative Test
Quantitative NMP22	5%	3.75 (2.73 to 5.16)	16%	0.37 (0.28 to 0.48)	1,9%
	20%		48%		8.5%
Qualitative NMP22	5%	4.89 (3.23 to 7.40)	20%	0.48 (0.33 to 0.71)	2.5%
	20%		55%		11%
Qualitative BTA	5%	3.26 (2.61 to 4.08)	15%	0.44 (0.36 to 0.54)	2.3%
	20%		45%		9.9%
Quantitative BTA	5%	2.38 (1.69 to 3.35)	11%	0.47 (0.36 to 0.62)	2.4%
	20%		37%		10%
FISH	5%	6.10 (2.37 to 15.7)	24%	0.35 (0.21 to 0.56)	1.8%
	20%		60%		8.0%
ImmunoCyt	5%	5.59 (3.32 to 9.40)	23%	0.47 to 0.69)	2.4%
	20%		58%		10%

BTA = bladder tumor antigen; FISH = fluorescent in situ hybridization; NMP22 = quantitative 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 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. 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 confidence intervals. 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 ROC 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 confidence intervals 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 because of small numbers of studies, 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 (six 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 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, 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 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.

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 (U.S.)[1] The American Cancer Society estimates there will be 72,570 new cases of bladder cancer in the U.S. in 2013 (about 54,610 men and 17,960 women), and about 15,210 deaths due to bladder cancer (about 10,820 men and 4,390 women).[1] The lifetime probability of developing bladder cancer in the U.S. 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 U.S. 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 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 percent).[7]

Table 1. Bladder cancer tumor staging

	Cancer Stage	Description
T stages (tumor)	CIS (also called Tis)	Very early, high grade, cancer cells are only in the innermost layer of the bladder lining.
	Ta	The cancer is just in the innermost layer of the bladder lining
	T1	The caner 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

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®), fluorescent 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., 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 U.S. Electromotive drug administration (EMDA) is a method for enhancing the effectiveness of intravesical chemotherapy that is increasingly used, especially in Europe. Clinical trials of EMDA are ongoing in the U.S., but the method is not widely available in the U.S., nor is it FDA-approved.

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.

Key Questions

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, 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., 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?

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?

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, 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 ethnicity?

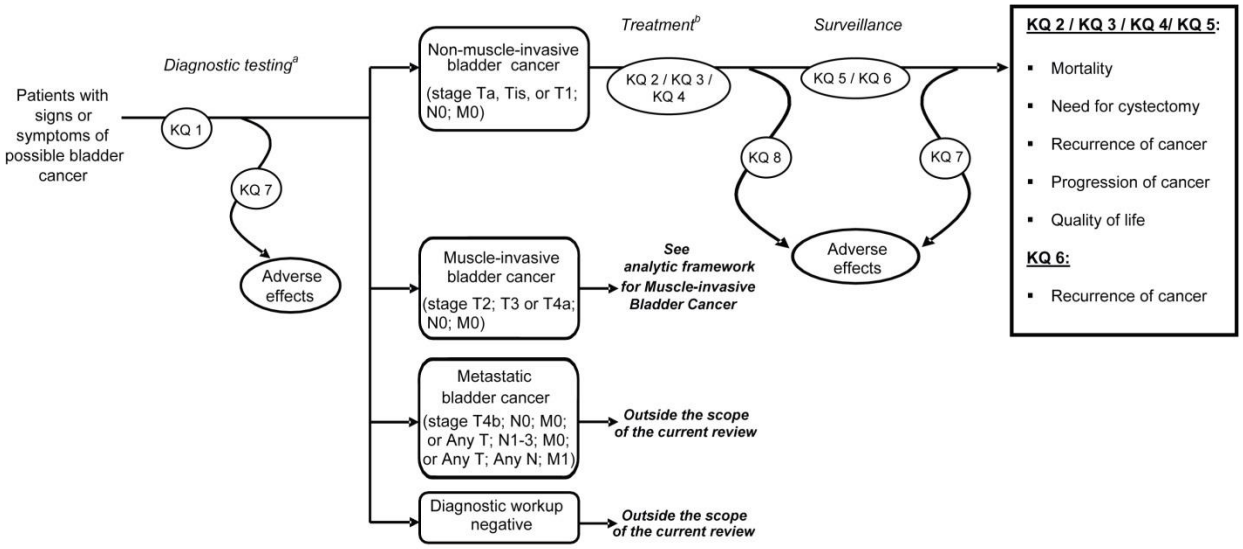
Key Question 6. For initial diagnosis or surveillance of patients treated for non-muscle-invasive bladder cancer, what is the effectiveness of blue light or other methods of augmented cystoscopy compared with standard cystoscopy for recurrence rates, progression of bladder cancer, mortality, or other 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 1. Analytic framework



[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® [BTA], Alere NMP22®, BladderChek® [NMP22], UroVysion® [FISH] and ImmunoCyt™ [immunocytology]) or available in the U.S. and classified as a Laboratory Developed Test by the FDA (CxBladder™)
[b] Intravesical agents of interest include: MMC; apaziquone; paclitaxel; gemcitabine; thiotepa; epirubicin; valrubicin; doxorubicin; bacillus Calmette-Guérin (BCG); and interferon

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 (SRC) developed preliminary Key Questions based on input from the topic nominator. The Evidence-based Practice Center (EPC) revised the Key Questions and developed eligibility criteria to identify the populations, interventions, comparators, outcomes, timing, and study designs (PICOTS) of interest. The EPC 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 (http://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 – January 2014), Cochrane Central Register of Controlled Trials (through December 2013), Cochrane Database of Systematic Reviews (through December 2013), Health Technology Assessment (through 4th Quarter, 2013), National Health Sciences Economic Evaluation Database (through 4th Quarter, 2013), and Database of Abstracts of Reviews of Effects (through 4th Quarter, 2013) 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 (SIPs) 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 SIP portal.

Library searches will be updated while the draft report is posted for public comment. Literature identified during the update search will be assessed by following the same process of dual review as used for studies identified during the initial searches. If any pertinent new literature is identified for inclusion, it will be 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., gross 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 U.S. 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 (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 controlled trials (RCTs) and cohort studies with concurrent controls, when RCTs 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]

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 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, sex, stage of disease 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, 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, 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, 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 will also provide comments and editorial review. The draft report will be posted on the AHRQ Web site for 4 weeks for public comment. A disposition of comments report with authors' responses to the

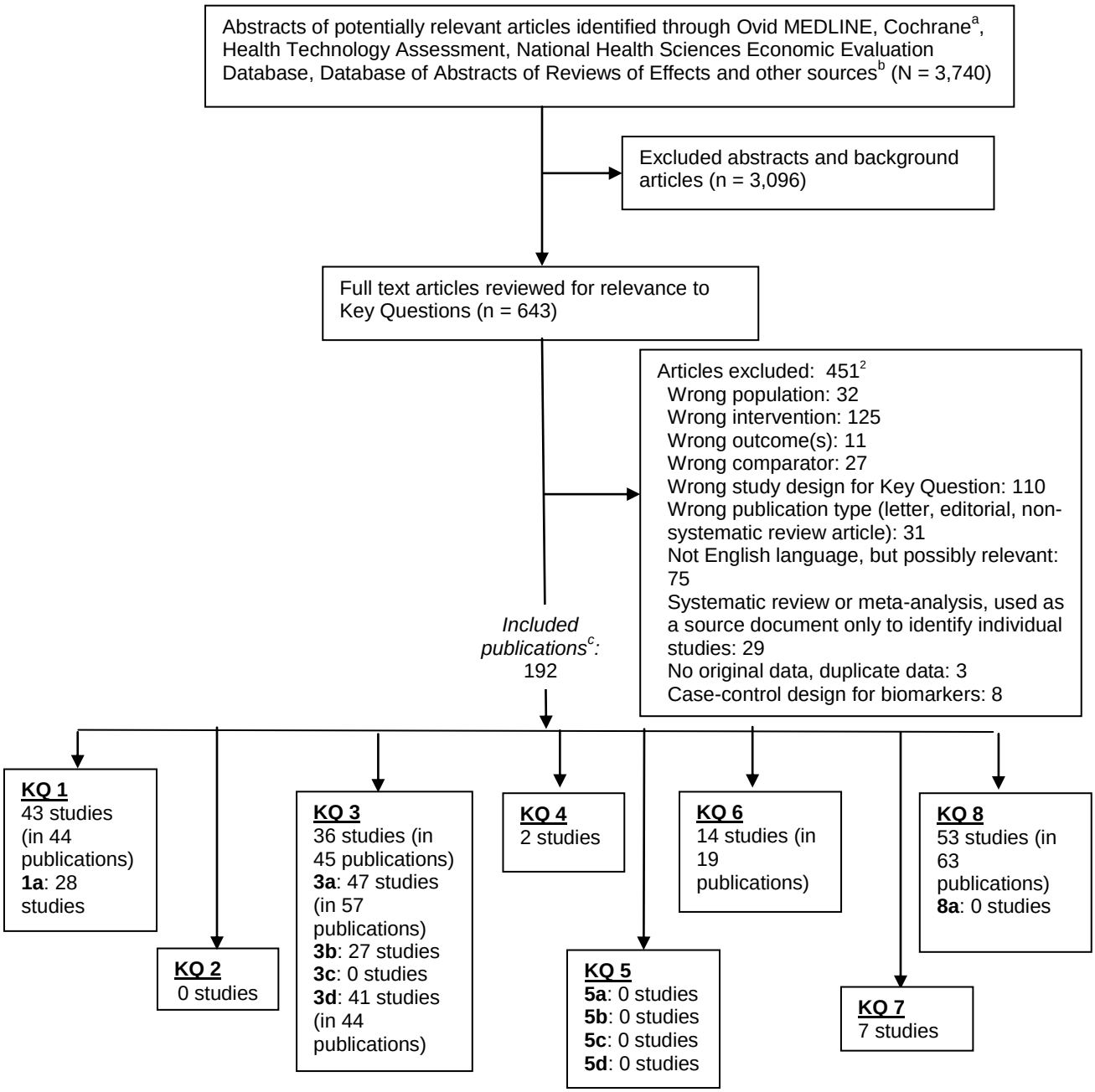
peer and public review comments will be posted after publication of the final CER on the public Web site.

Results

Results of Literature Searches

The search and selection of articles are summarized in the literature flow diagram (**Figure 2**). Database searches resulted in 3,738 potentially relevant articles. After dual review of abstracts and titles, 644 articles were selected for full-text dual review and 147 studies (in 192 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



[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 0.70 (95% CI 0.62 to 0.77) and specificity 0.81 (95% CI 0.75 to 0.87), based on 15 studies, for a positive likelihood ratio of 3.75 (95% CI 2.73 to 5.16) and negative likelihood ratio of 0.37 (95% CI 0.28 to 0.48) (SOE: moderate)
  - For evaluation of symptoms: Sensitivity was 0.68 (95% CI 0.56 to 0.78; eight studies) and specificity 0.86 (95% CI 0.79 to 0.91; six studies).
  - For surveillance: Sensitivity was 0.62 (95% CI 0.50 to 0.72; seven studies) and specificity 0.78 (95% CI 0.68 to 0.86; five 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 0.57 to 0.72, 17 studies) and specificity 0.80 (95% CI 0.75 to 0.84, 17 studies), for a positive likelihood ratio of 3.26 (95% CI 2.61 to 4.08) and negative likelihood ratio of 0.44 (95% CI 0.36 to 0.54 (SOE: moderate).
  - For evaluation of symptoms: Sensitivity was 0.78 (95% CI 0.67 to 0.86; six studies), and specificity 0.86 (95% CI 0.80 to 0.91; four studies).
  - For surveillance: Sensitivity was 0.62 (95% CI 0.55 to 0.69; seven studies) and specificity 0.84 (95% CI 0.76 to 0.89; five studies).
- Quantitative BTA: Sensitivity was 0.66 (95% CI 0.53 to 0.77) and specificity 0.72 (95% CI 0.59 to 0.83), based on three studies, for a positive likelihood ratio of 2.38 (95% CI 1.69 to 3.35) and negative likelihood ratio of 0.47 (95% CI 0.36 to 0.62) (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 0.57 (95% CI 0.42 to 0.71) and specificity 0.79 (95% CI 0.68 to 0.88), based on one study.
- FISH: Sensitivity was 0.69 (95% CI 0.53 to 0.82) and specificity 0.89 (95% CI 0.73 to 0.96), based on six studies, for a positive likelihood ratio of 6.10 (95% CI 2.37 to 15.7) and negative likelihood ratio of 0.35 (95% CI 0.21 to 0.56) (SOE: low).
  - For evaluation of symptoms: Sensitivity was 0.86 (95% CI 0.68 to 0.96) in one study (specificity was not reported).
  - For surveillance: Sensitivity was 0.59 (95% CI 0.44 to 0.72; five studies) and specificity was 0.81 (95% CI 0.61 to 0.92; four studies).

- ImmunoCyt: Sensitivity was 0.77 (95% CI 0.57 to 0.90) and specificity 0.77 (95% CI 0.71 to 0.82), based on four studies, for a positive likelihood ratio of 5.59 (95% 3.32 to 9.40) and negative likelihood ratio of 0.47 (95% CI 0.32 to 0.69) (SOE: low).
  - For evaluation of symptoms: Sensitivity was 0.92 (95% CI 0.83 to 0.96) and specificity was 0.77 (95% CI 0.69 to 0.84), based on two studies.
  - For surveillance: Sensitivity was 0.82 (95% CI 0.76 to 0.88) and specificity was 0.74 (95% CI 0.67 to 0.80), based on three 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 versus qualitative BTA in sensitivity (0.72, 95% CI 0.67 to 0.77 vs. 0.71, 95% CI 0.65 to 0.76, for a difference of 0.01, 95% CI -0.05 to 0.08) or specificity (0.78, 95% CI 0.65 to 0.87 vs. 0.78, 95% CI 0.65 to 0.87, for a difference of 0.002, 95% CI -0.05 to 0.08), based on five studies (SOE: moderate).
  - Evidence for other head-to-head comparisons of urinary biomarkers was too sparse to draw reliable conclusions regarding diagnostic accuracy (SOE: insufficient).
  - Ten studies found sensitivity of various urinary biomarkers plus cytology associated with higher sensitivity than the urinary biomarker alone (0.84, 95% CI 0.76 to 0.90 vs. 0.69, 95% CI 0.58 to 0.78, for a difference of 0.15, 95% CI 0.09 to 0.21), with no difference in specificity (SOE: moderate)

Detailed Synthesis

Forty-three studies in 44 publications evaluated the diagnostic accuracy of urinary biomarkers for diagnosis of bladder cancer (Table 2, Appendix E1, F1).[30-73] 15 studies evaluated quantitative NMP22,[30,32,33,39,52,53,57,60,61,63,65-67,72,73] four studies in five publications evaluated qualitative NMP 22,[35,36,38,47,52] 19 studies evaluated qualitative BTA,[32,33,39-42,44,45,49,51,56,58-60,62,64,67-70] three studies evaluated quantitative BTA,[34,42,69] five studies evaluated FISH,[37,43,55,62,71] five studies evaluated Immunocyt,[31,46,48,50,54] and one 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. Eight studies in nine publications focused on diagnostic testing for evaluation of patients with signs or symptoms suggestive of bladder cancer, 16 studies focused on diagnostic testing for surveillance in patients previously treated for non-muscle-invasive bladder cancer (NMIBC), and 19 studies focused on the reasons for testing for mixed. Thirty-nine studies in 40 publications were conducted in the U.S. or Europe[30-37,39-51,53-55,57,59-68,70-73] and 25 studies in 26 publications used a prospective design.[30,35-38,41,42,44-47,50,52,54,56-62,64,66,68,69,71] Two studies were rated low risk of bias,[35,36] 40 studies medium risk of bias,[30-34,37-39,41-46,48-73] and one study high risk of bias[40] (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]

Quantitative NMP22

Sensitivity of quantitative NMP22 was 0.70 (95% CI 0.62 to 0.77) and specificity was 0.81 (95% CI 0.75 to 0.87), based on 15 studies, for a positive likelihood ratio of 3.75 (95% CI 2.73 to 5.16) and negative likelihood ratio of 0.37 (95% CI 0.28 to 0.48) (Table 3; Figure 3).[30,32,33,39,52,53,57,60,61,63,65-67,72,73] All studies except for two[33,52] used a cutoff of >10 for a positive test. Excluding these two studies resulted in similar sensitivity (0.72, 95% CI 0.63 to 0.80) and specificity (0.81, 95% CI 0.73 to 0.87). Diagnostic accuracy was similar for evaluation of symptoms (sensitivity 0.68, 95% CI 0.56 to 0.78; eight studies and specificity 0.86, 95% CI 0.79 to 0.91; six studies)[30,33,52,53,60,61,67,73] and for surveillance (sensitivity 0.62, 95% CI 0.50 to 0.72; seven studies and specificity 0.78, 95% CI 0.68 to 0.86; five studies).[30,33,63,65-67,72] Restricting the analysis to studies that used a prospective design, were conducted in the U.S. or Europe, used a prespecified threshold to define a positive test, or used blinded interpretation of the reference standard, had little effect on pooled estimates and did not reduce statistical heterogeneity. All studies were rated medium risk of bias.

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 0.57 to 0.72, 17 studies)[32,33,39-42,44,45,49,51,56,58,60,64,67,68,70] and specificity was 0.80 (95% CI 0.75 to 0.84, 17 studies),[32,33,39,40,42,44,45,49,51,56,58-60,64,67,68,70] for a positive likelihood ratio of 3.26 (95% CI 2.61 to 4.08) and negative likelihood ratio of 0.44 (95% CI 0.36 to 0.54) (Table 3; Figure 5). Excluding one study rated high risk of bias[40] resulted in similar pooled estimates and did not reduce statistical heterogeneity. Sensitivity was higher for evaluation of symptoms (0.78, 95% CI 0.67 to 0.86; six studies)[33,45,51,56,60,67] than for surveillance (0.62, 95% CI 0.55 to 0.69; seven studies),[33,41,44,45,56,59,67,68] but specificity was similar (0.86, 95% CI 0.80 to 0.91; four studies and 0.84, 95% CI 0.76 to 0.89; five studies, respectively. Restricting analyses to studies that used a prospective design, were conducted in the U.S. 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 0.66 (95% CI 0.53 to 0.77) and specificity was 0.72 (95% CI 0.59 to 0.83), based on three studies, for a positive likelihood ratio of 2.38 (95% CI 1.69 to 3.35) and negative likelihood ratio of 0.47 (95% CI 0.36 to 0.62) (Table 3).[34,42,69] In the two studies that used a threshold of >14 to define a positive test, estimates were similar.[42,69] Only one

study 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 for surveillance (sensitivity 0.57, 95% CI 0.42 to 0.71; specificity 0.79, 95% CI 0.68 to 0.88).[69]

FISH

Sensitivity of FISH was 0.69 (95% CI 0.53 to 0.82) and specificity was 0.89 (95% CI 0.73 to 0.96), based on six studies, for a positive likelihood ratio of 6.10 (95% CI 2.37 to 15.7) and negative likelihood ratio of 0.35 (95% CI 0.21 to 0.56) (Table 3; Figure 6).[37,40,43,55,62,71] Estimates were similar when one study[40] rated high risk of bias was excluded, 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 0.59 (95% CI 0.44 to 0.72; five studies) and specificity was 0.81 (95% CI 0.61 to 0.92; four studies).[37,43,55,62,71] Only one study reported sensitivity of FISH for evaluation of symptoms (0.86, 95% CI 0.68 to 0.96).[55]

Immunocyt

Sensitivity of Immunocyt was 0.77 (95% CI 0.57 to 0.90) and specificity was 0.77 (95% CI 0.71 to 0.82), based on four studies, for a positive likelihood ratio of 5.59 (95% 3.32 to 9.40) and negative likelihood ratio of 0.47 (95% CI 0.32 to 0.69) (Table 3; Figure 7).[31,46,48,50] For evaluation of symptoms, sensitivity was 0.92 (95% CI 0.83 to 0.96) and specificity was 0.77 (95% CI 0.69 to 0.84), based on two studies,[46,50] and for surveillance, sensitivity was 0.82 (95% CI 0.76 to 0.88) and specificity was 0.74 (95% CI 0.67 to 0.80), based on three studies.[46,48,50] All studies were rated medium risk of bias.

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

Few studies directly compared the diagnostic accuracy of different urinary biomarkers in the same population against cystoscopy and biopsy (Table 4). In five studies, there were no differences between quantitative NMP22 versus qualitative BTA in sensitivity (0.72, 95% CI 0.67 to 0.77 vs. 0.71, 95% CI 0.65 to 0.76, for a difference of 0.01, 95% CI -0.05 to 0.08) or specificity (0.78, 95% CI 0.65 to 0.87 vs. 0.78, 95% CI 0.65 to 0.87, for a difference of 0.002, 95% CI -0.05 to 0.08).[32,33,39,60,67] Findings were similar when analyses were restricted to studies that used a cutoff of >10 U/mL for NMP22,[32,39,60,67] or when analyses were stratified according to different tumor stages or grades.

Two studies[40,62] compared qualitative BTA versus FISH and one study[42] compared qualitative versus quantitative BTA. There were no clear differences in diagnostic accuracy, but estimates were imprecise. In one study, CxBladder was associated with higher sensitivity than either quantitative or qualitative NMP22 (0.82 vs. 0.50 vs. 0.38, respectively).[52]

Ten studies found sensitivity of various urinary biomarkers plus cytology associated with higher sensitivity than the urinary biomarker alone (0.84, 95% CI 0.76 to 0.90 vs. 0.69, 95% CI 0.58 to 0.78, for a difference of 0.15, 95% CI 0.09 to 0.21), with no difference in specificity (Table 4).[31,34,36,38,45,48,50,53,55,69] In studies that stratified analyses according to tumor stage and

grade, there were no clear differences in sensitivity for Ta, T1, G1, or G2 tumors, but estimates were based on only two studies.[48,50]

Figure 3. Sensitivity and specificity of quantitative NMP22

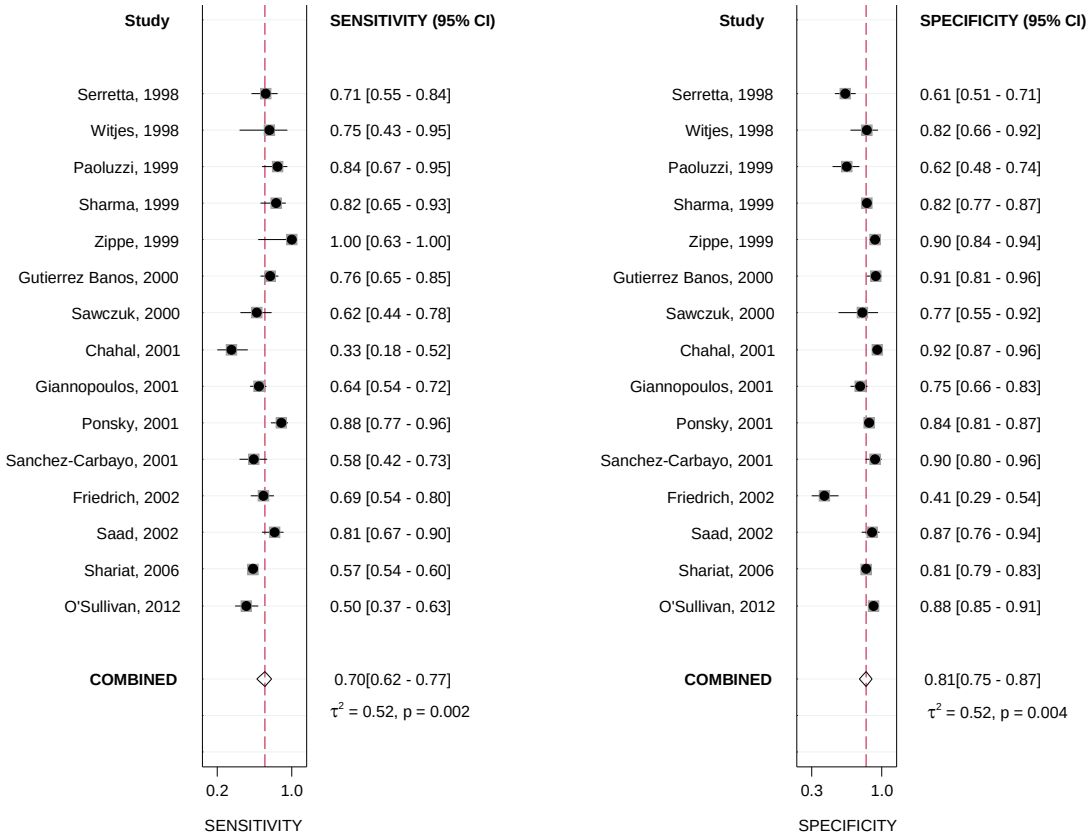


Figure 4. Sensitivity and specificity of qualitative NMP22

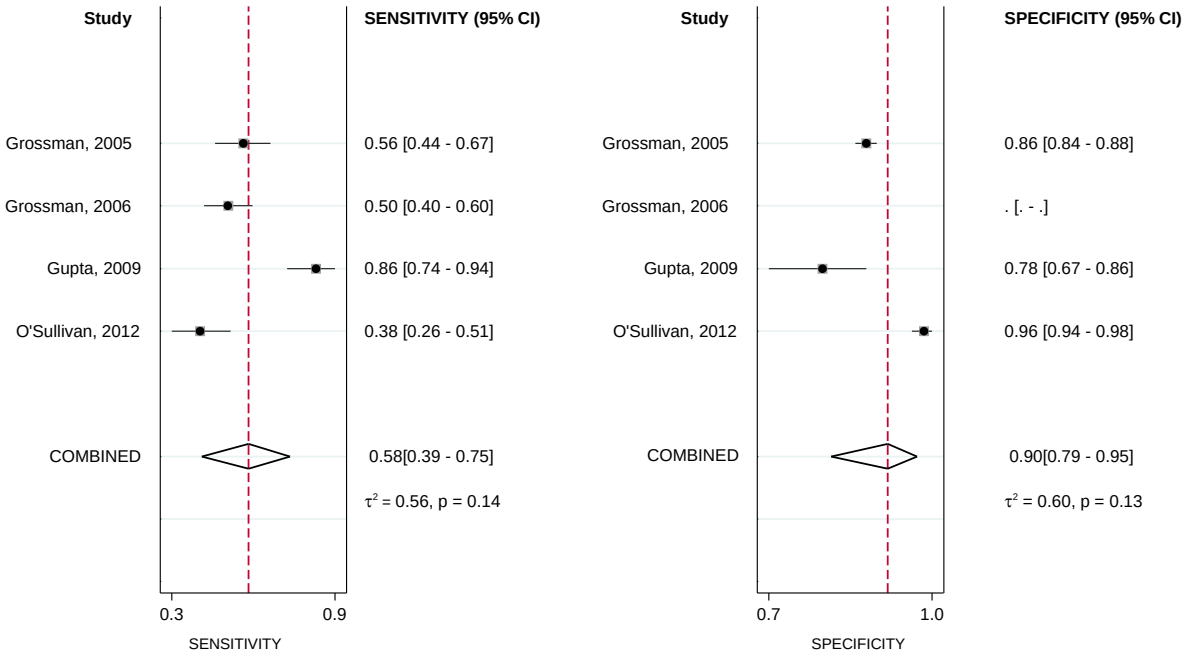


Figure 5. Sensitivity and specificity of qualitative BTA

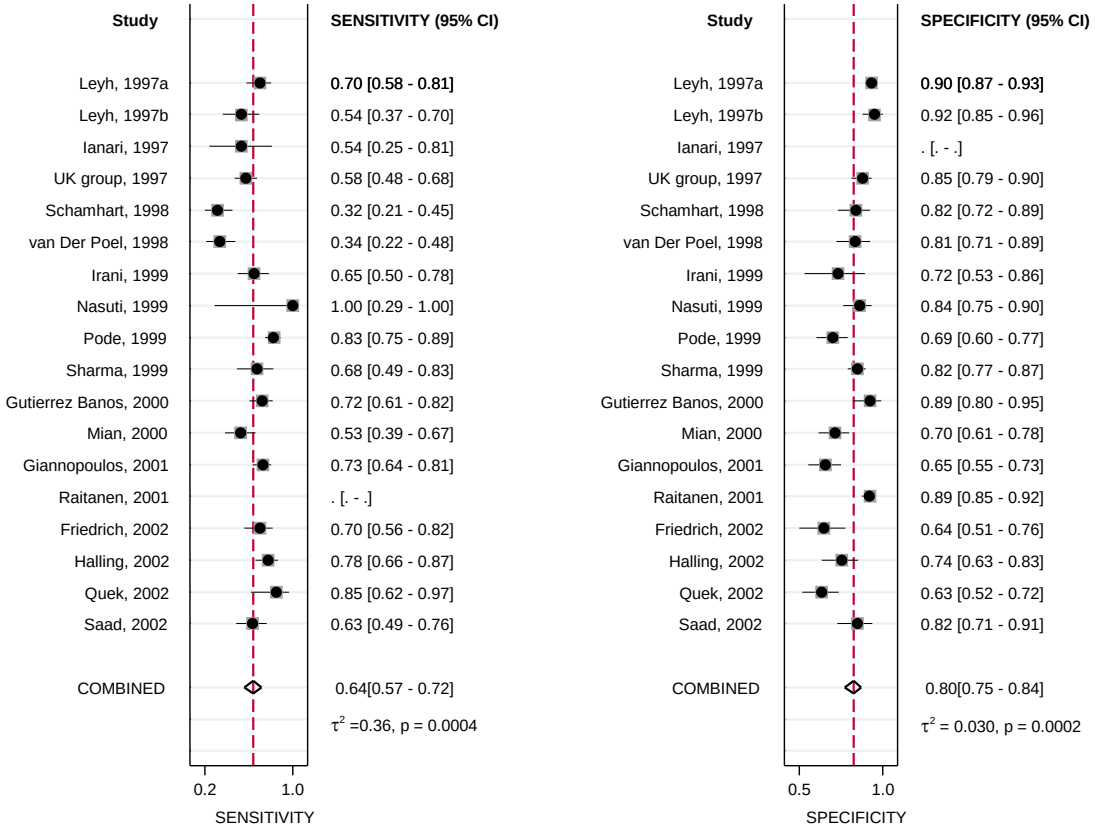


Figure 6. Sensitivity and specificity of FISH

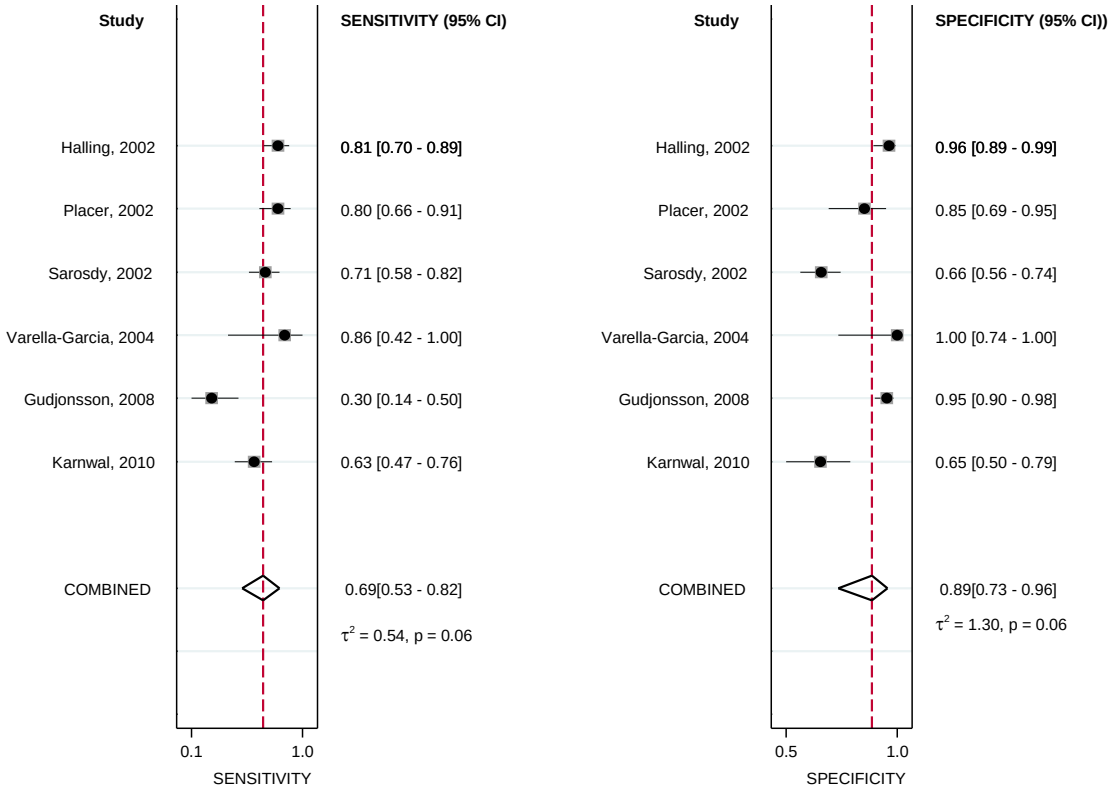
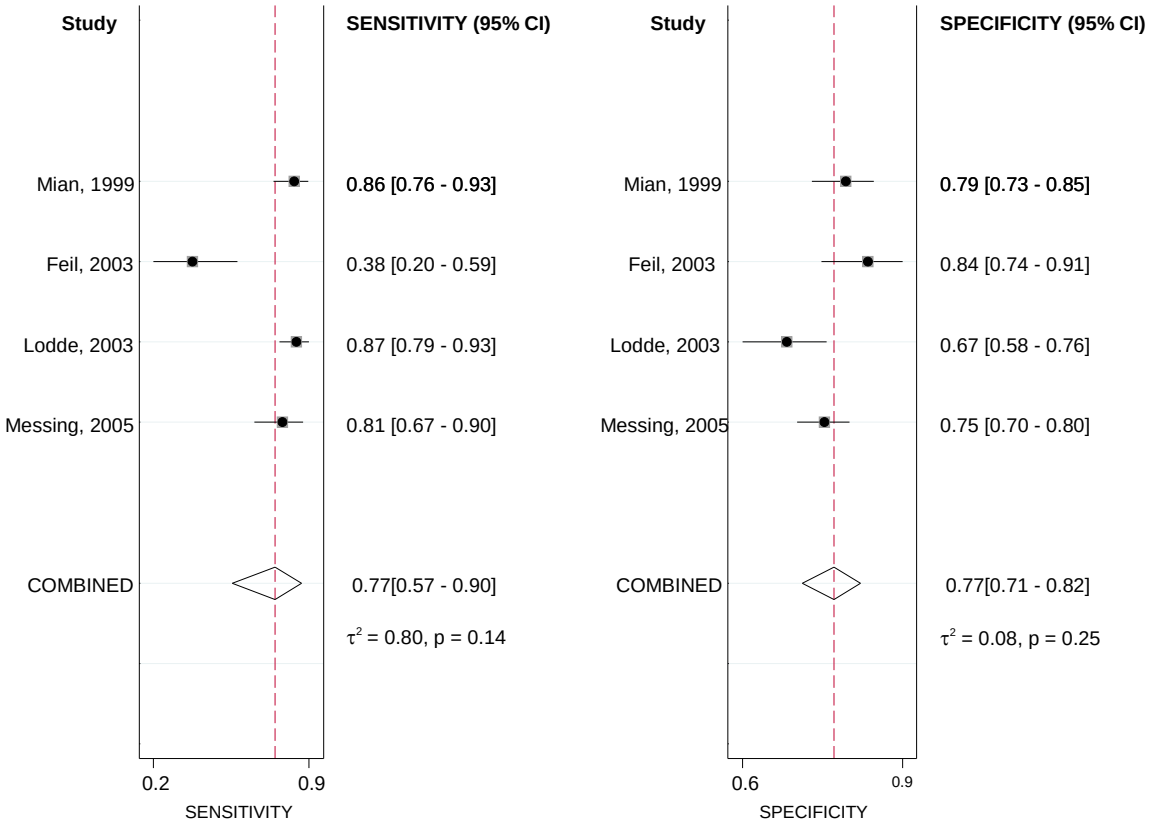


Figure 7. Sensitivity and specificity of immunocyt



Key Question 1a. 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 Points

- Effects of tumor stage: Across urinary biomarkers, sensitivity increased with higher tumor stage. Evidence was most robust for quantitative NMP22 (eight studies) and qualitative BTA (14 studies). Sensitivity for CIS tumors was intermediate between Ta and T1 (SOE: high).
- Effects of tumor grade: Across urinary biomarkers, sensitivity increased with higher tumor grade. Evidence was most robust for quantitative NMP22 (eight studies) and qualitative BTA (15 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 0.44 (95% CI 0.28 to 0.61; seven studies), for T1 tumors was 0.72 (95% CI 0.57 to 0.84; eight studies), and for ≥T2 tumors was 0.87 (95% CI 0.73 to 0.94; eight studies; p=0.002 for overall difference between categories).[30,32,33,39,52,60,61] The difference in sensitivity between T1 and Ta tumors was 0.28 (95% CI 0.17 to 0.39) and between ≥T2 and T1 tumors was 0.14 (95% CI 0.03 to 0.26). For qualitative BTA, sensitivity for Ta tumors was 0.47 (95% CI 0.38 to 0.56; 14 studies), for T1 tumors was 0.77 (95% CI 0.68 to 0.84; 13 studies), and for ≥T2 tumors was 0.93 (95% CI 0.86 to 0.96; 13 studies; p<0.0001 for overall difference between categories).[32,33,39,40,42,44,45,49,56,58,60,62,64,70] The difference in sensitivity between T1 and Ta tumors was 0.30 (95% CI 0.22 to 0.38) and between ≥T2 and T1 tumors was 0.16 (95% CI 0.08 to 0.24). For both quantitative NMP22 and qualitative BTA, sensitivity for CIS tumors was intermediate between Ta and T1.

Sensitivity also increased across urinary biomarkers with higher tumor grade (Table 5). For quantitative NMP22, sensitivity for G1 tumors was 0.38 (95% CI 0.23 to 0.55), for G2 tumors was 0.58 (95% CI 0.42 to 0.73), and for G3 tumors was 0.83 (95% CI 0.70 to 0.91), based on eight studies (p<0.0005 for difference between categories).[30,32,33,39,52,60,61,63] The difference in sensitivity between G2 and G1 tumors was 0.20 (95% CI 0.08 to 0.32) and between G3 and G2 tumors was 0.25 (95% CI 0.14 to 0.36). For qualitative BTA, sensitivity for G1 tumors was 0.37 (95% CI 0.27 to 0.49), for G2 tumors was 0.63 (95% CI 0.52 to 0.73), and for G3 tumors was 0.84 (95% CI 0.76 to 0.89), based on 15 studies (p<0.0001 for difference between categories).[32,33,39-42,44,45,49,56,58,60,62,64,70] The difference in sensitivity between G2 and G1 tumors was 0.26 (95% CI 0.17 to 0.35) and between G3 and G2 tumors was 0.20 (95% CI 0.13 to 0.28).

Similar patterns for effects of tumor stage and grade were observed for other urinary biomarkers (Table 5). However, estimates were based on small numbers of studies and were less precise, and differences were not always statistically significant. Differences in sensitivity by tumor stage were least pronounced for Immunocyt (sensitivity 0.73, 95% CI 0.49 to 0.88 for Ta; 0.78, 95% CI 0.52 to 0.92 for T1; and 0.87, 95% CI 0.62 to 0.96 for ≥T2), based on four studies.[31,46,48,50]

One study found higher sensitivity of 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] One study of quantitative NMP22 did not find difference in sensitivity between patients who had received prior intravesical therapy and those who had not.[65]

Four 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]

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 an 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,[74-78] 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 (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?

Key Points

BCG

- BCG was associated with decreased risk of bladder cancer recurrence (5 trials, RR 0.63, 95% CI 0.50 to 0.79, I^2=40%) and progression (6 trials, RR 0.50, 95% CI 0.32 to 0.77, I^2=69%) versus no intravesical therapy, but there was no difference in risk of all-cause (3 trials, RR 0.90, 95% CI 0.72 to 1.11, I^2=0%) and the effect on bladder cancer-specific mortality was not statistically significant (3 trials, RR 0.68, 95% CI 0.37 to 1.24, I^2=0%). (SOE: low for all-cause and bladder cancer mortality; SOE: moderate for recurrence and progression)

MMC

- Mitomycin C (MMC) was associated with decreased risk of bladder cancer recurrence versus no intravesical therapy (6 trials, RR 0.68, 95% CI 0.53 to 0.88, I2=75%), 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 (4 trials, RR 0.71, 95% CI 0.39 to 1.29, 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 (8 trials, RR 0.80, 95% CI 0.74 to 0.88, I^2 = 42%), no difference in risk of bladder cancer progression (5 trials, RR 1.03, 95% CI 0.72 to 1.46, I^2 = 0.0%), 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 0.66, 95% CI 0.56 to 0.77, I^2 = 54%) (SOE: moderate) but the effect on bladder cancer progression was not statistically significant (8 trials, RR 0.72, 95% CI 0.44 to 1.17, I^2 = 26%) (SOE: low).

Gemcitabine

- One trial found no difference between 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 (IFN-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 (IFN-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 in two trials (RR 0.34, 95% CI 0.16 to 0.72 and RR 0.58, 95% CI 0.37 to 0.93) (SOE: low).

Detailed Synthesis

36 trials (reported in 45 publications) evaluated intravesical therapy plus TURBT versus TURBT without intravesical therapy (Tables 6, 7, 8, 9, 10, 11, 12; Appendixes E2, F2).[79-121] 8 trials evaluated BCG,[79-92] 7 trials MMC,[92-99] 9 trials doxorubicin,[93,94,96,97,100-106] 10 trials epirubicin,[83,100,107-115] 3 trials interferon –alpha,[113,114,117,118] 1 trial interferon-gamma,[119] 2 trials thiotepa,[120,121] and 1 trial gemcitabine.[116] 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,[85,90] and 35 trials medium risk of bias (Appendix F2)[79-84,86-89,91-121] Two trials reported blinding of outcomes assessors;[108,113,114] 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 13.

BCG

Eight trials (reported in 14 publications) randomized patients to BCG versus no intravesical therapy following TURBT (Table 6; Appendixes E2, F2).[79-92] 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.[86]

There was no differences between BCG versus no intravesical therapy in risk of all-cause mortality (3 trials, RR 0.90, 95% CI 0.72 to 1.11, I^2=0%) (Figure 8).[79-81] BCG was associated with decreased risk of bladder cancer mortality that was not statistically significant (3 trials, RR 0.68, 95% CI 0.37 to 1.24, I^2=0%).[79,81,82] BCG was associated with reduced risk of bladder cancer recurrence (5 trials, 40% vs 60%, RR 0.63, 95% CI 0.50 to 0.79, I^2=40%) (Figure 9)[80,81,83,84,92] and progression (6 trials, 27% vs. 45%, RR 0.50, 95% CI 0.32 to 0.77, I^2=69%).[81,83-86,91] Two trials found no difference between BCG versus intravesical in risk of cystectomy (RR 0.78, 95% CI 0.35 to 1.74, I^2=30%).[79,86] and one trial (n=90) found no differences between BCG versus no intravesical therapy in quality of life or symptom scores based on the Japanese version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30.[81,122]

Statistical heterogeneity was present in analyses of recurrence and progression. Estimates were similar using the profile likelihood method and subgroup and other sensitivity analyses did not reduce statistical heterogeneity or resulted in similar findings.

MMC

Seven trials (reported in 8 publications) evaluated MMC versus no intravesical therapy.[92-99] (Tables 7, 8; Appendixes E2, F2). The doses of MMC ranged from 5 mg to 40 mg. The number of installations varied from one to 38: three trials evaluated a single installation,[95,98,99] one trial

evaluated an induction regimen (8 installations over 4 weeks),[93,97] and 3 trials evaluated maintenance regimens (ranging from 5 installations over 1 year to 38 installations over 2 years).[92-94,96,99] 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 installations/ 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).[99]

MMC was associated with decreased risk of bladder cancer recurrence versus no intravesical therapy (6 trials, RR 0.68, 95% CI 0.53 to 0.88, I^2 = 75%) (Figure 10).[92,93,95-98] Results were similar using the profile likelihood method (RR = 0.68, 95% CI 0.46 to 0.92). Results favored MMC in all trials, as well as in subgroup and sensitivity analyses. Findings were also consistent in a seventh trial that could not be pooled, but 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).[99]

MMC was associated with lower risk than no intravesical therapy of bladder cancer progression, but the difference was not statistically significant (4 trials, RR 0.71, 95% CI 0.39 to 1.29, I^2=0%) (Figure 11).[94-96,98] 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.[99]

Doxorubicin

Nine trials (reported in 11 publications) evaluated doxorubicin versus no intravesical therapy.[93,94,96,97,100-106] (Tables 9, 10; Appendixes E2, F2) The doses of doxorubicin ranged from 10 mg to 80 mg; with 20 mg, 30 mg, and 50 mg the most commonly studied dosages. The number of installations varied from one to 21: one trial used a single installation,[106] one trial used an induction regimen (8 installations over 4 weeks),[93,97] and one trial used a regimen of six installations in the two weeks prior to TURBT.[104] The remaining trials used maintenance regimens (ranging from 15 installations over 1 year to 21 installations over 2 years). Duration of followup for recurrence ranged from 240 days 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.[101] 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].[102]

Doxorubicin was associated with decreased risk of bladder cancer recurrence versus no intravesical therapy (8 trials, RR 0.80, 95% CI 0.74 to 0.88, I^2 = 41.6%) (Figure 12).[93,96,97,100-102,104,105] 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 0.95, 95% CI 0.79 to 1.13).[96] 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).[106]

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%).[94,96,100,101,103] 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).[83,100,107-115] 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 installations varied from one to 24: five trials used a single installation,[107-109,112,113] one trial evaluated 2 installations over 2 days,[115] two trials used an induction regimen (6 installations over 6 weeks) followed by up to 7 additional maintenance doses over 2 years for recurrence-free patients,[83,111] and three trials used maintenance regimens (ranging from 18 installations over 1 year to 24 installations over 2 years).[100,107,110] 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 0.66, 95% CI 0.56 to 0.77, I^2 = 54%)(Figure 13).[83,100,107-113] 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 (two installations) compared with no adjuvant therapy (38 months vs. 13 months, log-rank test, p = 0.05).[115]

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 0.72, 95% CI 0.44 to 1.17, I^2 = 26%) **(Figure 14)**.[83,100,107,108,110-112,115] In stratified analyses, single instillation therapy with epirubicin was not associated with decreased risk of bladder cancer progression (3 trials, RR 1.12, 95% CI 0.63 to 1.99, I^2 = 0.0%).[107,108,112] Excluding these trials resulted in a statistically significant decrease in risk of bladder cancer progression (6 trials, RR 0.54, 95% CI 0.30 to 0.97, I^2=12.6%).[83,100,107,110,111,115] An outlier trial found a maintenance regimen of epirubicin 20 mg (24 installations 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.[110]

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

Gemcitabine

One trial (n = 248) evaluated a single installation of gemcitabine versus placebo (Appendixes E2, F2).[116] 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.se.

Interferon-alpha

Three trials (reported in four publications) evaluated interferon-alpha (IFN-alpha) versus no intravesical therapy(Appendixes E2, F2).[113,114,117,118] The doses of IFN-alpha ranged from 40

million units (MU) to 80 MU. One trial evaluated a single installation[113,114] and two trials evaluated maintenance regimens (21 or 22 installations over 1 year).[118,123] Duration of followup ranged from 2 years to a median of 72 months.

One trial found no difference between IFN-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].[118]

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 15)[113,118,123] Results were similar using the profile likelihood method. One trial found interferon-alpha associated with decreased risk[123] and two trials no effect.[113,118] The trial that found IFN-alpha associated with decreased risk of bladder cancer evaluated IFN-alpha using doses of 40, 60, and 80 MU; only the 80 MU dose was associated with decreased risk of recurrence (RR 0.35, 9%% CI 0.14 to 0.89).[123] The other two trials evaluated doses of 60 MU or less and one[113,114] evaluated single instillation therapy.

IFN-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 16).[118,123]

Interferon-gamma

One trial (n=54) found induction therapy (8 instillations over 8 weeks) with IFN-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) (Appendixes E2, F2).[119] 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

Two trials evaluated thiotepa versus no intravesical therapy (Appendixes E2, F2).[120,121] One trial (n = 93) found thiotepa 30 mg (32 instillations over 2 years) for primary G1 or G2 tumors associated with decreased risk of bladder cancer recurrence versus no intravesical therapy (15% vs. 46%, RR 0.34, 95% CI 0.16 to 0.72).[120] A second trial evaluated maintenance therapy (one installation every 4 weeks for a maximum of 2 years) with two different doses of thiotepa (30 mg and 60 mg) for recurrent or multifocal NMIBC (stage and grade not reported).[121] Both doses of thiotepa were associated with decreased risk of bladder cancer recurrence versus no intravesical, though the difference was only statistically significant for the 60 mg dose (37% vs. 60%, RR 0.66, 95% CI 0.37 to 1.15 and 31% vs. 60%, RR 0.51, 95% CI 0.26 to 0.99 for 30 and 60 mg doses, respectively).

Figure 8. Meta-analysis of bacillus Calmette–Guérin versus no intravesical therapy: Risk of all-cause mortality

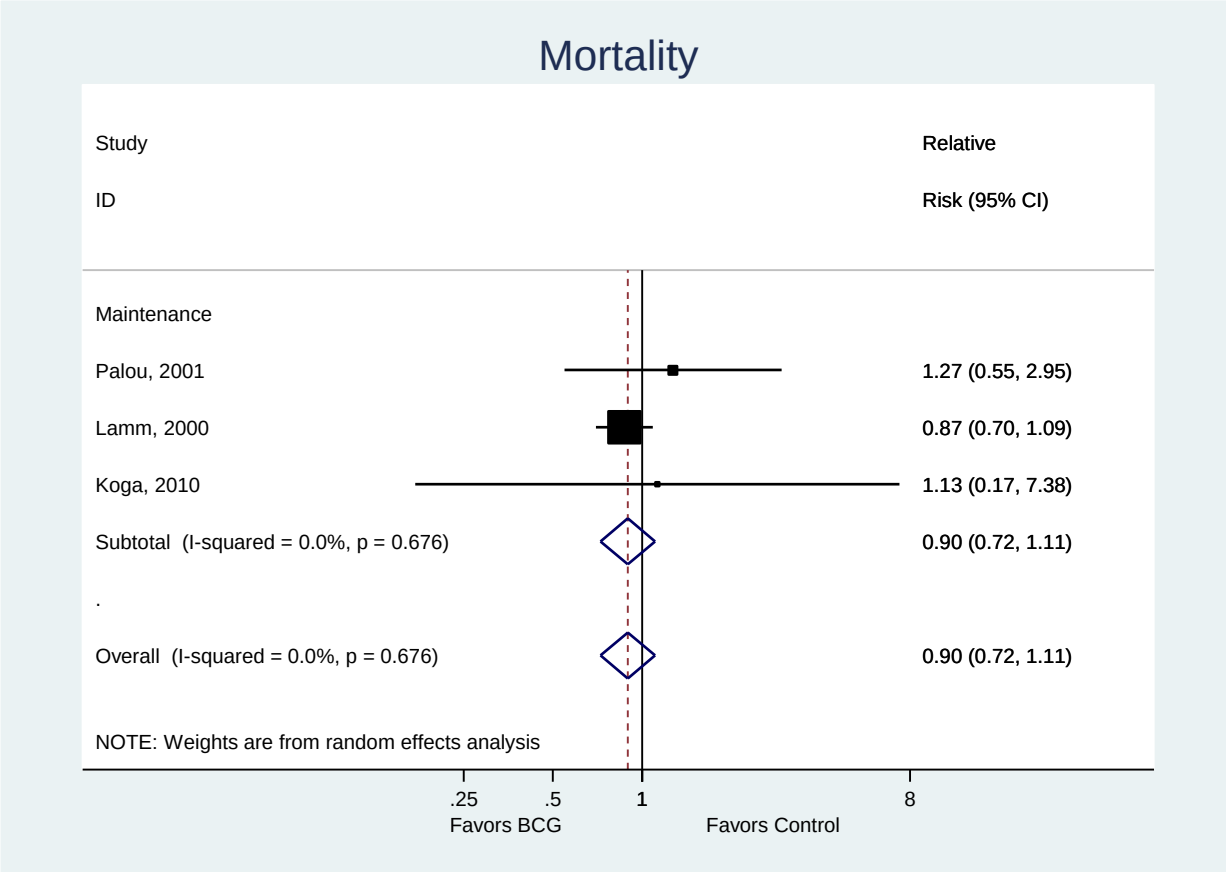


Figure 9. Meta-analysis of bacillus Calmette–Guérin versus no intravesical therapy: Risk of recurrence

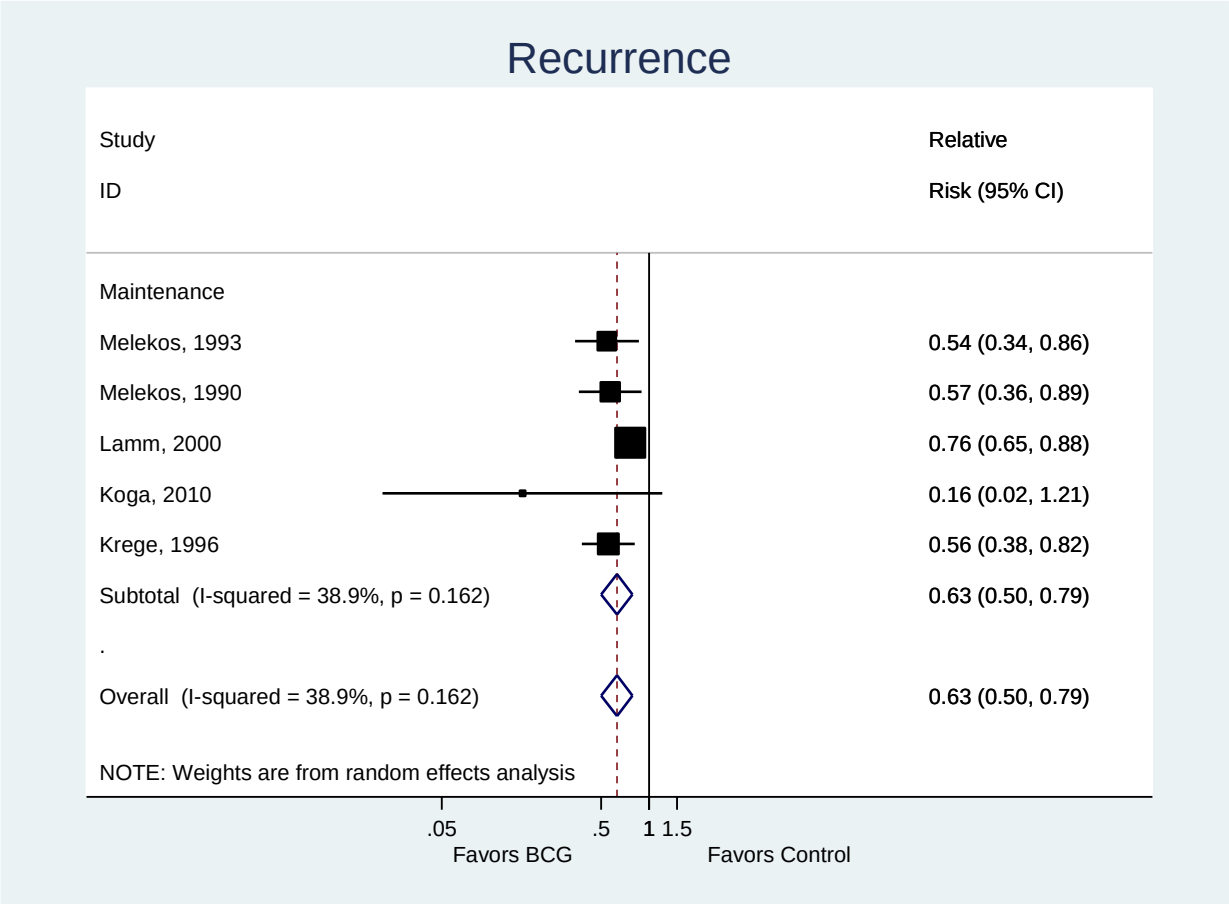


Figure 10. Meta-analysis of MMC versus no intravesical therapy: Risk of recurrence

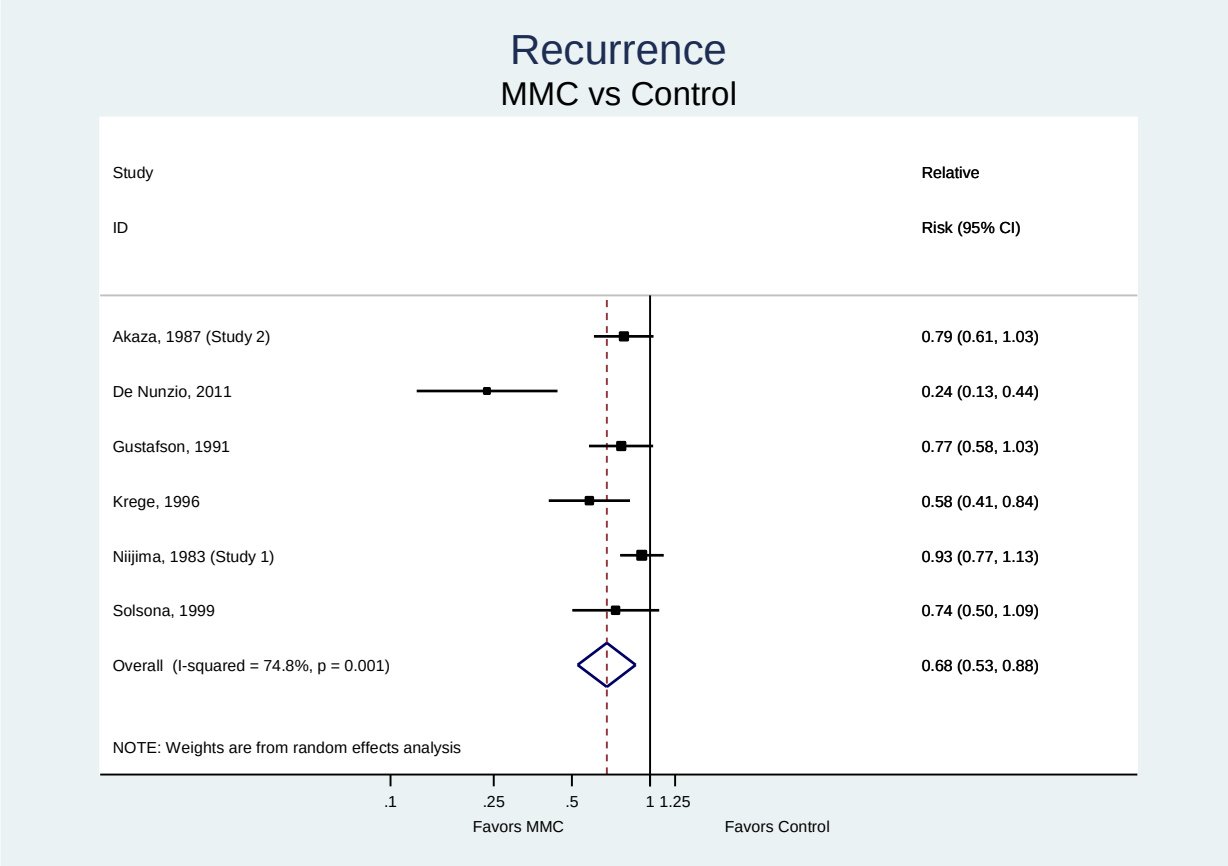


Figure 11. Meta-analysis of MMC versus no intravesical therapy: Risk of progression

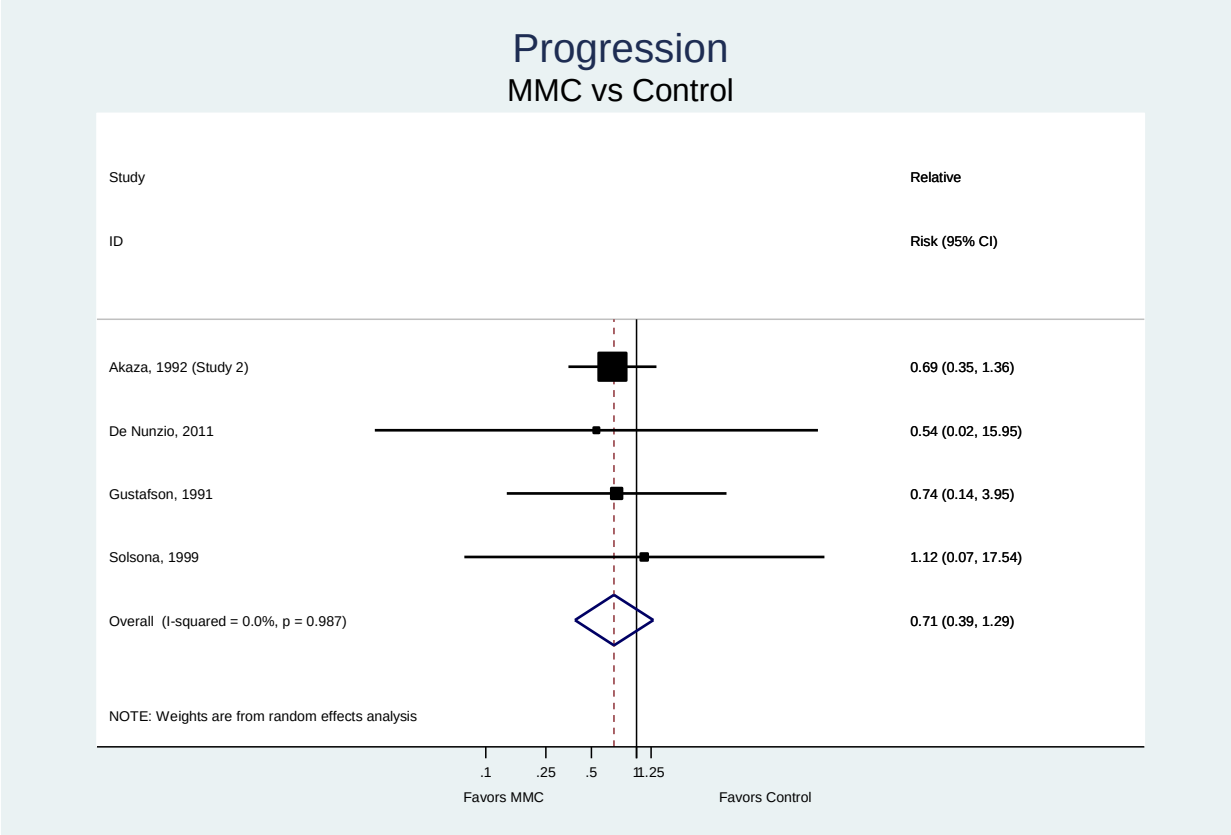


Figure 12. Meta-analysis of doxorubicin versus no intravesical therapy

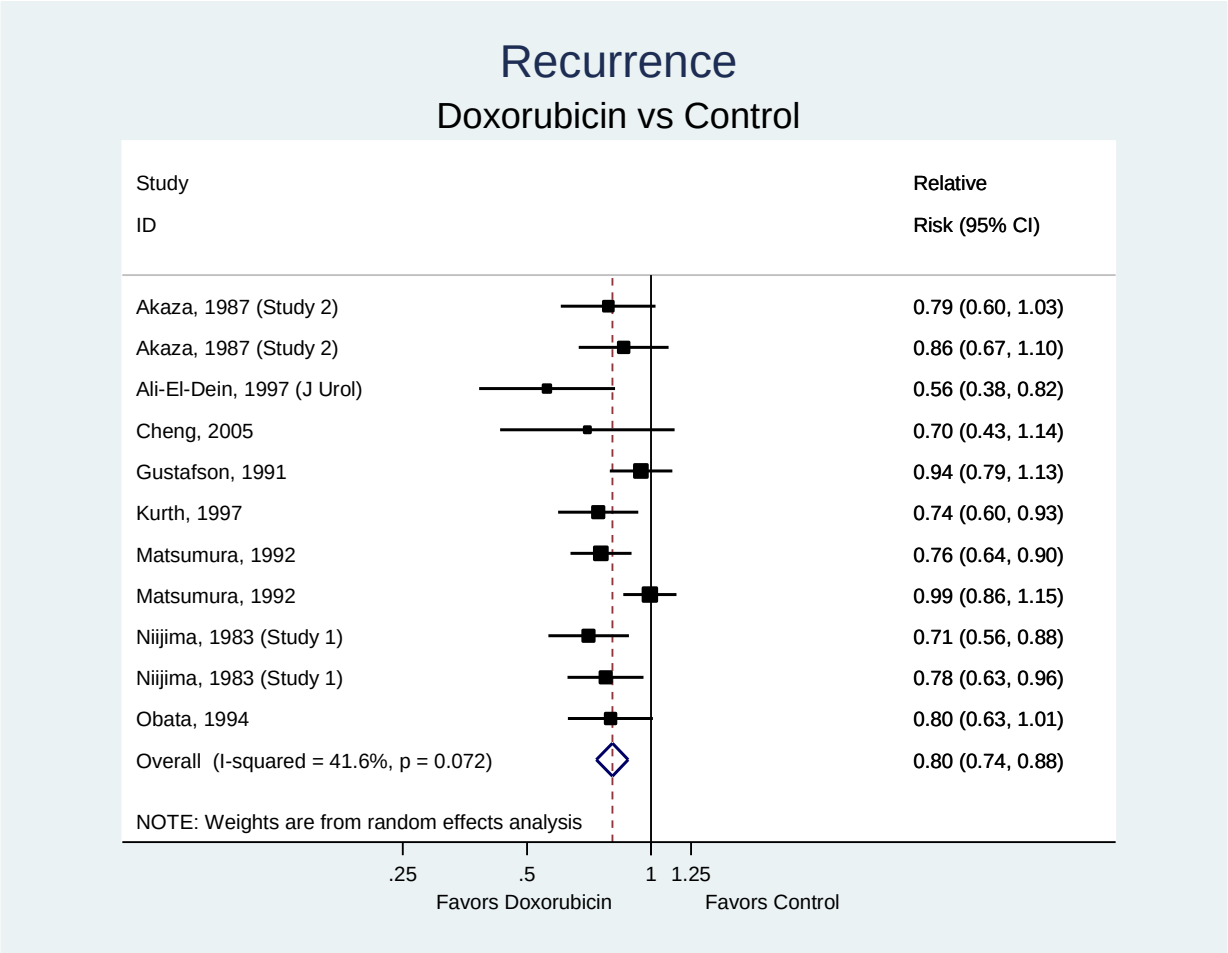


Figure 13. Meta-analysis of epirubicin versus no intravesical therapy: Risk of recurrence

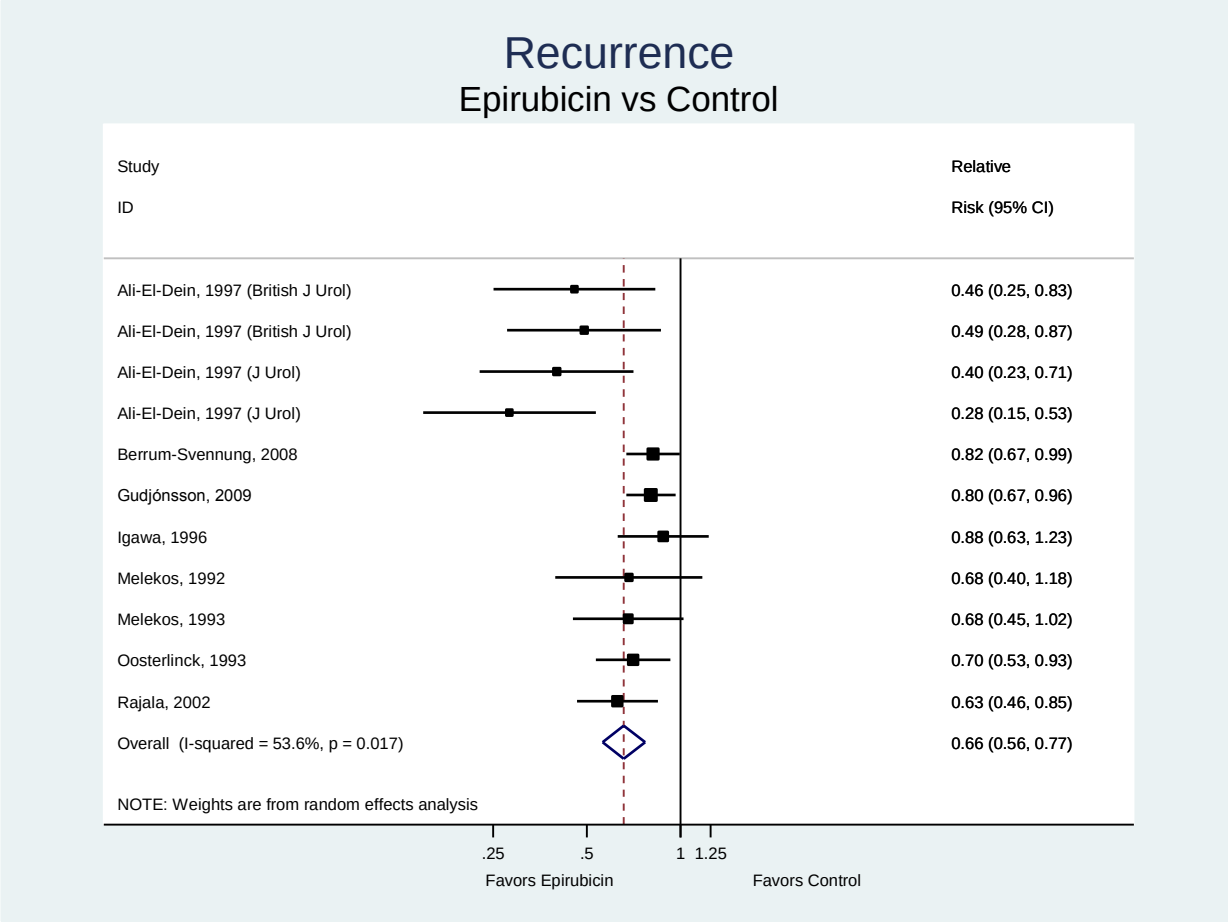


Figure 14. Meta-analysis of epirubicin versus no intravesical therapy: Risk of progression

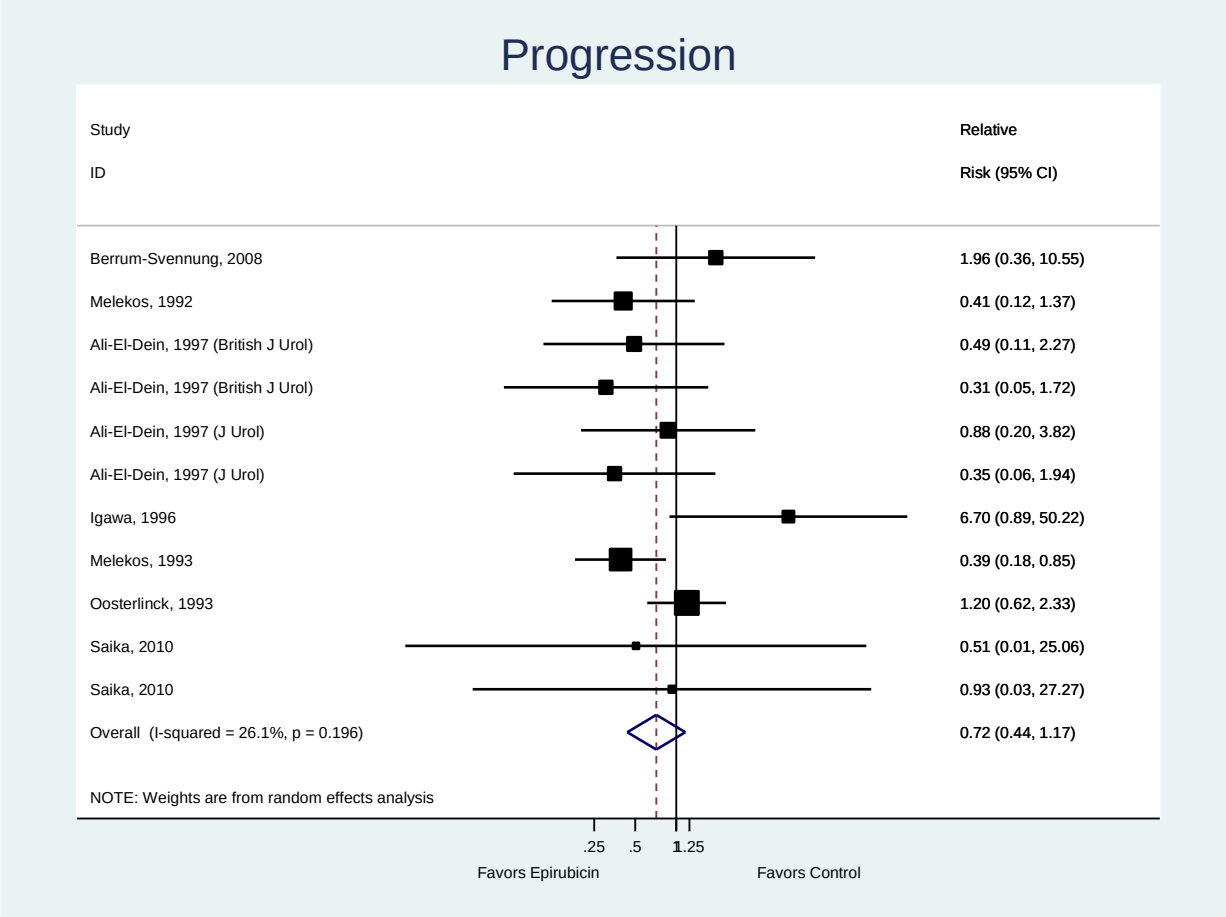


Figure 15. Meta-analysis of interferon-alpha-2b versus no intravesical therapy: Risk of recurrence

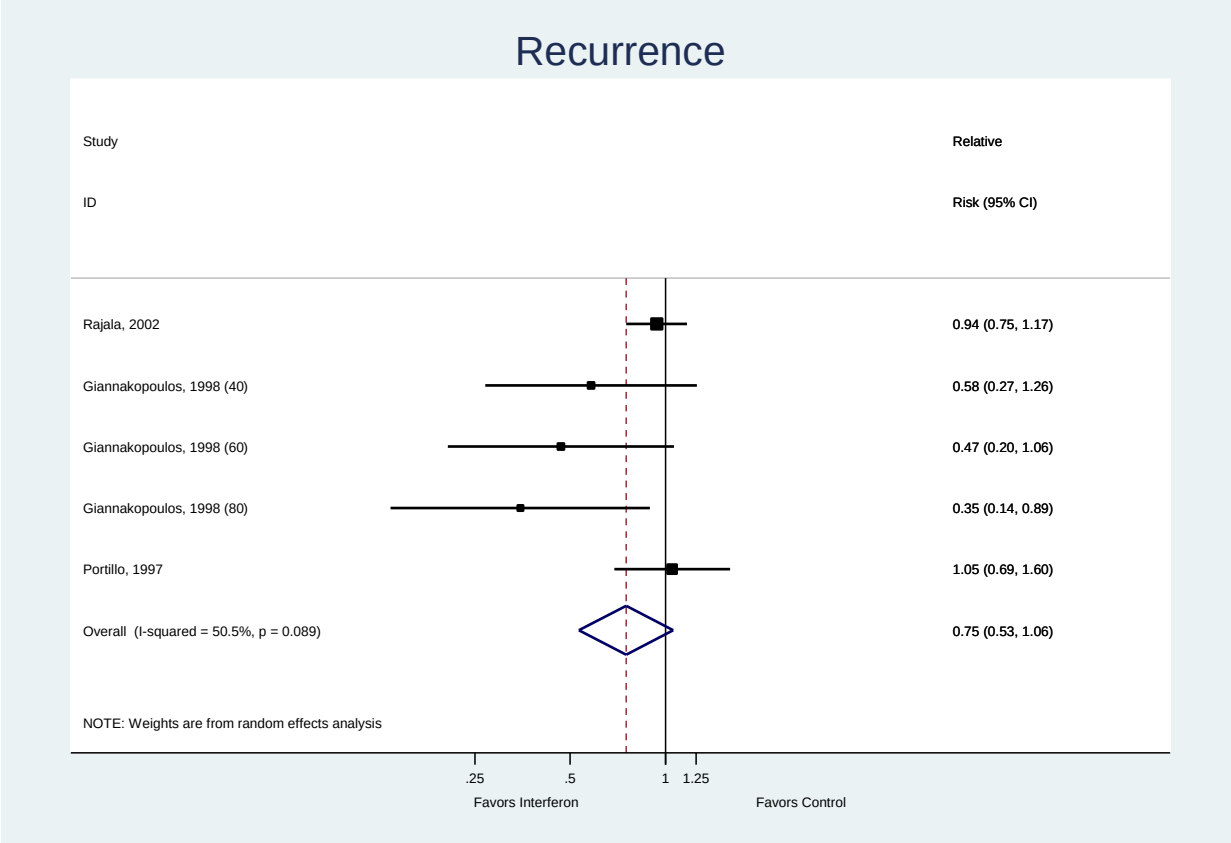
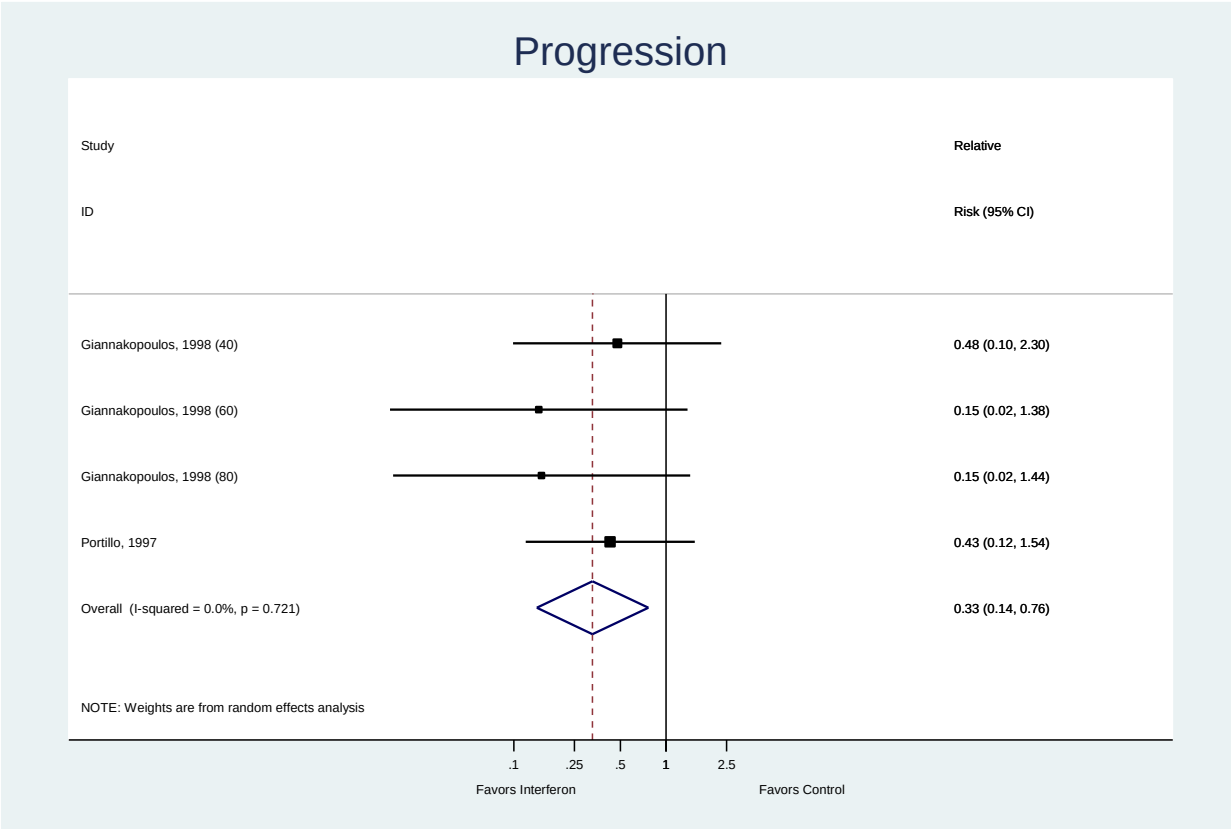


Figure 16. Meta-analysis of interferon-alpha-2b versus no intravesical therapy: Risk of progression



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 (9 trials, RR 0.97, 95% CI 0.78 to 1.16, I^2=68%), but BCG was associated with decreased risk in the subgroup of trials that evaluated maintenance regimens (5 trials, RR 0.77, 95% CI 0.68 to 0.88, 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 0.6 and RR 0.75, 95% CI 0.6 to 0.88), but there were no difference in risk of all-cause mortality (2 trials, RR 0.40, 95% CI 0.1 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

- One trial found BCG associated with reduced risk of bladder cancer recurrence versus thiotepa (RR 0.38, 95% CI 0.19 to 0.76) but the difference in risk of progression was not statistically significant (RR 0.42, 95 5CI 0.19 to 0.76). (SOE: low for recurrence and progression).

MMC Versus Doxorubicin

- There was no difference between mitomycin (MMC) versus doxorubicin in risk of bladder cancer recurrence (4 trials, RR 1.02, 95% CI 0.86 to 1.21, I^2=30%), but MMC was associated with decreased risk of bladder cancer progression (3 trials, RR 0.48, 95% CI 0.26 to 0.90, I^2 = 53%) (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

- MMC was associated with no difference 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) versus interferon-alpha (SOE: low).

MMC Versus Interferon-gamma

- MMC was associated with increased risk of bladder cancer recurrence versus IFN-gamma in one trial (RR 1.61, 95% CI 0.97 to 2.67) (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 Verus 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 IFN-alpha in one trial (RR 0.67, 95% CI 0.49 to 0.91) (SOE: low).

Detailed Synthesis

Forty-seven trials (reported in 57 publications) compared effects of intravesical therapy using one drug versus another (Tables 6, 7, 8, 9, 10, 11, 12; Appendixes E2, F2).[83,92-94,96,97,100,113,114,117,124-134,135Witjes, 1998 #2638,136-173] Fourteen trials evaluated BCG versus MMC,[92,124-134,135Witjes, 1998 #2638,136-141,173] 2 trials BCG and MMC versus MMC,[142-145], 4 trials BCG versus doxorubicin,[146-148] 9 trials BCG versus epirubicin,[83,149-157] 1 trial BCG versus epirubicin plus interferon,[158,159] 4 trials BCG versus gemcitabine,[160-163] 3 trials BCG versus interferon-alpha,[164-166] and 1trial BCG versus thiotepa.[148] 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.[93,94,96,97,100,113,114,117,167-172] Four trials evaluated MMC versus doxorubicin,[93,94,96,97,167] 1 trial MMC versus epirubicin,[168] 1 trial MMC versus interferon-alpha,[169] 1 trial MMC versus interferon-gamma,[117] 1 trial MMC versus gemcitabine,[170] 3 trials doxorubicin versus epirubicin,[100,171,172] 1 trial doxorubicin versus thiotepa,[148] and 1 trial epirubicin versus interferon-alpha.[113,114]
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%. 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% to73% and the proportion with CIS lesions ranged from 0% to 100%. 34 trials focused on patients with primary tumors and 29 trials focused on patients with recurrent tumors. 3 trials were rated high risk of bias,[156,162,172] 41 trials medium risk of bias,[83,92-94,96,97,100,113,114,117,124-131,133-155,157,159,161,163-171,173] and 3 trials low risk of bias (Appendix F2).[132,158,160] Two trials reported blinding of outcomes assessors;[114,135] 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 14.

BCG Versus MMC

Ten trials (reported in 16 publications) randomized patients to BCG versus MMC[92,124-137,173] and four trials randomized patients to BCG versus BCG plus MMC given sequentially (Table 6; Appendixes E2, F2).[138-141] The dose of BCG ranged from 13.5 to 120 mg and the dose of MMC from 20 to 40 mg with the number of instillations ranging from a single instillation[138] to 42 administered over three years.[131]

There was no difference between BCG versus MMC in risk of bladder cancer recurrence (9 trials, RR 0.97, 95% CI 0.78 to 1.16, I^2=68%) (Figure 17)[92,124,128,130-133,137,173] 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 0.77, 95% CI 0.68 to 0.88, I^2=0%),[124,128,130,132,137] but not in trials that evaluated induction regimens (4 trials, RR 1.22, 95% CI 0.99 to 1.51, I^2=50%).[92,131,133,173]

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 18)[124,128,130,132,134,137,173] or disease-specific mortality (5 trials, RR 0.77, 95% CI 0.54 to 1.10, I^2=0%) (Figure 19).[124,128,134,137,173] There were also no differences in risk of bladder cancer progression (Figure 20) (7 trials, RR 0.88, 95% CI 0.66 to 1.17, I^2=18%).[124,128,132-134,137,173] 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).[92]

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)[140] or bladder cancer mortality (Figure 21) (2 trials, RR 1.10, 95% CI 0.50 to 2.38, I^2=17%),[139,140] bladder cancer recurrence (Figure 22) (4 trials, RR 1.03, 95% CI 0.70 to 1.52,I^2=75%),[138-141] progression (Figure 23) (3 trials, RR 0.87, 95% CI 0.40 to 1.91, I^2=22%),[138-140] or cystectomy (4 trials, RR 0.87, 95% CI 0.41 to 1.84, I^2=0%).[138-141]

Statistical heterogeneity was present for analyses of bladder cancer recurrence. However, estimates were similar using the profile likelihood method, and subgroup and other sensitivity analyses 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 E2, F2).[142-145] The Finnbladder study enrolled 256 patients and reported results for patients with (27%) and without CIS separately.[143-145] All patients received 5 instillations of MMC and were then randomized to 15 additional instillations of MMC versus alternating MMC and BCG instillations over two years. The second trial analyzed 182 patients, of whom 36% had CIS.[142] Doses of BCG ranged from 50-75 mg and MMC dose from 20-40 mg. Patients received 4 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).[142] 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).[143])

There was no difference between BCG plus MMC given sequentially versus MMC alone in risk of bladder cancer recurrence (Figure 23)(2 trials, RR 0.88, 95% CI 0.75 to 1.03, I^2=0%).[142-144] 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).[173] 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).[143] 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 Doxorubicin

Three trials randomized patients to BCG versus doxorubicin (Table 6; Appendixes E2, F2).[146-148] 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.[146]

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.[148] 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).[147] 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[148] and 61% vs 81%, RR 0.75, 95% CI 0.64 to 0.88).[147] 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).[148]

BCG Versus Epirubicin

Six trials (reported in 7 publications) randomized patients to BCG versus epirubicin[83,149-154] and three trials randomized patients to BCG versus BCG plus epirubicin given sequentially (3 studies) (Table 6; Appendixes E2, F2).[155-157] 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 epirubicin bladder instillations ranged from a single instillation in one trial[155] to greater than 20 over 3 years in two trials;[149,153] all but one trial evaluated maintenance regimens.[157]

BCG was associated with decreased risk of all-cause (Figure 24) (3 trials, RR 0.72, 95% CI 0.44 to 1.19, I^2=87%)[149,150,153] and disease-specific mortality (Figure 25) (3 trials, RR 0.72, 95% CI 0.25 to 2.08,I^2=80%)[149,150,153] versus epirubicin, but the differences were not statistically significant. Estimates were similar using the profile likelihood method. Excluding the trial[149] 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 non-statistically 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 26).[83,149-152] 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%)[149,150,152] but not in trials that included patients with CIS (2 trials, RR 0.80, 95% CI 0.60 to 1.07, I^2=0%).[83,151] 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 27).[83,149-152] Estimates and findings were similar using the profile likelihood method. Statistical heterogeneity was reduced when one trial[152] 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 28) (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 29).[155-157] Trials did not report mortality.

BCG Verus 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 E2, F2).[158,159] Six weekly induction treatments were followed by maintenance therapy to two years. The trial was rated low risk of bias.

There were no differences between BCG versus epirubicin plus interferon in risk of bladder BCG was associated with reduced risk of bladder cancer recurrence (RR 0.66, 95% CI 0.51 to 0.85), cancer mortality at five years (RR 0.79, 95% CI 0.32 to 1.63), progression-free survival at two or five years, and risk of cystectomy at two years (RR 0.68, 95% CI 0.30 to 1.54)[158,159] 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[160-162] and one trial to BCG versus BCG plus gemcitabine administered sequentially (Table 6; Appendixes E2, F2).[163] 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),[160,161] one enrolled patients at intermediate risk[162] and one enrolled patients who were intermediate or high risk.[163] The dose of BCG ranged from 12.5 mg to 50 mg. The dose of gemcitabine was 2000 mg in all studies, although the dose immediately after TURBT was 1000 mg in one study.[163] Total gemcitabine instillations ranged from two[163] to 15-18 over one year.[160,162] One study administered maintenance gemcitabine over three years (13 total doses).[161]

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).[160] No trial reported bladder cancer specific mortality.

Three trials reported effects of BCG versus gemcitabine on risk of bladder cancer recurrence.[160-162] 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)[160] 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)[161] 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).[162]

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[160] and RR 0.52, 95% CI 0.13 to 2.06).[162] One trial found no difference between BCG versus gemcitabine on all quality of life dimensions as

measured by the EORTC-QLQ-C30[122] or the EORTC QLQ-BLS24,[162] 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).[162]

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).[163]

BCG Versus Interferon

One trial randomized patients to BCG versus interferon alpha-2a,[164] one trial randomized patients to BCG versus alternating BCG plus interferon alpha-2b,[165] and one trial to BCG versus combination therapy with BCG plus interferon alpha-2b (Table 6; Appendixes E2, F2).[166] 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.[165] 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 one year alternating with BCG[165] to 24 given in addition to BCG over three years.[166] Up to 17 interferon instillations were given over 9 months in the trial of BCG versus interferon given alone.[164]

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).[164] 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).[165] 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).[166] 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

One trial (n=123) randomized patients to BCG versus thiotepa (Table 6; Appendixes E2, F2).[148] It initially enrolled patients with Ta or T1 tumors but later restricted enrollment to T1 tumors due to the low probability of recurrence with Ta disease. BCG 150 mg or thiotepa 50 mg was administered weekly for four weeks, then monthly for 11 months. BCG was associated with reduced risk of bladder cancer recurrence versus thiotepa (13% vs. 36%, RR 0.38, 95% CI 0.19 to 0.76), but the effect on risk of progression was not statistically significant (RR 0.42, 95% CI 0.19 to 0.76).[148] There were too few cases of death or cystectomy (one case each) to evaluate effects.

MMC Versus Doxorubicin

Four trials (reported in five publications) evaluated MMC versus doxorubicin (Tables 7, 8; Appendixes E2, F2).[93,94,96,97,167] Three trials evaluated an MMC dose of 20 mg[93,94,97,167] and in one trial doses ranged from 5 mg to 40 mg depending on the patient's bladder capacity.[96]

Doxorubicin doses ranged from 10 to 80 mg. Three trials[93,94,96,167] evaluated maintenance regimens (range 15 to 42 instillations) and one trial evaluated an induction regimen (8 doses over 4 weeks).[93,97] Duration of followup ranged from a mean of 27 to 60 months.

There was no difference between MMC versus doxorubicin in risk of bladder cancer recurrence (4 trials, RR 1.02, 95% CI 0.86 to 1.21, I^2=30%) (Figure 30).[93,96,97,167] Findings were similar in a subgbroup analysis restricted to three trials that evaluated maintenance therapy (3 trials, RR 0.88, 95% CI 0.73 to 1.06, I^2=0.0%).[93,96,167] MMC was also associated with decreased risk of bladder cancer progression versus doxorubicin (3 trials, RR 0.48, 95% CI 0.26 to 0.90, I^2=53.4%).[94,96,167] 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 E2, F2).[168] It found no difference in risk of bladder cancer recurrence at five 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 E2, F2).[170] 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 E2, F2).[169] 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].[169] 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-gamma15 MU for primary G2 tumors (CIS excluded) (Tables 7, 8; Appendixes E2, F2).[117] 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.

Doxorubicin Versus Epirubicin

Three trials evaluated doxorubicin versus epirubicin (Tables 9, 10; Appendixes E2, F2).[100,171,172] 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, $I^2 = 0.0$).[100,171,172] 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[100] and another trial reported no instances of progression in either treatment group.[172] 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 E2, F2).[148] 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 E2, F2).[113,114] 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 17. Meta-analysis of bacillus Calmette–Guérin versus MMC: Risk of recurrence

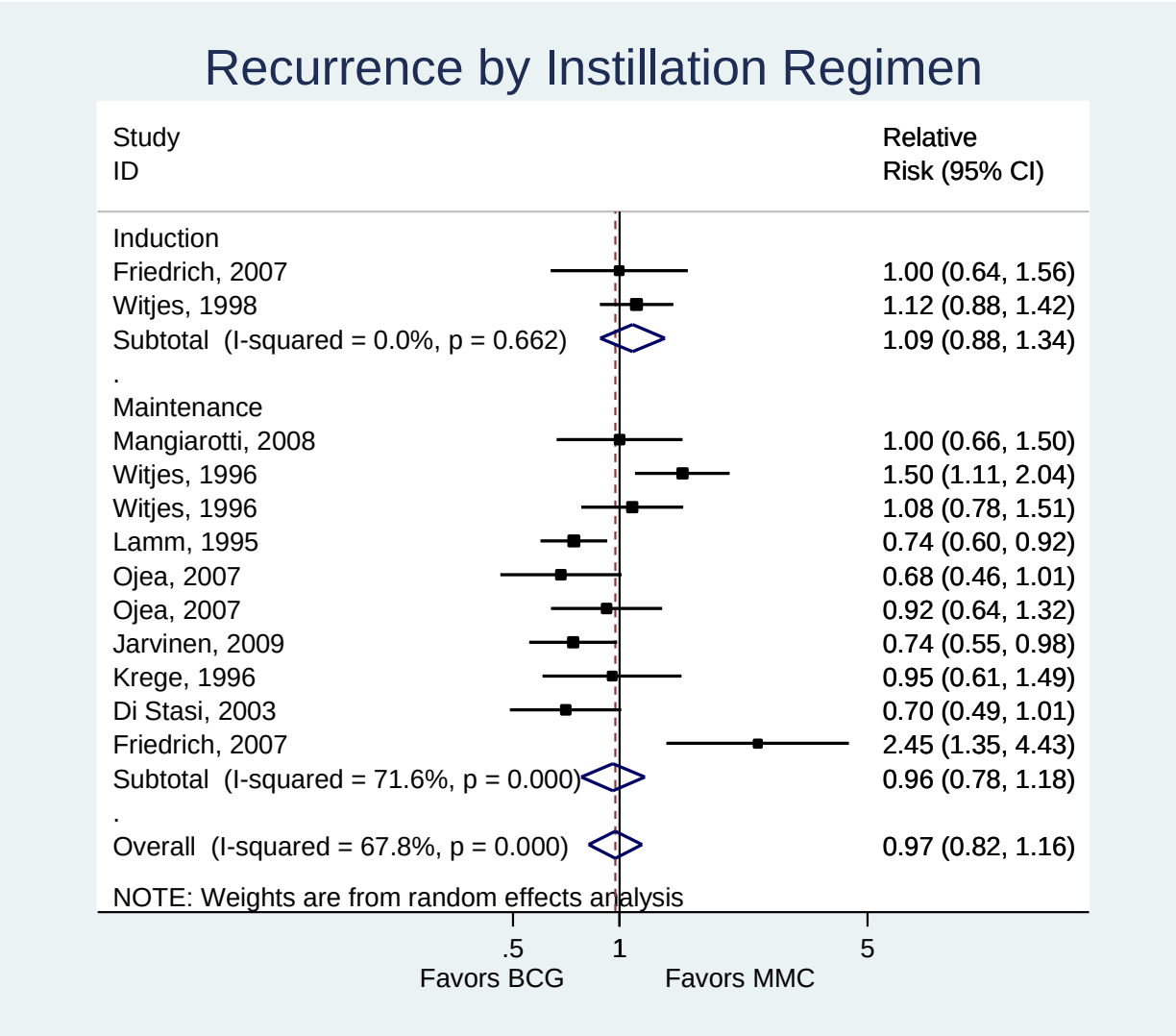


Figure 18. Meta-analysis of bacillus Calmette–Guérin versus MMC: Risk of mortality

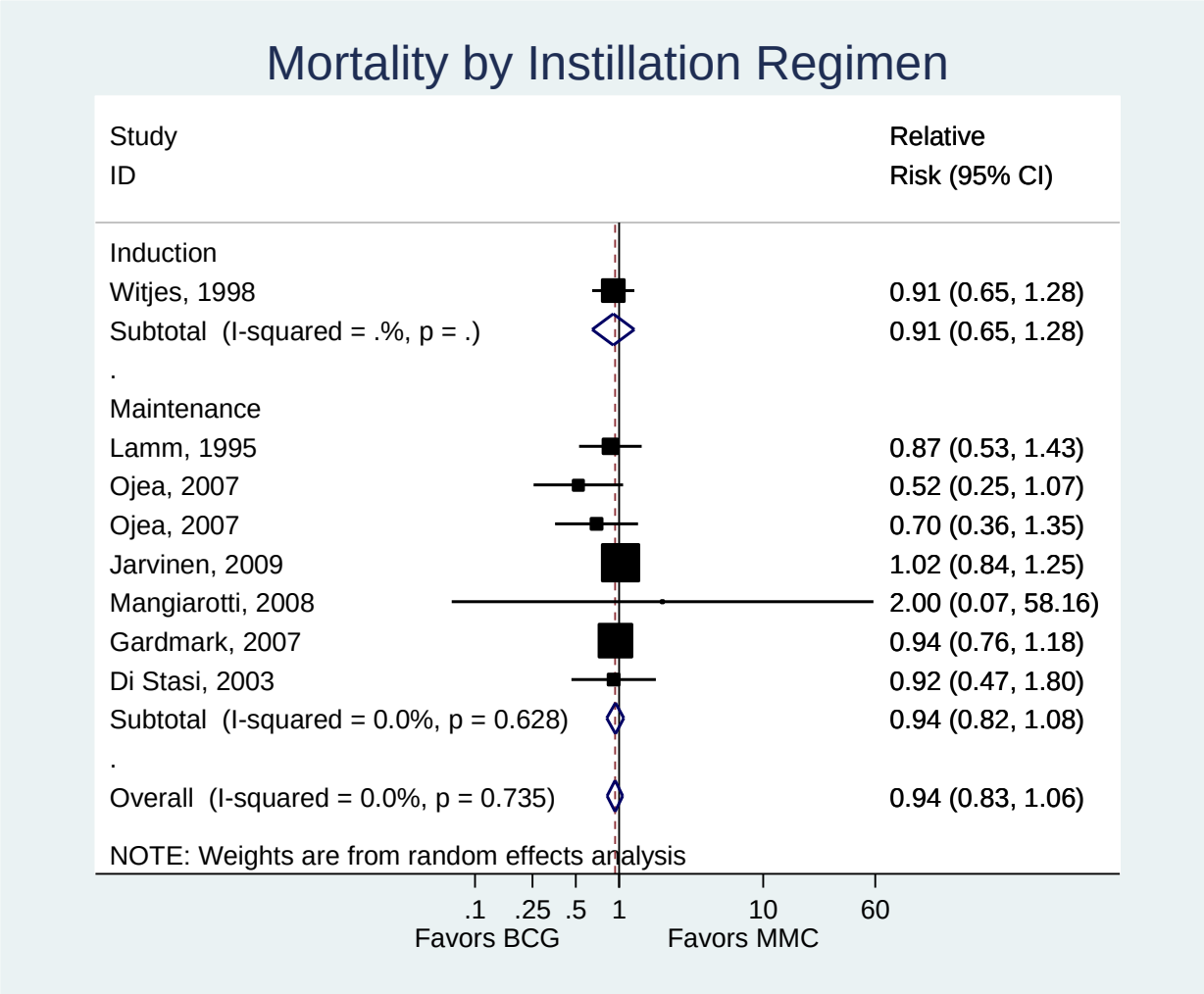


Figure 19. Meta-analysis of bacillus Calmette–Guérin versus MMC: Risk of bladder cancer-specific mortality

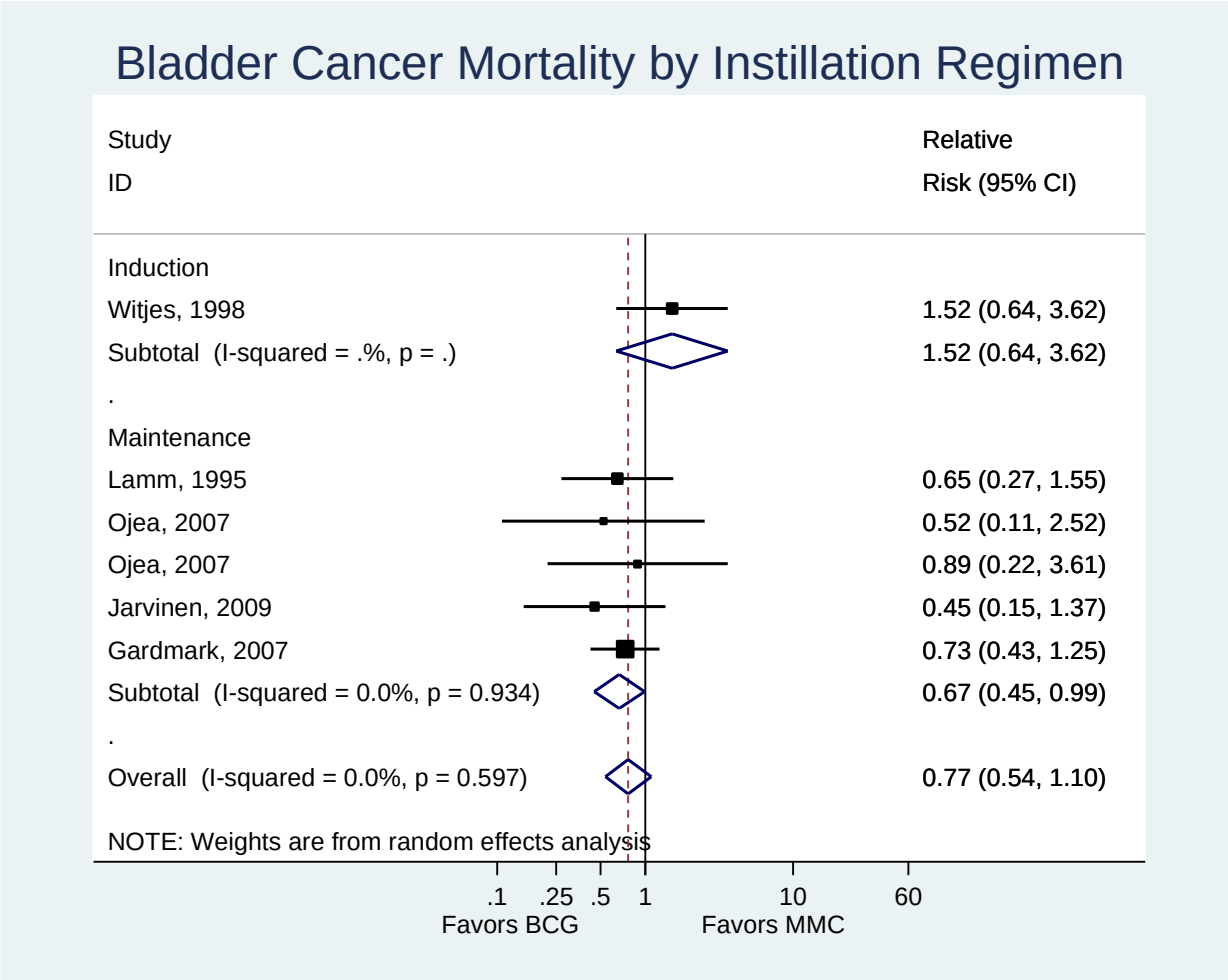


Figure 20. Meta-analysis of bacillus Calmette–Guérin versus MMC: Risk of progression

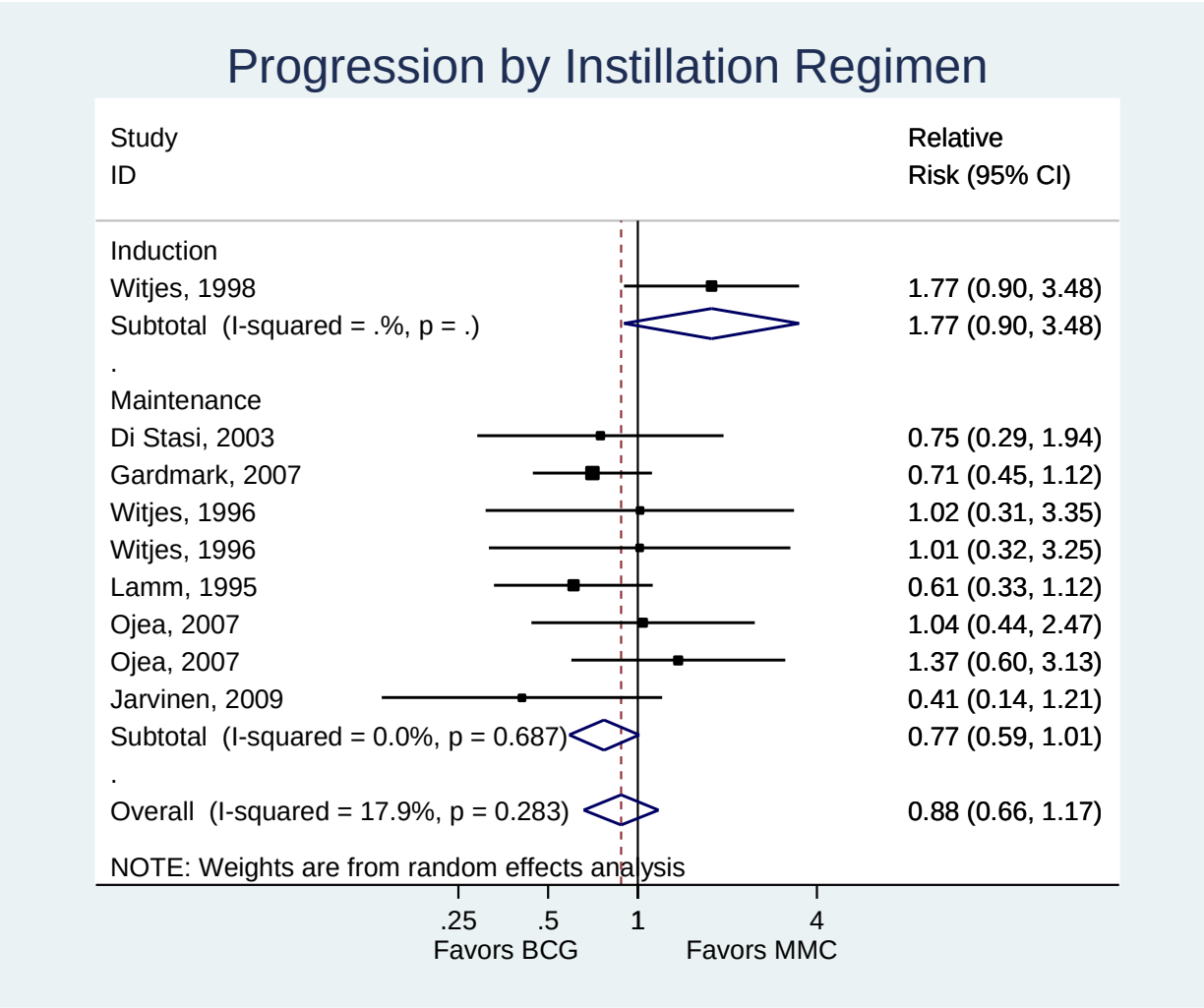


Figure 21. Meta-analysis of bacillus Calmette–Guérin versus bacillus Calmette–Guérin plus MMC: Risk of bladder cancer-specific mortality

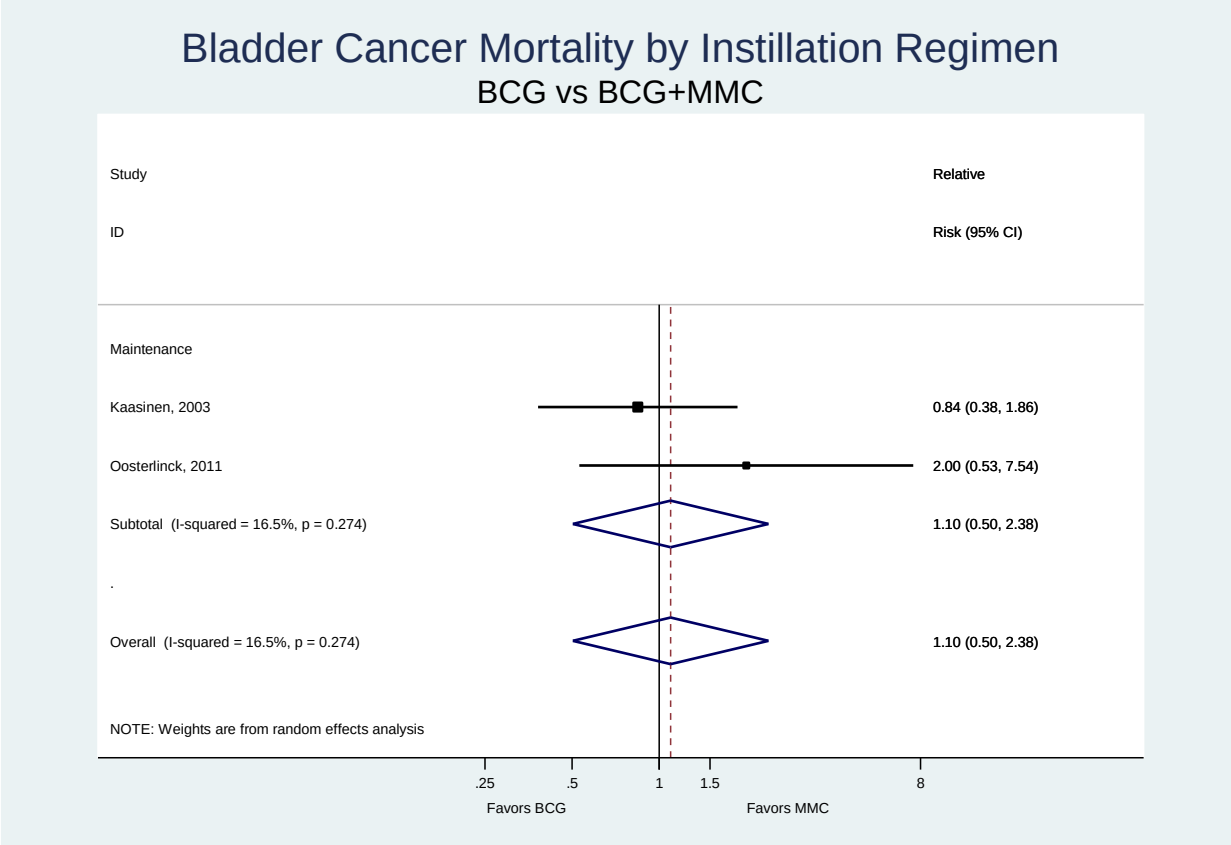


Figure 22. Meta-analysis of bacillus Calmette–Guérin versus bacillus Calmette–Guérin plus MMC: Risk of recurrence

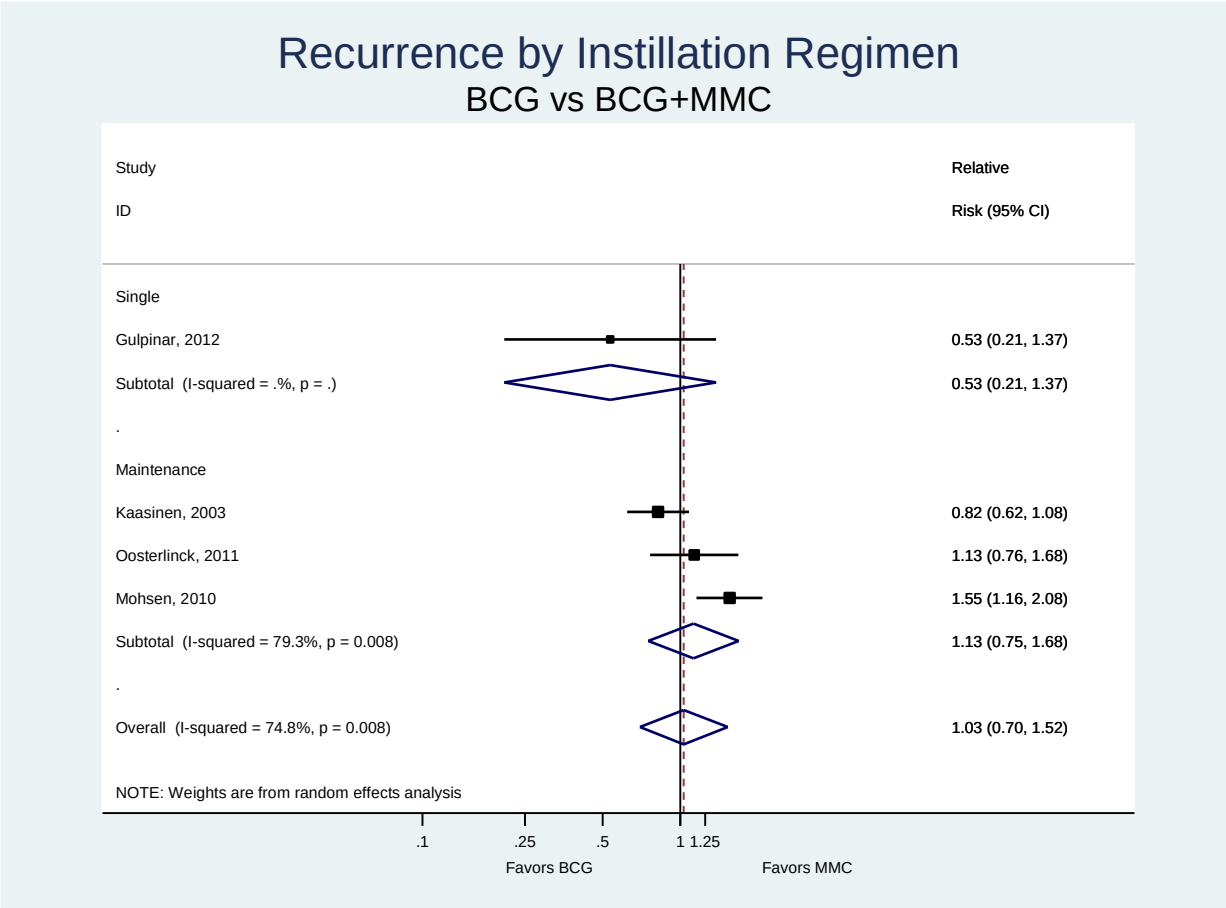


Figure 23. Meta-analysis of bacillus Calmette–Guérin plus MMC versus MMC: Risk of recurrence

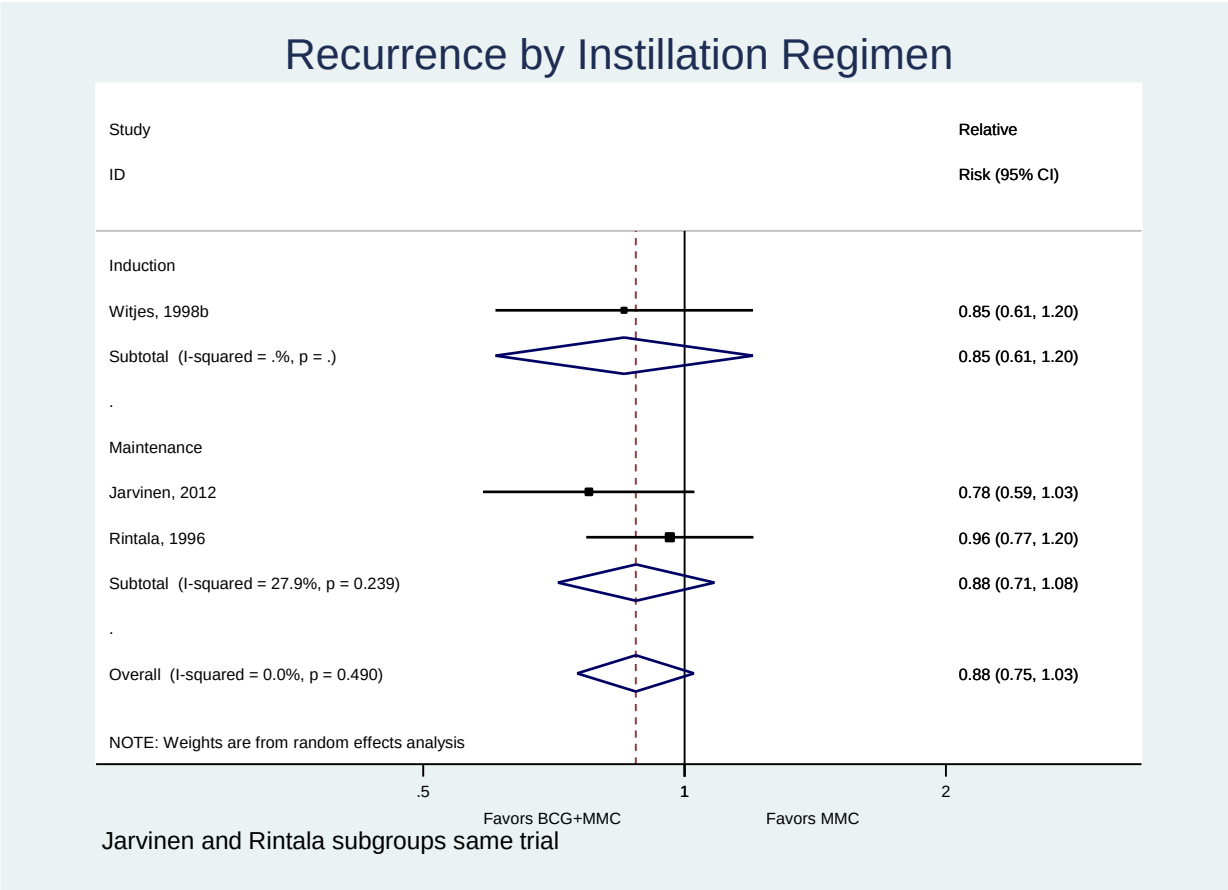


Figure 24. Meta-analysis of bacillus Calmette–Guérin versus epirubicin: all-cause mortality

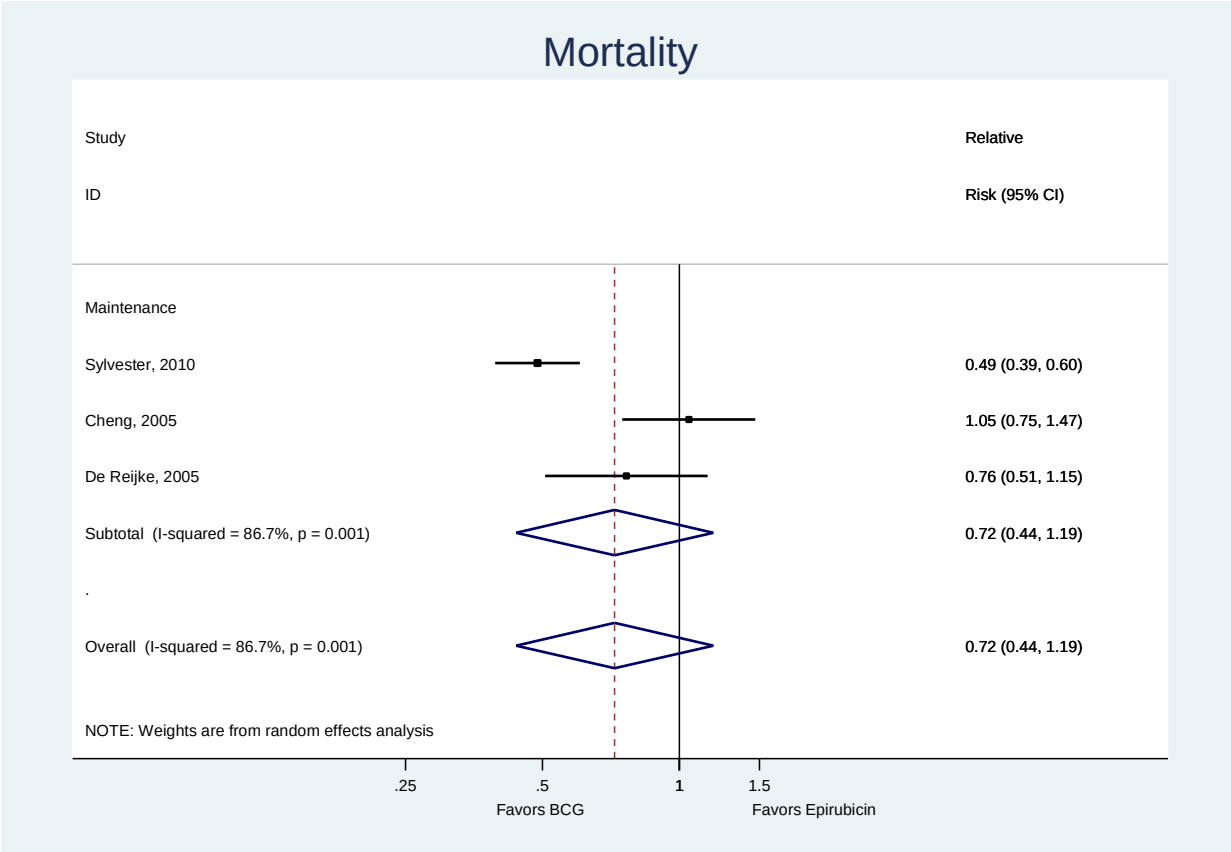


Figure 25. Meta-analysis of bacillus Calmette–Guérin versus epirubicin: bladder cancer mortality

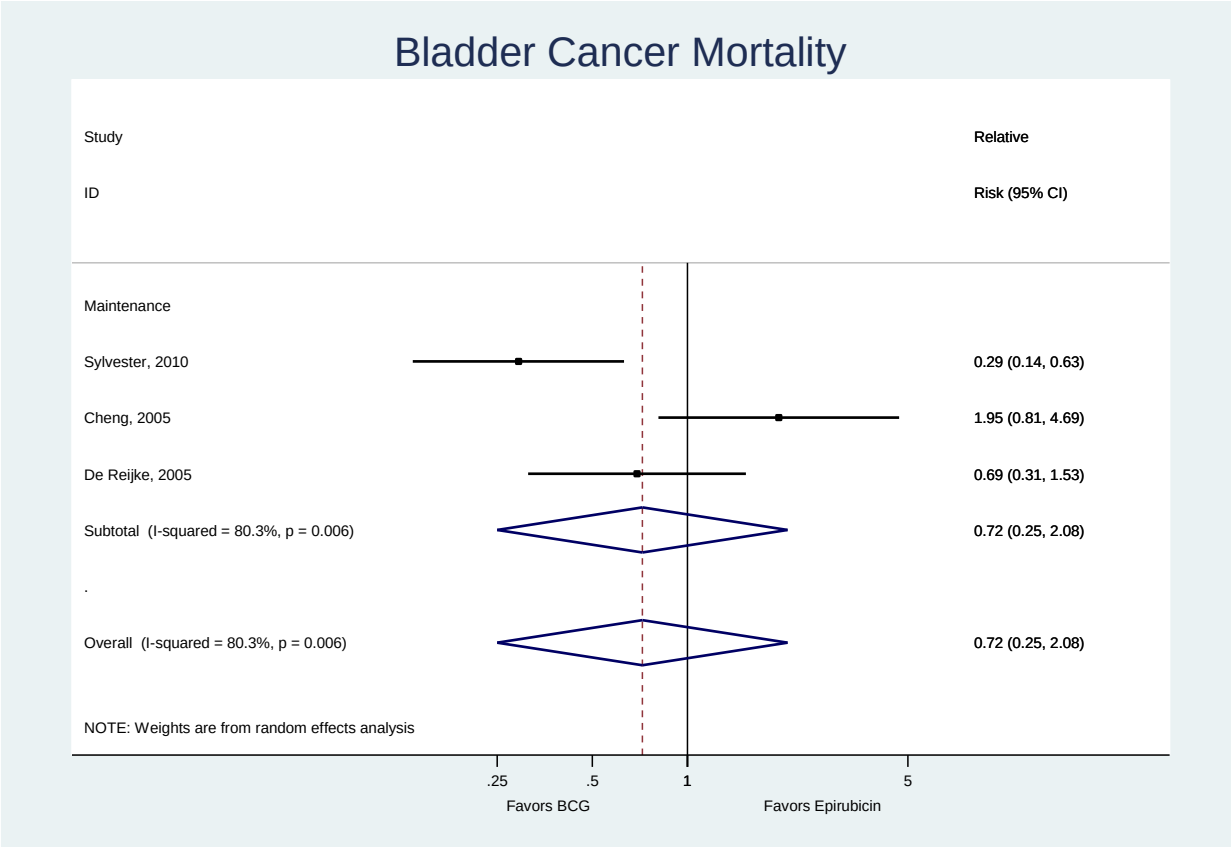


Figure 26. Meta-analysis of bacillus Calmette–Guérin versus epirubicin: Risk of recurrence

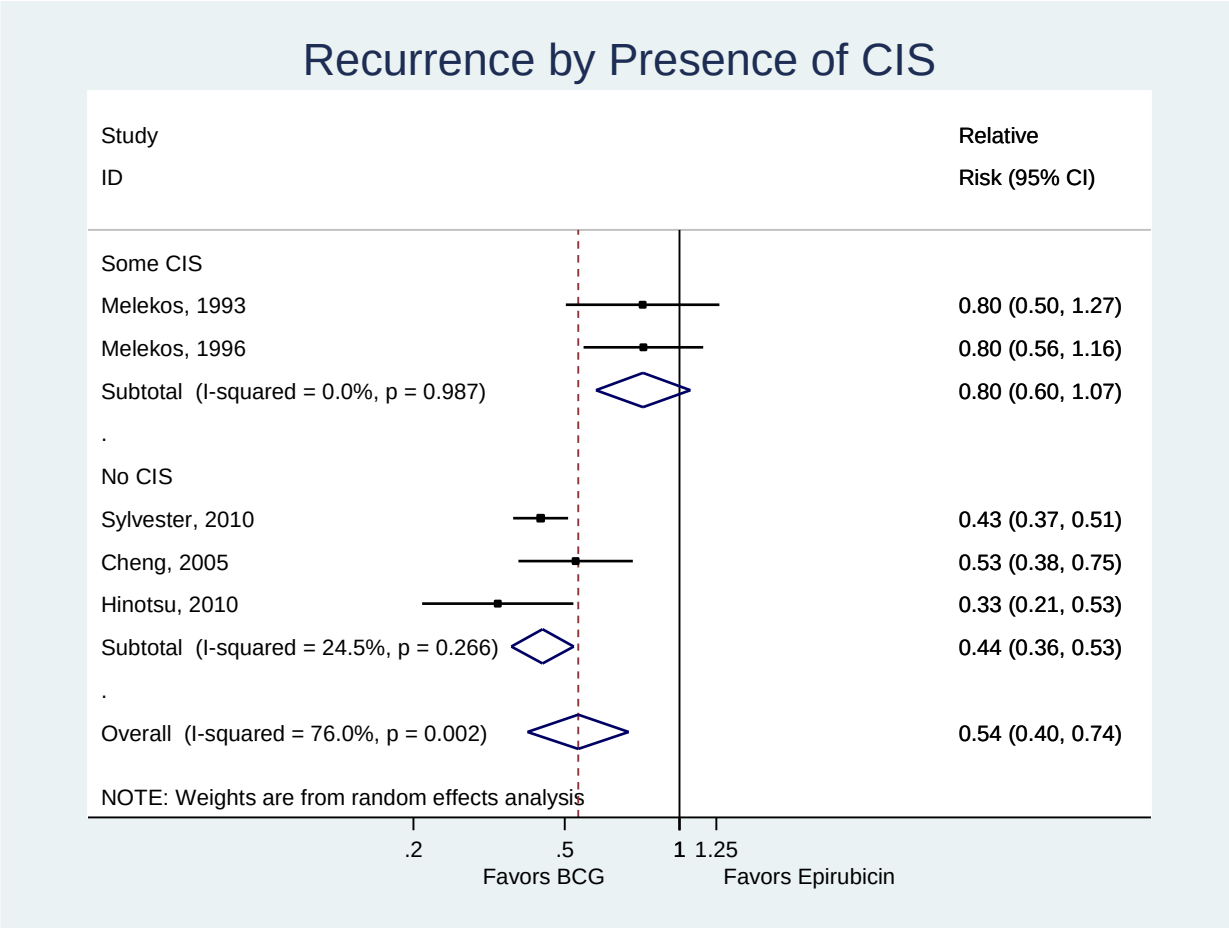


Figure 27. Meta-analysis of bacillus Calmette–Guérin versus epirubicin: Risk of progression

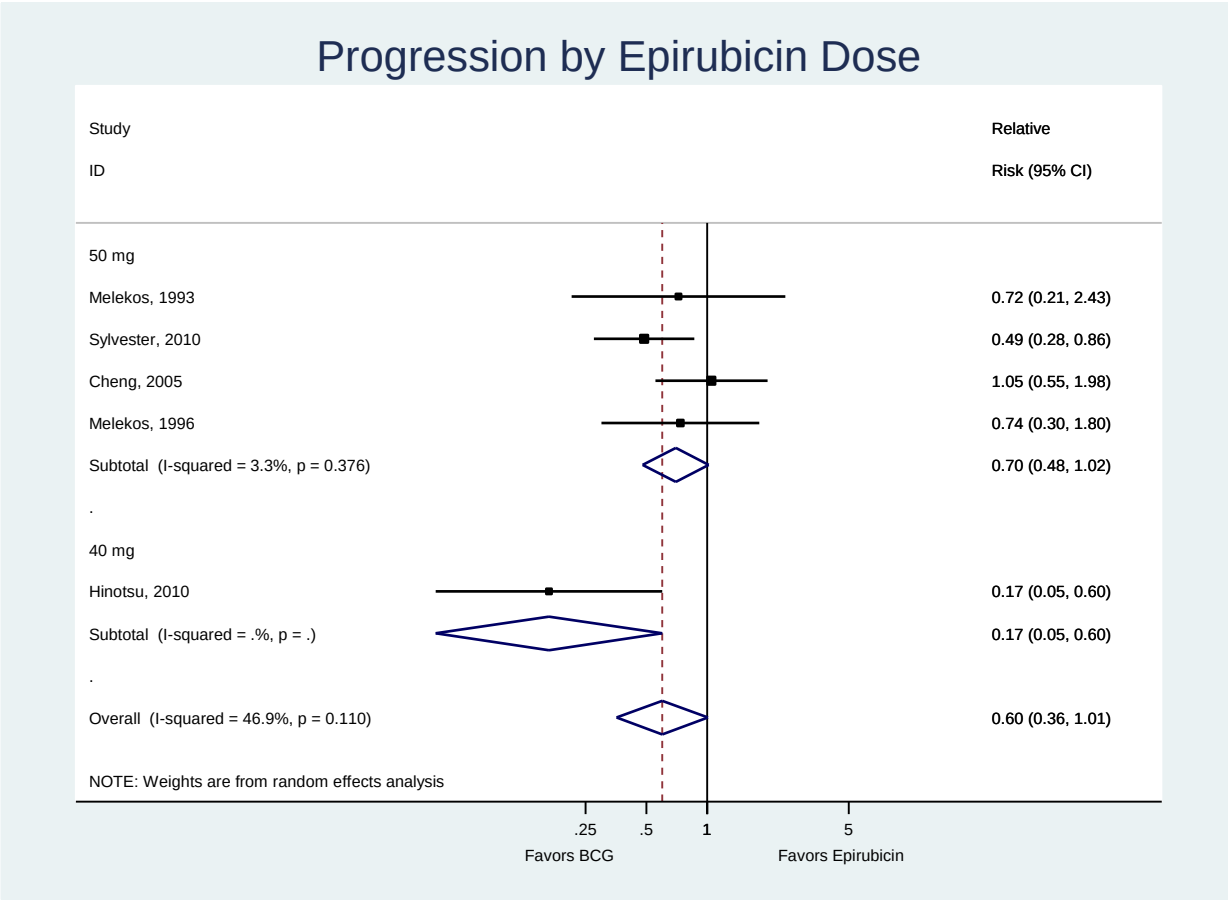


Figure 28. Meta-analysis of bacillus Calmette–Guérin versus bacillus Calmette–Guérin plus epirubicin: Risk of recurrence

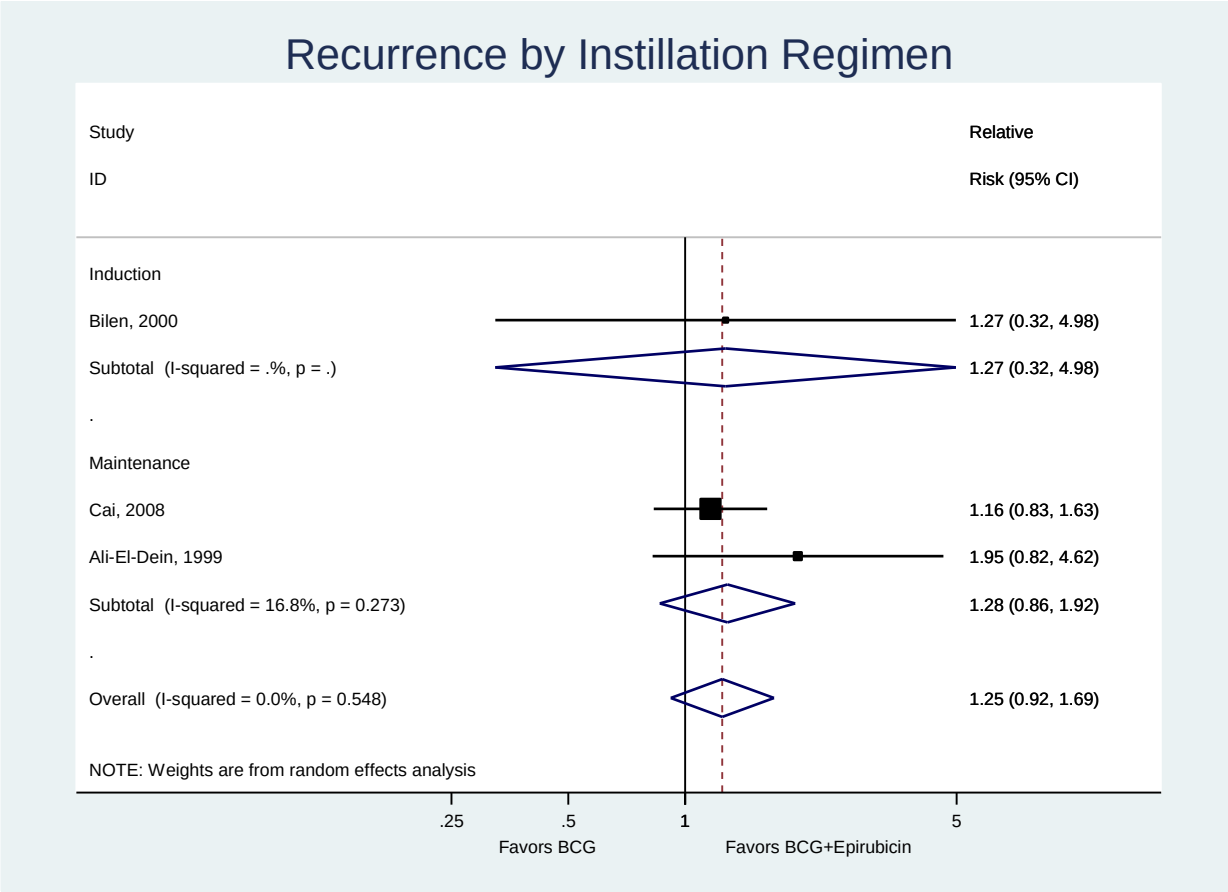


Figure 29. Meta-analysis of bacillus Calmette–Guérin versus bacillus Calmette–Guérin plus epirubicin: Risk of progression

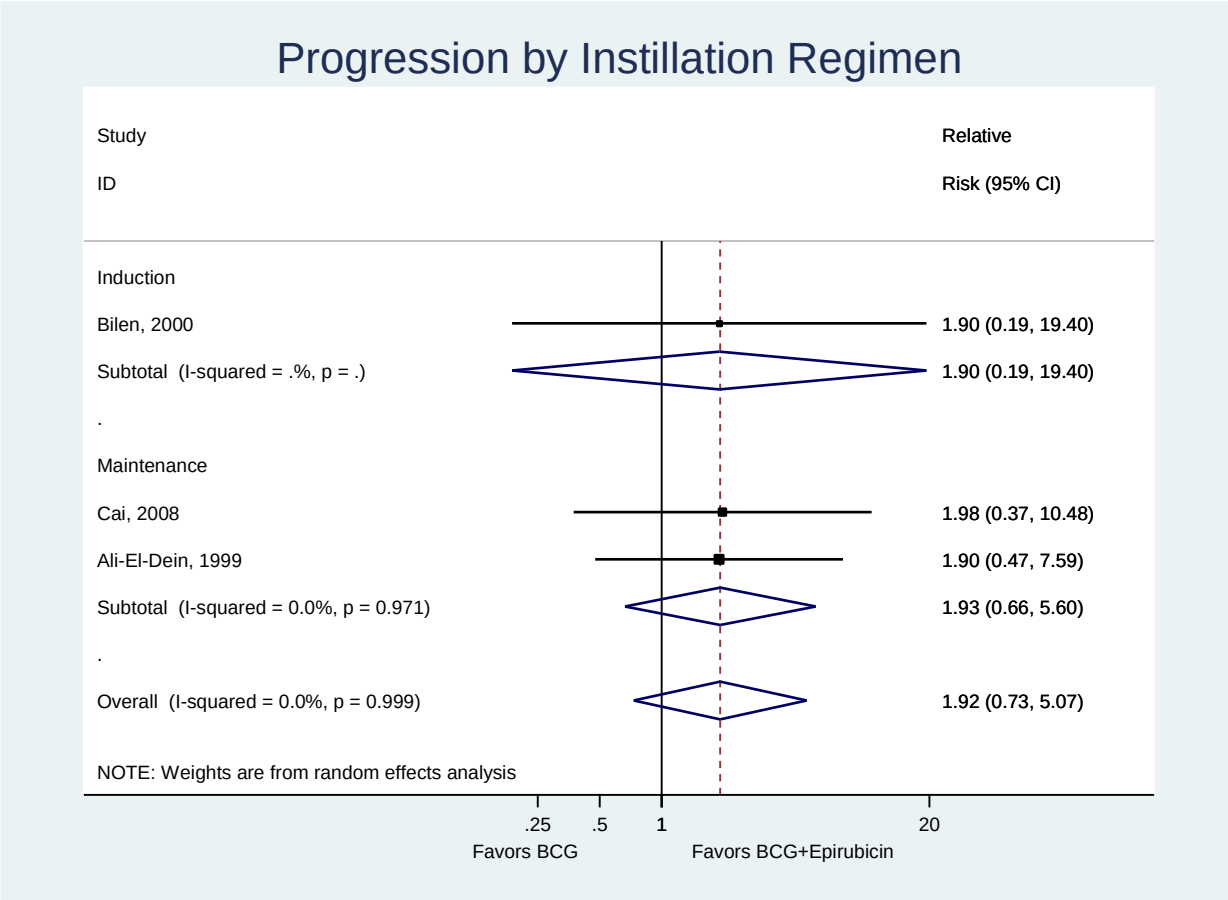
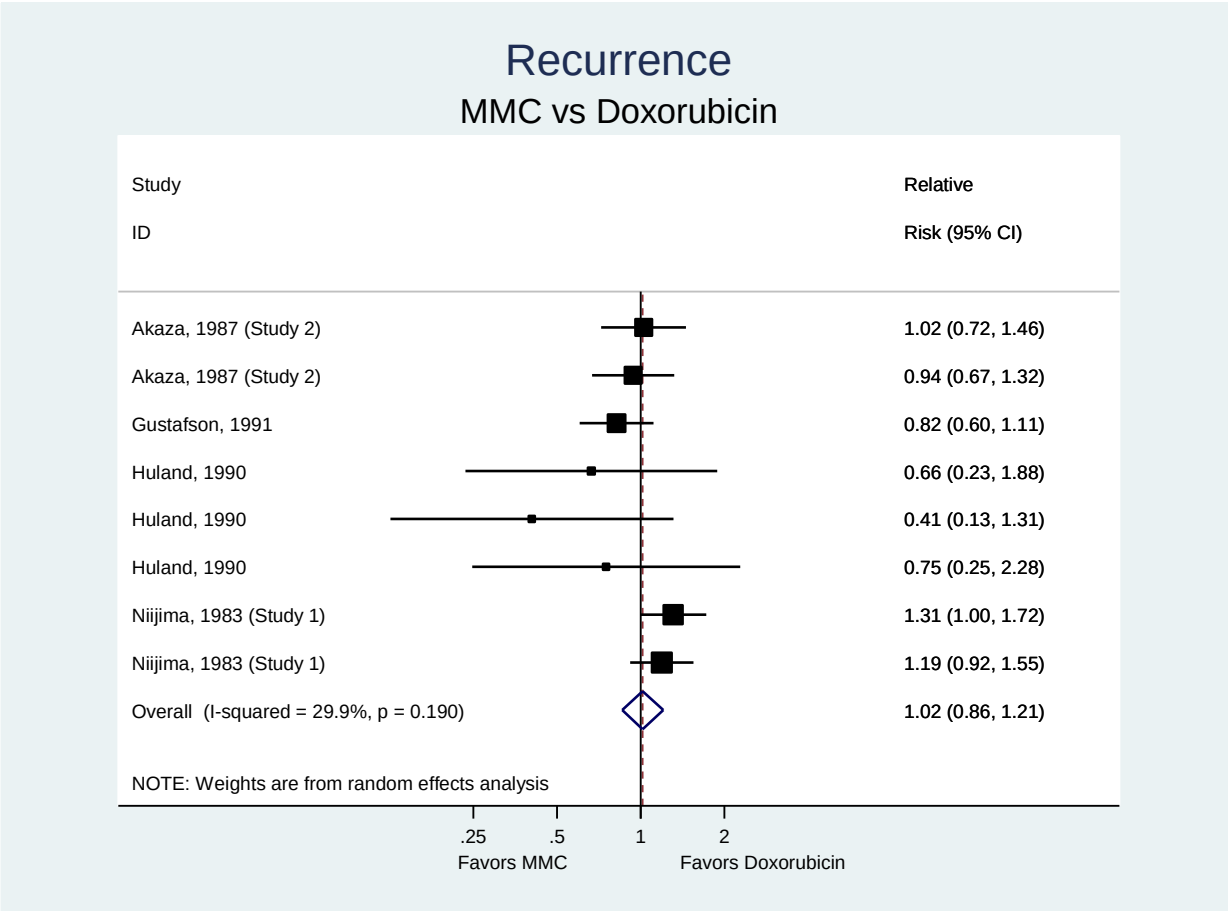


Figure 30. Meta-analysis of MMC versus doxorubicin: Risk of recurrence



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

Tumor Characteristics

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,[83,86,93,100,111,113,114,118,120,123,148,156,167,169-171] presence or absence of CIS,[129,147,148,173] tumor grade,[83,93,100,111,113,114,116,118,120,123,132,148,149,164,167,170,171] tumor multiplicity,[83,100,109,111,113,114,116,120,148,156,164,170,171] tumor size,[156,164,170] primary versus recurrent tumor,[37,83,93,100,103,105,111-114,116,156,167,170,171] or DNA ploidy.[156] 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.

Patient Characteristics

No trial evaluated how estimates of effectiveness of intravesical therapy vary in subgroups defined by patient characteristics such as age, sex, ethnicity, performance status, and co-morbidities.

Key Question 3c. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, 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, ethnicity, performance status, and co-morbidities. (SOE: insufficient)

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 (SOE: low).
- Two trials found more prolonged courses of BCG associated with decreased risk of bladder cancer recurrence versus induction therapy in patients with higher-risk NMIBC (RR 0.54, 95% CI 0.31 to 0.95), but increased risk of adverse events (SOE: low).
- One trial of patients with solitary T1G3 or multiple Ta-T1/G1-G3 tumors found no difference between 1 versus 3 years of BCG maintenance therapy in risk of recurrence, progression, mortality, or adverse events (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 (two 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

- Three 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 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

Forty-one trials in 43 publications of intravesical therapy compared different doses or instillation regimens of the same drug or different BCG strains (Tables 15, 16; Appendixes E4, F2).[93,94,97,99,100,104,107,115,121,123,125,128,131,133,152,167,168,174-199] Eleven trials in 12 publications evaluated comparisons involving BCG,[125,128,133,152,178,181,185,186,189,191,193,196] seven trials evaluated MMC,[99,131,167,174-176,195] five trials in six publications evaluated doxorubicin,[93,94,97,104,177,194,199] 13 trials evaluated epirubicin,[100,107,115,168,179,182,183,187,188,190,192,197,198] two trials in one publication evaluated thiotepa,[121] and three trials evaluated interferon alpha-2b.[123,180,184] 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 U.S. or Europe.[99,121,123,125,128,131,133,167,174,175,177,179,180,184-187,191,193-195,197] Thirty-nine trials were rated medium risk of bias[93,94,97,99,100,104,107,115,121,123,125,128,131,133,152,167,168,174-180,182-188,190-192,194-199] and three trials high risk of bias.[181,189,193] No trial reported blinding of patients or care providers to the treatment regimen received. Only five trials[99,115,152,178,196] reported in adequate detail use of an appropriate randomization method and only one trial[184] 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[181,189] and reporting of only interim results.[193]

BCG

Comparisons of Different Doses

Seven trials compared different doses of intravesical BCG.[128,181,185,186,189,191,193] 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.[128,185,186] 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.[185] 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 RCT (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.[186] 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.[128]

Four trials evaluated dose comparisons involving other BCG strains.[181,189,191,193] 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 (six 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.[181] 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.[191] 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. 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.[189] 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).[193] In addition, only interim results have been published from this trial.

Standard dose BCG therapy was consistently associated with increased risk of local and systemic adverse events versus reduced doses.[181,185,186,189,191] One trial found no differences between 27 (1/3 dose) versus 13.5 mg (1/6 dose) in local or systemic adverse events.[128]

Comparisons of Different Instillation Regimens

Two trials compared induction therapy with BCG for 6 weeks versus more prolonged courses in patients with high-risk (recurrent or multifocal) NMIBC. 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.[152] In the other trial (n=70), a 12-week course of Pasteur strain BCG 120 mg was associated with a trend towards decreased risk of recurrence after 2 years versus a 12-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).[178] In a pooled analysis, the difference in risk bladder cancer recurrence was statistically significant (2 trials, RR 0.54, 95% CI 0.31 to 0.95, I^2=10%).[152,178] One trial[152] found no difference in risk of progression (0% vs. 6.1%, RR 0.15, 95% CI 0.01 to 2.7) and the other trial[178] found no differences in risk of mortality or radical cystectomy, but estimates were imprecise. 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.[152,178] In the trial of 18 months maintenance versus 6 weeks of induction therapy, rates of urinary frequency were 93 vs. 71 percent (RR 1.3, 95% CI 1.1 to 1.6), dysuria 93 vs. 69 percent (RR 1.3, 95% CI 1.1 to 1.7), hematuria 93 vs. 71 percent (RR 1.3, 95% CI 1.1 to 1.6), and fever 43 vs. 26 percent (RR 1.6, 95% CI 0.88 to 3.0).[152] In the trial of 12 versus 6 weeks of BCG, there fewer adverse events and differences were not statistically significant.[178]

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).[191] There were also no differences in risk of progression or mortality. There were no differences in risk of local or systemic adverse events.

Comparisons of Different BCG Strains

Two trials found no clear differences between intravesical therapy using different BCG strains.[125,133,196] One trial found no differences between a 6-week course of BCG-Tice versus BCG RIVM for papillary NMIBC (not selected for being higher risk) in likelihood of remaining recurrence-free after 5 years (36% vs. 54%, log-rank p=0.07) or risk of stage progression (5% vs. 6%).[125,133] There were also no differences when analyses were restricted to patients with G3 tumors or CIS. One trial of higher-risk NMIBC (multiple tumors and recurrence-free interval <3 months) found no difference between an 8-week course of Tokyo versus Connaught strain BCG in likelihood of remaining recurrence-free (62% vs. 56%) at 5 years.[196] Findings were similar in patients with or without CIS. Both trials found no differences in risk of local or systemic adverse events.

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).[99] 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).[131] 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 one 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).[195] 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%).[167]

"Optimized" Versus Nonoptimized Administration

Two trials compared "optimized" administration of intravesical MMC (through alkalinization of urine) versus instillation without additional optimization.[174,176] One of the trials also optimized MMC administration by restricting fluids and emptying the bladder prior to instillation.[174] 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.[176] 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.[93,97] 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.[93,94] 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 versus 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.[177] 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%).[194]

Two trials of doxorubicin involved comparisons regarding timing of therapy.[104] 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.[104] 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.[199] 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 (Table xx).[100,115,187] 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.[107] Lower-dose therapy was associated with a higher recurrence rate (0.83 vs. 0.60 per 100 patient-months, p<0.05). Two other trial evaluated patients with NMIBC not selected for being at higher risk.[115,187] One trial (n=54) found no differences between epirubicin 50 vs. 100 mg (administered as five 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.[187] The other trial (n=163) found no differences between epirubicin 20 mg vs. 50 mg

(administered as two 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.[115] 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);[187] 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 versus multiple instillations.[100,168,198] 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.[198] 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.[168] 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.[100] 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.[192,197] 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 (six 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%).[197] One trial (n=138) of patients with papillary NMIBC found no difference between epirubicin 40 mg induction therapy (six 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%).[192] Both trials found no differences in risk of local adverse events.

Five trials compared different epirubicin regimens that included maintenance therapy.[179,182,183,188,190] 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.[179] 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.[182] 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).[190] 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).[183] 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 three instillations within the first 5-7 days after TURBT).[188] 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.

Thiotepa

Comparisons of Different Doses

Two trials (reported in the same publication) compared different doses of thiotepa.[121] 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 versus 60 mg (once every 4 weeks for up to 2 years) in likelihood of being recurrence-free at 12 months (63% vs. 69%).[121] 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).[121] 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

Three trials compared different doses of intravesical interferon alpha-2b.[123,180,184] One trial compared 100 MU versus 10 MU (once weekly for 10 weeks, then once monthly for a total of 1 year),[180] one trial compared 80, 50, and 40 MU (weekly for 12 weeks),[184] 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).[123] 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=24, 81, 89) with imprecise estimates. The only statistically significant difference was in recurrence rate in the trial that compared 80, 60, and 40 MU (1.19 vs. 0.88 vs. 0.63 per 100 patient-months, respectively).[123] There were no clear differences in risk of local or systemic adverse events.[123,180,184]

Multiple Drugs

One trial found no difference between initiation of intravesical therapy (nine 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).[175] 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.

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).[200] 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).[201]

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 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 (three trials, RR 1.27, 95% CI 0.56 to 2.87, 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, eight trials, RR 0.56, 95% CI 0.34 to 0.94, I^2=72%), intermediate-term (3 months to <1 year, four trials, RR 0.71, 95% CI 0.53 to 0.95, I^2=26%), and long-term followup (≥1 year, 11 trials, RR 0.80, 95% CI 0.67 to 0.94, I^2=58%), 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 (six trials, RR 0.83, 95% CI 0.53 to 1.28, 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 17; Appendix E6).[202-220] Thirteen trials evaluated fluorescent cystoscopy following instillation of 5-ALA (six studies)[202,207,213,217,218,220] or HAL (seven studies).[206,208,209,211,212,216,219] One trial evaluated narrow band imaging.[215] 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 U.S., Canada, and Europe;[210,219] the remainder were conducted in Europe. One trial restricted enrolment to patients with new bladder cancer;[216] 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;[217] 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,[215] four trials reported adequate allocation concealment,[208,209,216,218] four trials reported followup cystoscopic examinations blinded to initial cystoscopy method,[208,209,218,220] and one trial reported initial cystoscopic examination blinded to instillation of fluorescent photosensitizer versus placebo.[220] Four trials reported high attrition[213,218-220] 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, eight trials, RR 0.56, 95% CI 0.34 to 0.94, I^2=72%, Figure 31),[202,206,208,209,212,213,216,220] intermediate-term (3 months to <1 year, four trials, RR 0.71, 95% CI 0.53 to 0.95, I^2=26%, Figure 32),[206,209,211,219] and long-term followup (≥1 year, 11 trials, RR 0.80, 95% CI 0.67 to 0.94, I^2=58%, Figure 33) (Table 18).[202,206,207,209,211,212,216-220] 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) (nine trials, RR 0.78, 95% CI 0.62 to 0.97, I^2=64%).[202,206,209,211,212,216,218-220] 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).[220] 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).[216] 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.[202,206-208,217]

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.[221] 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 (six trials, RR 0.83, 95% CI 0.53 to 1.28, I^2=0%, Figure 34).[202,207,209,217-219] 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.[217]

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 1.27, 95% CI 0.56 to 2.87, I^2=41%, Figure 35).[216,218,219] 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[217] 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).[215] It did not report effects of narrow band imaging on risk of bladder cancer progression or mortality.

Figure 31. **Meta-analysis of fluorescent cystoscopy versus white light cystoscopy: Risk of bladder cancer recurrence at short-term (<3 months)**

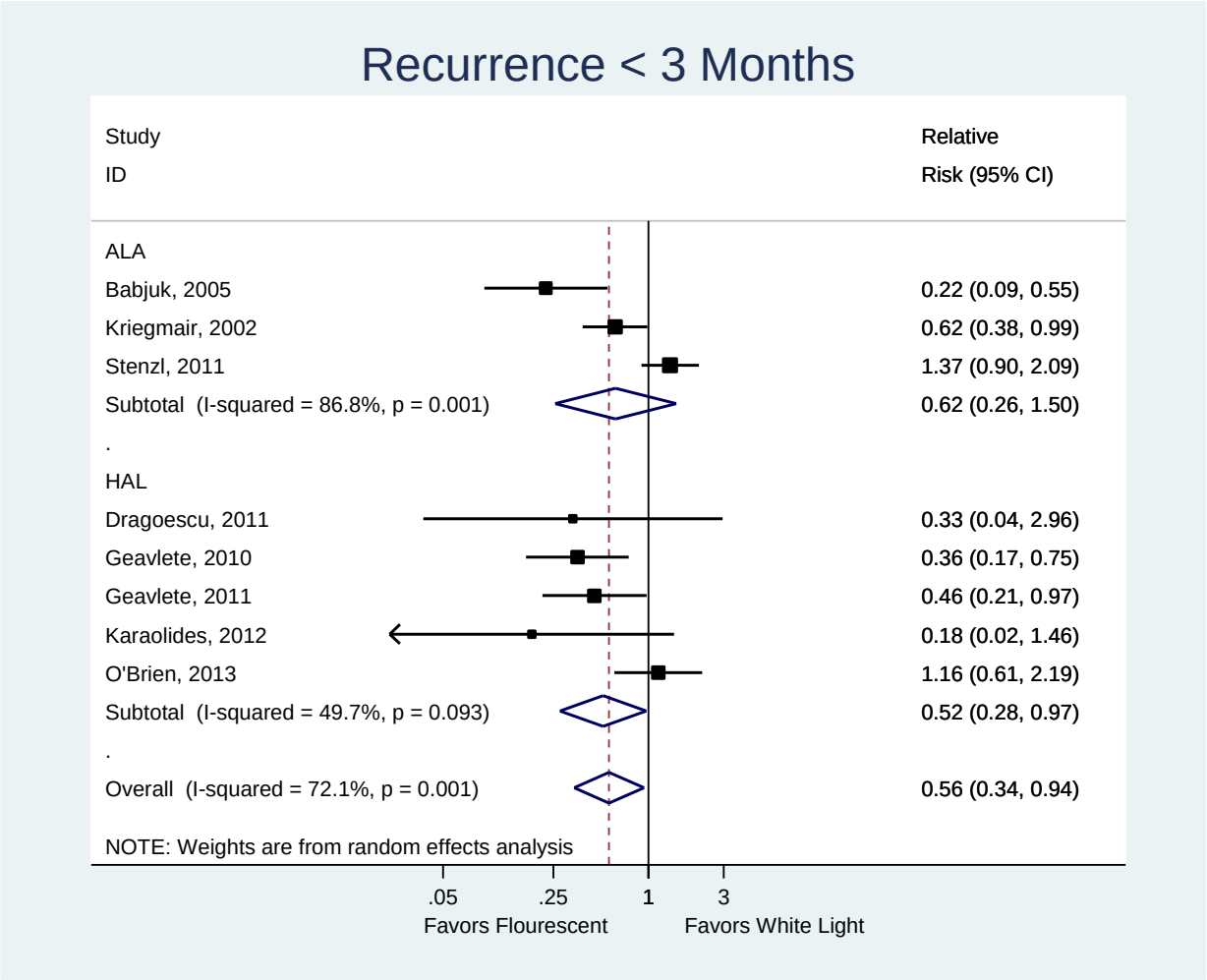


Figure 32. Meta-analysis of fluorescent cystoscopy versus white light cystoscopy: Risk of bladder cancer recurrence at intermediate term (3 months to <1 year)

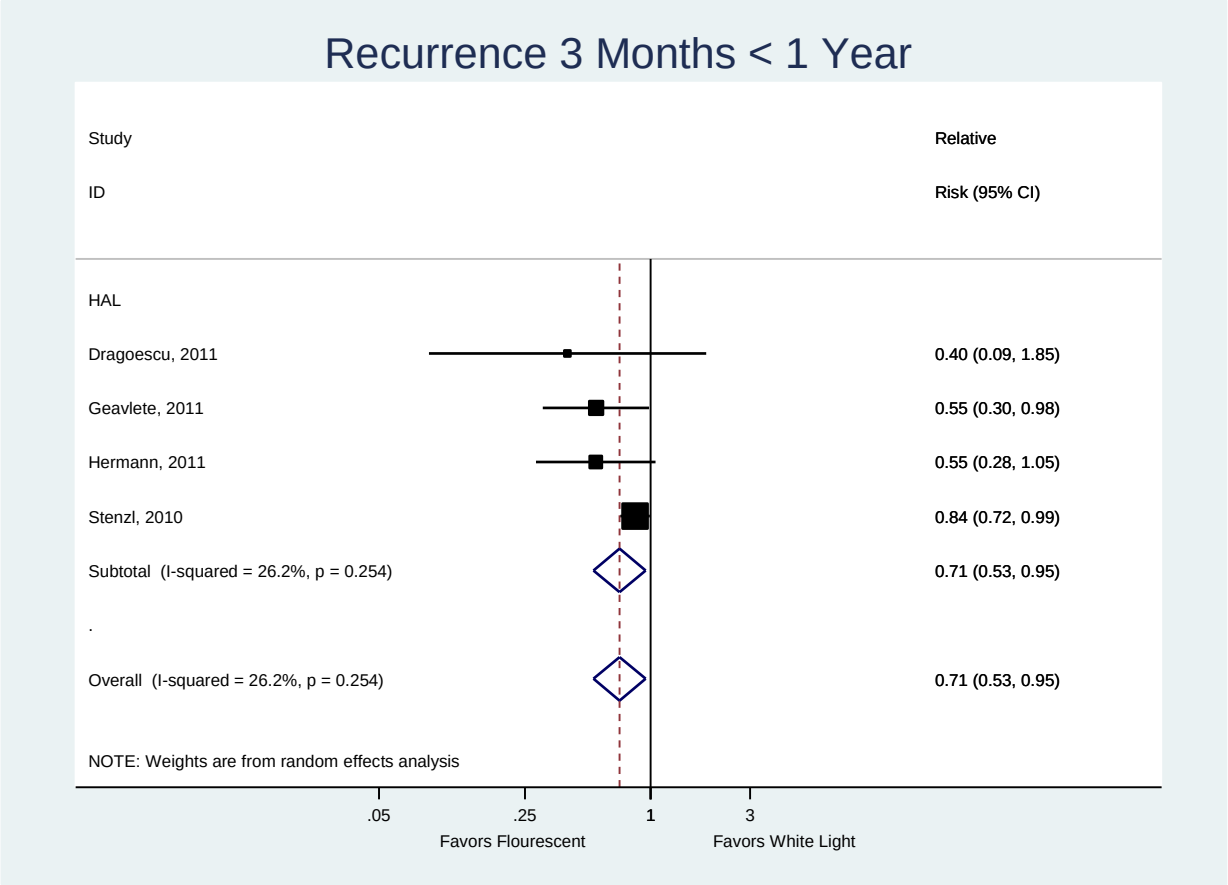


Figure 33. Meta-analysis of fluorescent cystoscopy versus white light cystoscopy: Risk of bladder cancer recurrence at long term (≥1 year)

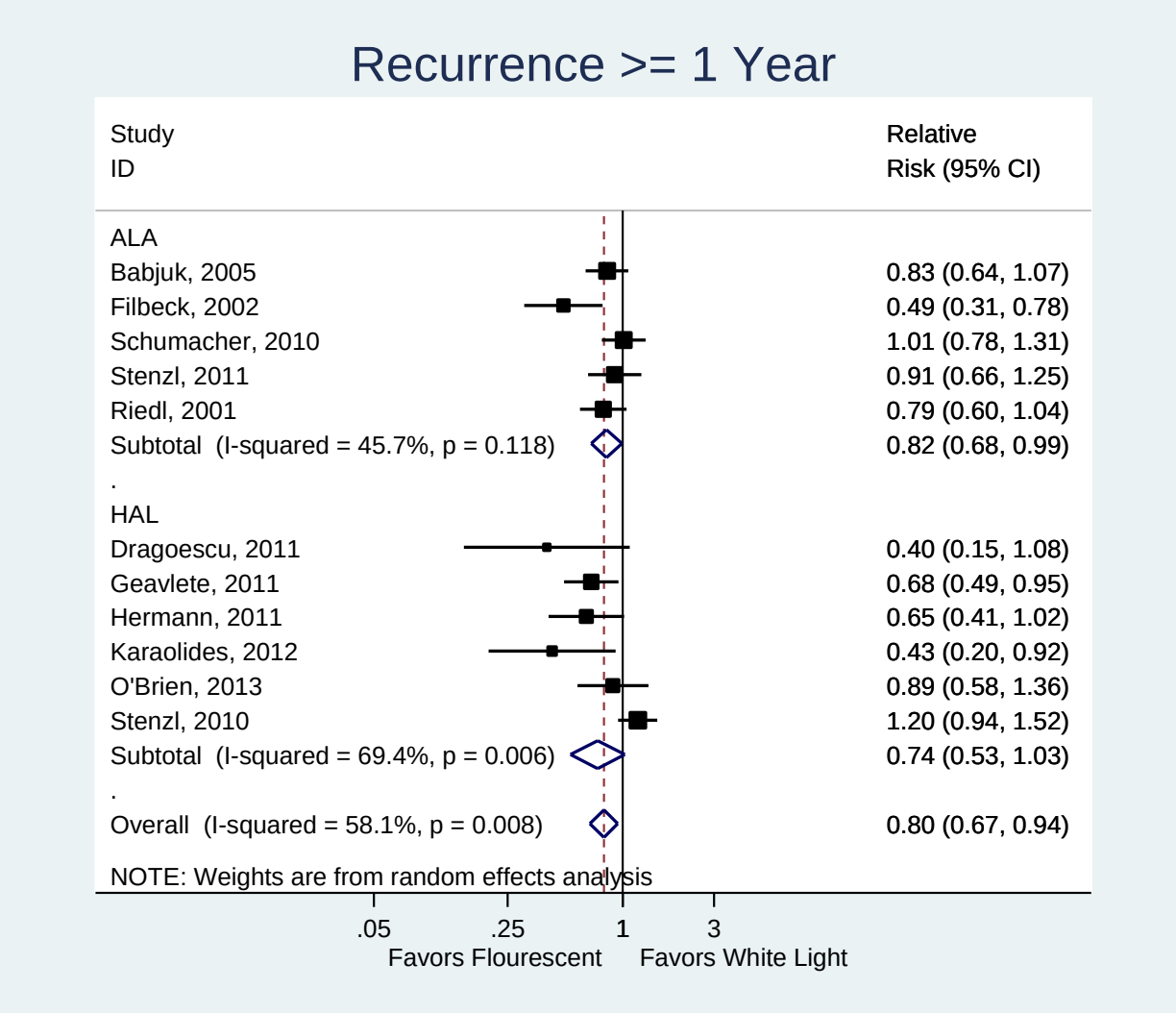


Figure 34. Meta-analysis of fluorescent cystoscopy versus white light cystoscopy: Risk of progression to muscle invasive bladder cancer

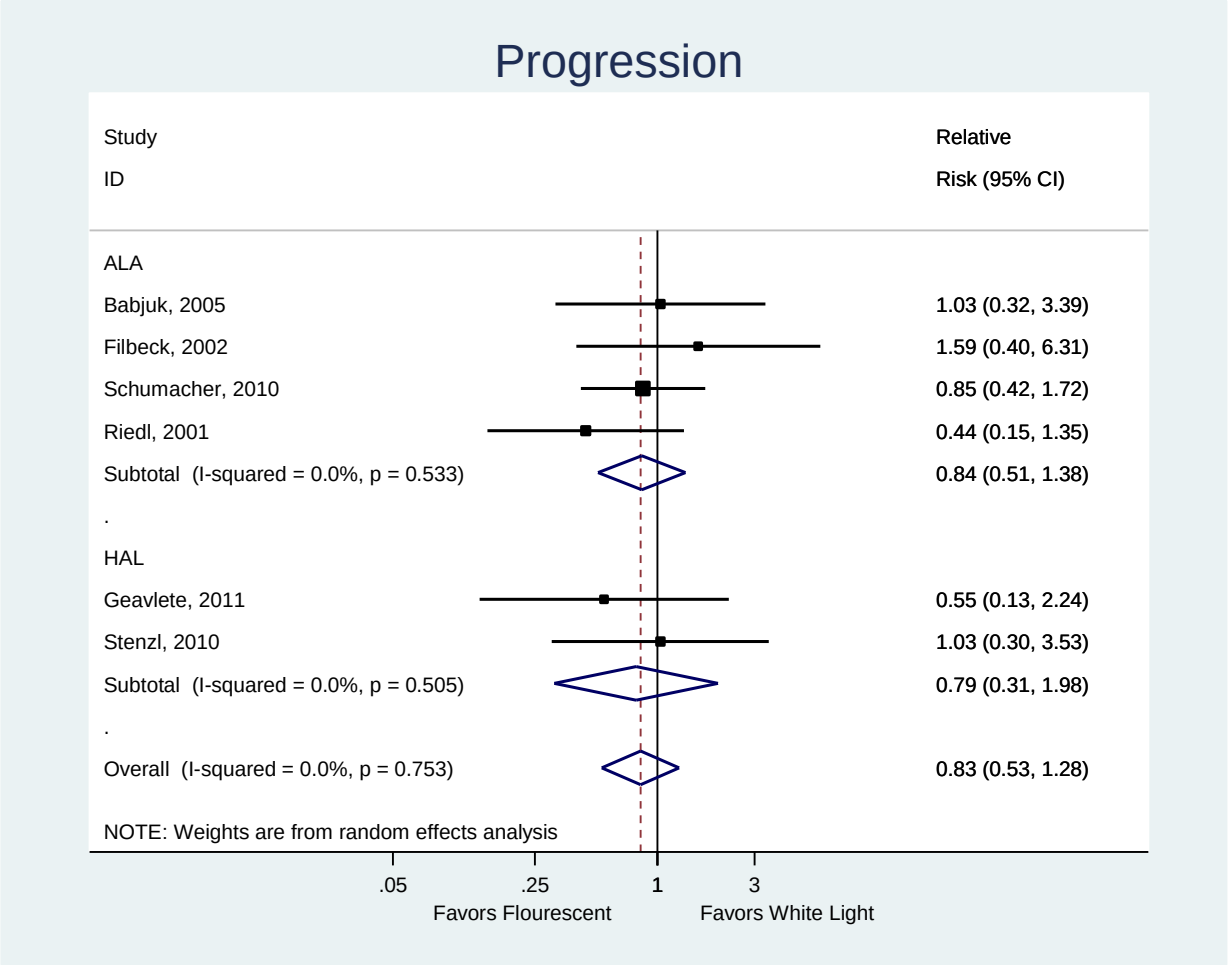
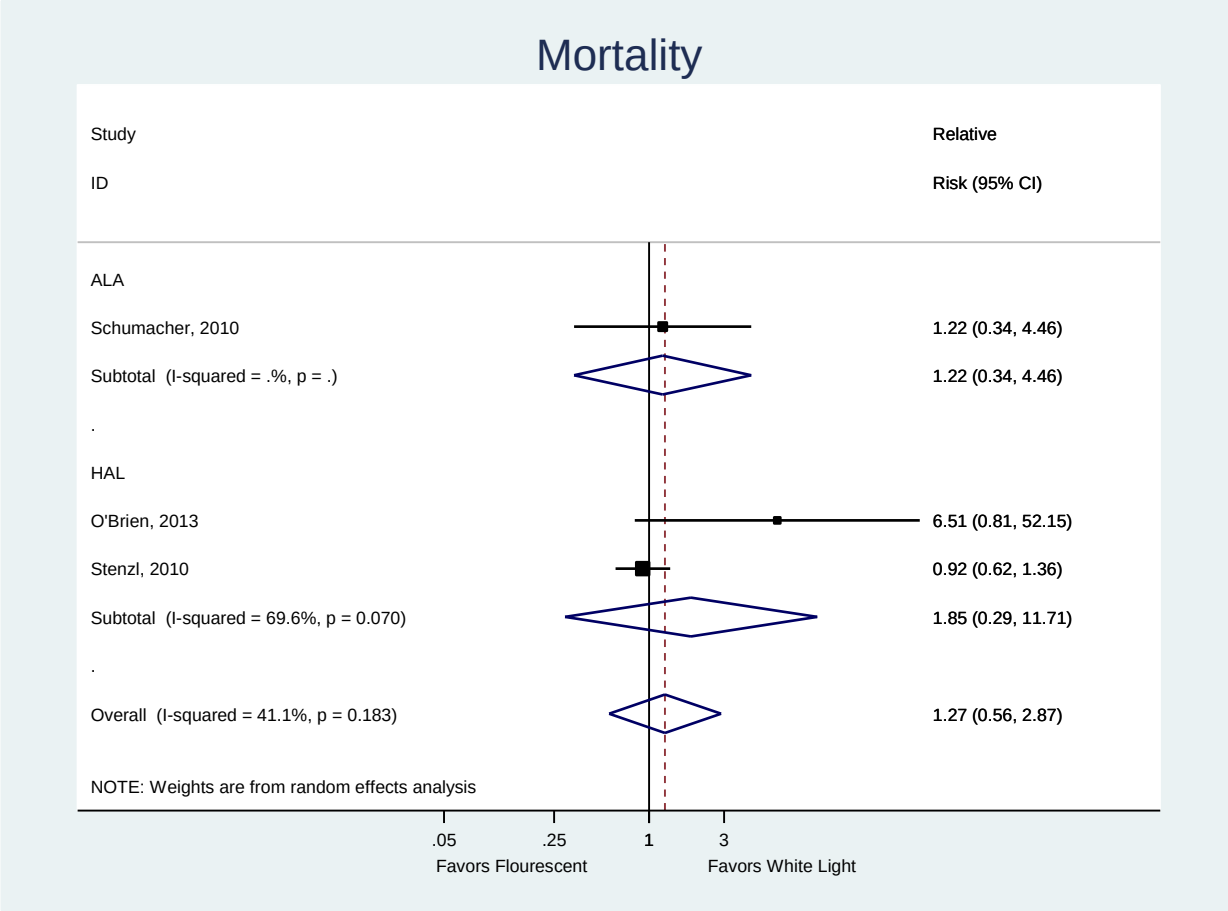


Figure 35. Meta-analysis of fluorescent cystoscopy versus white light cystoscopy: Risk of mortality



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.[209,216] 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).[211,219] There were also no clear differences between fluorescent cystoscopy versus white light cystoscopy in risk of renal and genitourinary adverse events[218,219] or serious adverse events.[219,220] One trial found no difference between narrow band imaging versus white light cystoscopy in risk of false-positives.[215]

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 chemical 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 (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%), chemical 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 chemical 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 chemical cystitis (1 trial, RR 1.30, 95% CI 0.88 to 1.93) (SOE: low for local adverse events and chemical 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), chemical 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; chemical 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), chemical 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, chemical 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 four 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 IFN-alpha in risk of dysuria or fever (SOE: low).

Detailed Synthesis

Thirty-two trials of BCG versus other intravesical therapies reported harms. Ten trials (reported in 16 publications) evaluated BCG versus MMC,[92,124-137,173] four trials BCG versus BCG plus MMC given sequentially,[138-141] two trials (reported in four publications) BCG plus MMC given sequentially versus MMC,[142-145] four trials (reported in five publications) BCG versus epirubicin,[83,149,151,153,154] two trials BCG versus BCG plus epirubicin given sequentially,[156,157] three trials BCG versus gemcitabine[160-162] one trial BCG versus BCG plus gemcitabine administered sequentially,[163] one trial BCG versus interferon alpha-2a[164] one trial BCG versus BCG plus interferon alpha-2b given sequentially,[165] one trial BCG versus co-administration of BCG and interferon alpha-2b,[166] three trials BCG versus doxorubicin,[146-148] one trial BCG versus thiotepa,[148] and one trial BCG versus epirubicin plus interferon.[158]

Four trials of BCG versus no intravesical therapy reported harms, but only in patients who received intravesical therapy.[81,84,89,90]

Intravesical Drugs Versus No Intravesical Therapy

Eight trials evaluated harms of intravesical therapy versus no intravesical therapy.[98,112,114,116,118,119,121,123] One trial evaluated MMC,[98] two trials epirubicin,[112,114] two trials interferon-alpha,[118,123] one trial interferon-gamma,[119] one trial thiotepa,[121] and one trial gemcitabine.[116] 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. Chemical cystitis or irritative vesical symptoms were reported in 27%[90] to 84%[84] of patients, macroscopic hematuria in 21%[84] to 72%,[81] and fever from 27%[84] to 44%.[89]

MMC

One trial (n=121) found no difference between a single installation of MMC 40 mg versus TURBT alone in risk of chemical cystitis [3.5% (2/57) vs. 1.6% (1/64)].[98]

Doxorubicin

No study evaluated harms of doxorubicin versus no intravesical therapy.

Epirubicin

One trial found single instillation epirubicin 80 mg (up to four repeat installations 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).[112] A second trial of single installation 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].[114]

Gemcitabine

One trial (n=328) found no difference between a single installation 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)].[116]

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) .[118] 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.[123]

Interferon-gamma

One trial (n=54) of induction therapy with IFN-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.[119]

Thiotepa

One trial (n =93) evaluated a maintenance regimen with thiotepa 60 or 30 mg versus no intravesical therapy.[121] Urinary tract symptoms were reported in 17% (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).[Koontz, 1981 #3951]

Intravesical Drugs Versus Intravesical Drugs

Thirteen trials evaluated harms of one drug administered for intravesical therapy versus another. Three trials evaluated MMC vs. doxorubicin,[93,96,97,167] 1 trial MMC vs. epirubicin,[168] 2 trials MMC vs. interferon-alpha,[169,184] 1 trial MMC vs. gemcitabine,[170] 3 trials doxorubicin vs. epirubicin,[100,171,172] 1 trial doxorubicin vs. thiotepa,[148] and 1 trial epirubicin vs. interferon-alpha.[114] 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%).[128,133] Regarding specific local adverse events, BCG was also associated with increased risk of chemical cystitis (5 trials, 31% vs. 19%, RR 1.71, 95% CI 1.22 to 2.41, I^2=58%),[92,130,132,133,136]

dysuria (3 trials, 48% vs. 32%, RR 1.23, 95% CI 1.03 to 1.46, I^2=34%),[124,129,131] and hematuria (36% vs 18%, 6 trials, RR 1.78, 95% CI 1.24 to 2.56, I^2=62%).[92,124,129-131];[132] Estimates were similar using the profile likelihood method. For chemical cystitis, excluding one trial[136] 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%)[128,133,136] and fever (4 trials, 18% vs 3%, RR 4.51, 95% CI 2.31 to 8.82,I^2=25%).[124,129,130,132]

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.[126,129,130,136] 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)[130] 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%).[126,129,136]

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)[139]

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 chemical cystitis (RR 1.30, 95% CI 0.88 to 1.93).[142] 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)[145] or in patients with Ta or T1 tumors (RR 0.93, 95% CI 0.52 to 1.65).[144]

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).[148] Findings for dysuria were mixed, with one trial finding decreased risk with BCG (RR 0.49, 95% CI 0.30 to 0.82),[146] one trial increased risk with BCG (RR 3.16, 95% CI 1.50 to 6.67),[148] and one trial no difference (RR 1.24, 95% CI 0.99 to 1.56).[147] The three trials differed in the dose of BCG (80 mg-150 mg) and doxorubicin administered (20mg-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),[146] but a second trial found no difference (RR 1.36, 95% CI 0.95 to 1.95).[147] One trial found BCG associated with increased risk of fever versus doxorubicin (RR 5.03, 95% CI 2.75 to 9.19),[147] but a second trial found no difference (RR 0.82, 95% CI 0.64 to 1.05).[146]

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).[153] BCG was also associated with increased risk of chemical cystitis (4 trials, 48% vs. 28%, RR 1.86, 95% CI 1.35 to 2.56, I^2=65%),[83,151,153,154] dysuria (1 trial, 24% vs 10%, RR 2.43, 95% CI 1.13 to 5.24),[153] and hematuria (4 trials, 33% vs. 19%, RR 1.77, 95% CI 1.41 to 2.22, I^2=0%)[83,151,153,154] For chemical 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%)[83,153] 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),[153] though another trial found no difference (RR 0.95, 95% CI 0.85 to 1.05).[154]

BCG was associated with increased risk of chemical cystitis versus sequentially administered BCG plus epirubicin (1 trial, 62% vs 27%, RR 2.28, 95% CI 1.46 to 3.54),[156] but there was no difference in risk of dysuria (1 trial, RR 1.22, 95% CI 0.56 to 2.66).[157] or hematuria (2 trials, RR 2.27, 95% CI 0.86 to 6.00, I^2=0%)[156,157]

BCG was associated with increased risk of any systemic adverse event versus alternating BCG plus epirubicin (1 trial,36% vs 6%, 1 trial, RR 5.97, 95% CI 2.18 to 16),[156] but there was no difference in risk of fever (2 trials, RR 2.09, 95% CI 0.48 to 9.02, I^2=0%).[156,157] 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)[156]

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).[158] 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).[161] 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%).[160,162] No trial reported risk of chemical 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).[161] 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%).[160,162]

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).[163] No cases of fever were reported.[163]

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).[164]

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.[166]

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.[148] No patient randomized to thiotepa reported cystitis or fever, resulting in very wide confidence intervals.

MMC Versus Doxorubicin

Four trials reported inconsistent effects of MMC versus doxorubicin administered as induction or maintenance therapy in risk of dysuria or chemical cystitis.[93,96,97,167] 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[97] and 21% vs. 48%, RR 0.31, 95% CI 0.23 to 0.42.)[167] Three trials found no statistically significant differences in risk of dysuria or urinary frequency,[93,96,97] and two trials found no difference in risk of hematuria.[93,97] 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 installation or maintenance therapy with epirubicin 80 mg in risk of urinary symptoms [13% (2/15) vs. 7% (1/14) vs. 13% (2/15), respectively)].[168]

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].[169] 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).[184] 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].[170] 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% 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].[100] Three patients (5.0%) 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[171] There was also no difference in risk of hematuria [three trials, RR 1.53, 95% CI 0.50 to 4.66; $I^2 = 0.0$].[100,171,172]

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].[148] Other harms were not reported

Epirubicin Versus Interferon-alpha

One trial (n=134) found no difference between a single installation of epirubicin versus IFN-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)].[114] Other harms were not reported.

Key Question 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?

Key Points

- No study evaluated how harms of treatment vary in subgroups defined by patient characteristics such as age, sex, 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
Chahal, 2001[30] United Kingdom	NMP22 (quantitative)	Prospective	Mixed	Age: Not reported Sex: Not reported Race: 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 (16%) 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: 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
Giannopoulos, 2001[33] Greece	NMP22 (quantitative, Bladderchek) BTA stat	Unclear	Mixed	Mean age: 66 years Male: 85% Race: 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: 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

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
Grossman, 2005[35] United States (also Lotan 2009[47])	NMP22 (qualitative, BladderChek)	Prospective	Evaluation of symptoms	Mean age: 59 yearsMale: 57%Race: 82% White, non-Hispanic; 9% Smoker: Not reportedSigns 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: 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
Gudjonsson, 2008[37] Sweden	FISH (UroVysion)	Prospective	Surveillance	Mean age: Not reported Sex: Not reported Race: 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: 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: 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

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: 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
Ianari, 1997[41] Italy	BTA stat	Prospective	Surveillance	Median age: 66 years Male: 83% Race: 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: 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
Karnwal, 2010[43] United States	FISH (UroVysion)	Retrospective	Surveillance	Mean age: 56 years Male: 68% Race: 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

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, 1997a[44] Germany, UK, and France	BTA stat	Prospective	Mixed	Mean age: 60 yearsMale: 64%Race: Not reportedSmoker: Not reportedSigns 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 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
Leyh, 1997b[45] Germany and France	BTA stat	Prospective	Surveillance	Mean age: 67 years Male: 77% Race: 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
Lodde, 2003[46] Italy	uCyt+ (Immunocyt)	Prospective	Mixed	Mean age: Not reported Sex: Not reported Race: 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
Messing, 2005[48] United States	ImmunoCyt	Unclear	Surveillance	Age: Not reported Sex: Not reported Race: 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

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
Mian, 1999[50] Italy	ImmunoCyt	Prospective	Mixed	Mean age: 66 yearsMale: 77%Race: 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: 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: 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
O'Sullivan, 2012[52] New Zealand	CxBladder NMP22 (qualitative, Bladderchek) NMP22 (quantitative)	Prospective	Evaluation of symptoms	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	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: Not reported Smoker: Not reported Signs or symptoms: 100% gross or microscopic hematuria	32/90 (36%) Tumor stage: Not reported Tumor grade: Not reported
Pfister, 2003[54] France	ImmunoCyt	Prospective	Mixed	Mean age: 66 years Male: 79% Race: 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

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: 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: 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: Not reported Smoker: Not reported Signs or symptoms: 143 gross 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
Quek, 2002[58] Singapore	BTA stat	Prospective	Mixed	Mean age: 54 years 68% male Race: Not reported Smoker: Not reported Signs or symptoms: 60 gross 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

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
Raitanen, 2001[59] Finland	BTA stat	Prospective	Surveillance	Mean age: 69 years79% male Race: 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: 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: 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
Sarosdy, 2002[62] United States	FISH (UroVysion) BTA stat	Prospective	Surveillance	Mean age: 71 years 75% male Nonwhite race: 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: 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

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: 0% Smoker: Not reported 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: 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
Serretta, 1998[65] Italy	NMP22 (quantitative)	Unclear	Surveillance	Mean age: 65 years Male: 89% Race: 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
Shariat, 2006[66] United States, Europe, Japan, Canada	NMP22 (quantitative)	Prospective	Surveillance	Median age: 68 years Male: 76% Race: 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: Not reported Smoker: Not reported Signs or symptoms: 40% microscopic hematuria, 28% gross 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

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
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%) recurrentTumor stage: 55 Ta, 24 T1, 16 T2-T4, 5 CISTumor grade: 25 G1, 41 G2, 34 G3
United Kingdom and Eire Bladder Tumour Antigen Study Group, 1997[68] UK	BTA stat	Prospective	Surveillance	Age: Not reported Sex: Not reported Race: 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: 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: 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
Witjes, 1998[72] the Netherlands	NMP22 (quantitative)	Unclear	Surveillance	Age: Not reported Sex: Not reported Race: 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: 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

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

	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	0.70 (0.62 to 0.77); 0.52 (p=0.002)	15	0.81 (0.75 to 0.87); 0.52 (p=0.004)	15	3.75 (2.73 to 5.16)	0.37 (0.28 to 0.48)
Excluding studies that didn't use cutoff of >10	0.72 (0.63 to 0.80); 0.44 (p=0.004)	13	0.81 (0.73 to 0.87); 0.58 (p=0.001)	13	3.84 (2.66 to 5.54)	0.34 (0.25 to 0.46)
Prospective design	0.66 (0.54 to 0.76); 0.38 (p=0.002)	7	0.87 (0.81 to 0.91); 0.36 (p=0.001)	7	4.92 (3.18 to 7.63)	0.39 (0.28 to 0.55)
U.S. or Europe	0.71 (0.63 to 0.78); 0.34 (p=0.003)	14	0.81 (0.74 to 0.86); 0.50 (p=0.0004)	14	3.69 (2.66 to 5.12)	0.36 (0.27 to 0.46)
Prespecified threshold for positive test	0.74 (0.67 to 0.81); 0.23 (p=0.003)	12	0.80 (0.72 to 0.86); 0.48 (p=0.0004)	12	3.66 (2.59 to 5.18)	0.32 (0.24 to 0.42)
Blinded interpretation of reference standard	0.73 (0.52 to 0.88); 0.41 (p=0.002)	3	0.89 (0.79 to 0.95); 0.40 (p=0.0005)	3	6.78 (3.46 to 13.3)	0.30 (0.15 to 0.59)
Evaluation of symptoms	0.68 (0.56 to 0.78); 0.36 (p=0.04)	8	0.86 (0.79 to 0.91); 0.29 (p=0.03)	6	4.94 (3.38 to 7.23)	0.37 (0.26 to 0.52)
Surveillance	0.62 (0.50 to 0.72); 0.32 (p=0.06)	7	0.78 (0.68 to 0.86); 0.33 (p=0.04)	5	2.80 (2.06 to 3.79)	0.49 (0.39 to 0.62)
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)
U.S. 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)
Qualitative BTA						
Overall	0.64 (0.57 to 0.72); 0.36 (p=0.0004)	17	0.80 (0.75 to 0.84); 0.30 (p=0.0002)	17	3.26 (2.61 to 4.08)	0.44 (0.36 to 0.54)
Prospective design	0.63 (0.53 to 0.72); 0.35 (p=0.0004)	11	0.82 (0.76 to 0.86); 0.28 (p=0.0002)	11	3.43 (2.60 to 4.53)	0.46 (0.36 to 0.58)
U.S. or Europe	0.64 (0.56 to 0.71); 0.35 (p=0.0003)	15	0.82 (0.77 to 0.86); 0.23 (p=0.0003)	15	3.51 (2.82 to 4.37)	0.44 (0.36 to 0.54)

	Sensitivity (95% CI); τ^2 (p value)	Number of Studies	Specificity (95% CI); τ^2 (p value)	Number of Studies	LR+	LR-
Blinded interpretation of reference standard	0.63 (0.40 to 0.81); 0.37 (p=0.0004)	2	0.91 (0.84 to 0.95); 0.19 (p=0.0003)	2	7.20 (4.07 to 12.7)	0.41 (0.23 to 0.71)
Evaluation of symptoms	0.78 (0.67 to 0.86); 0.24 (p=0.12)	6	0.86 (0.80 to 0.91); 0.09 (p=0.21)	4	5.69 (3.76 to 8.61)	0.25 (0.16 to 0.39)
Surveillance	0.62 (0.55 to 0.69); 0.07 (p=0.12)	7	0.84 (0.76 to 0.89); 0.28 (p=0.04)	5	3.83 (2.64 to 5.57)	0.45 (0.38 to 0.53)
Quantitative BTA						
Overall	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	0.70 (0.60 to 0.78); 0.008 (p=0.87)	2	0.68 (0.59 to 0.75); 0.002 (p=0.90)	2	2.16 (1.67 to 2.80)	0.44 (0.33 to 0.60)
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	0.57 (0.42 to 0.71)	1	0.79 (0.68 to 0.88)	1	2.77 (1.66 to 4.61)	0.54 (0.39 to 0.76)
FISH						
Overall	0.69 (0.53 to 0.82); 0.54 (p=0.06)	6	0.89 (0.73 to 0.96); 1.30 (p=0.06)	6	6.10 (2.37 to 15.7)	0.35 (0.21 to 0.56)
Prospective design	0.59 (0.38 to 0.78); 0.35 (p=0.09)	3	0.91 (0.67 to 0.98); 1.31 (p=0.06)	3	6.33 (1.47 to 27)	0.45 (0.26 to 0.77)
Excluding high risk of bias studies	0.64 (0.46 to 0.79); 0.49 (p=0.11)	5	0.84 (0.67 to 0.94); 0.95 (p=0.09)	5	4.14 (1.89 to 9.08)	0.42 (0.27 to 0.66)
Blinded interpretation of reference standard	0.77 (0.47 to 0.93); 0.53	2	0.85 (0.46 to 0.97); 1.18	2	5.19 (0.97 to 27.8)	0.27 (0.09 to 0.80)
Evaluation of symptoms	0.86 (0.68 to 0.96)	1	--	0	--	--
Surveillance	0.59 (0.44 to 0.72); 0.30 (p=0.12)	5	0.81 (0.61 to 0.92); 0.94 (p=0.09)	4	3.14 (1.64 to 6.01)	0.51 (0.40 to 0.65)
Immunocyt						
Overall	0.77 (0.57 to 0.90); 0.80 (p=0.14)	4	0.77 (0.71 to 0.82); 0.08 (p=0.25)	4	5.59 (3.32 to 9.40)	0.47 (0.32 to 0.69)
Prospective design	0.87 (0.73 to 0.94); 0.31 (p=0.19)	2	0.74 (0.66 to 0.81); 0.05 (p=0.26)	2	3.37 (2.64 to 4.30)	0.18 (0.09 to 0.36)
Evaluation of symptoms	0.92 (0.83 to 0.96); <0.0001 (p=1.0)	2	0.77 (0.69 to 0.84); <0.0001 (p=1.0)	2	4.07 (2.92 to 5.68)	0.10 (0.05 to 0.23)
Surveillance	0.82 (0.76 to 0.88); 0.0003 (p=0.95)	3	0.74 (0.67 to 0.80); 0.04 (p=0.51)	3	3.13 (2.43 to 4.05)	0.24 (0.17 to 0.34)
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)

LR+ = positive likelihood ratio; LR- = negative likelihood ratio

[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

	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)								
Overall	0.72 (0.67 to 0.77)	0.71 (0.65 to 0.76);	0.01 (-0.05 to 0.08); 0.01 (p=0.33)	5	0.78 (0.65 to 0.87)	0.78 (0.65 to 0.87)	0.002 (-0.05 to 0.08); 0.49 (p=0.06)	5
Restricted to NMP22 studies using a cutoff of >10 U/mL	0.76 (0.70 to 0.82)	0.69 (0.62 to 0.75)	0.07 (-0.01 to 0.16); 0.007 (p=0.50)	4	0.78 (0.62 to 0.89)	0.81 (0.66 to 0.90)	-0.02 (-0.08 to 0.03); 0.57 (p=0.12)	4
Tumor stage Ta	0.55 (0.46 to 0.64)	0.54 (0.45 to 0.62)	0.02 (-0.11 to 0.14); <0.0001 (p=1.0)	4	No data	No data	--	--
T1	0.80 (0.71 to 0.87)	0.78 (0.69 to 0.85)	0.02 (-0.09 to 0.12); 0.004 (p=0.95)	4	No data	No data	--	--
Tumor grade G1	0.52 (0.40 to 0.63)	0.45 (0.34 to 0.58)	0.06 (-0.11 to 0.23); <0.0001 (p=1.0)	4	No data	No data	--	--
G2	0.68 (0.59 to 0.75)	0.68 (0.60 to 0.76)	-0.01 (-0.12 to 0.11); <0.0001 (p=1.0)	4	No data	No data	--	--
Evaluation of symptoms	0.74 (0.65 to 0.81)	0.69 (0.60 to 0.76)	0.05 (-0.06 to 0.16); <0.0001 (p=1.0)	3	0.87 (0.76 to 0.93)	0.82 (0.71 to 0.90)	0.04 (-0.08 to 0.17); <0.0001 (p=1.0)	3
Surveillance	0.67 (0.54 to 0.78)	0.71 (0.58 to 0.81)	-0.04 (-0.18 to 0.11); 0.02 (p=0.73)	2	No data	No data	--	--
BTA qualitative vs. FISH								
Overall	0.78 (0.66 to 0.87)	0.81 (0.70 to 0.89)	0.03 (-0.16 to 0.10); (p=0.65)[a]	1	0.74 (0.64 to 0.83)	0.96 (0.92 to 1.0)	-0.22 (-0.33 to -0.12); (p=0.0001)[a]	1
Tumor stage Ta	0.57 (0.45 to 0.68)	0.65 (0.53 to 0.75)	-0.08 (-0.24 to 0.08); <0.0001 (p=1.0)	2	No data	No data	--	--
CIS	0.78 (0.26 to 0.97)	1.00 (0.86 to 1.0)	-0.22 (-0.61 to 0.17); 1.95 (p=0.40)	2	No data	No data	--	--

	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
Tumor grade G1	0.35 (0.21 to 0.52)	0.48 (0.32 to 0.65)	-0.13 (-0.37 to 0.10); <0.0001 (p=1.0)	2				
G2	0.74 (0.56 to 0.86)	0.76 (0.60 to 0.88)	-0.03 (-0.24 to 0.18); <0.0001 (p=1.0)	2				
BTA qualitative (A) vs. BTA quantitative (B)	0.65 (0.52 to 0.79)	0.78 (0.66 to 0.89)	-0.12 (-0.30 to 0.05); (p=0.26)[a]	1	0.72 (0.56 to 0.87)	0.62 (0.46 to 0.79)	0.09 (-0.14 to 0.32); (p=0.42)[a]	1
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
Biomarker + cytology (A) versus biomarker alone (B)								
Overall	0.84 (0.76 to 0.90)	0.69 (0.58 to 0.78)	0.15 (0.09 to 0.21); 0.48 (p=0.005)	10	0.77 (0.73 to 0.81)	0.77 (0.73 to 0.81)	0.00 (-0.04 to 0.04); 0.04 (p=0.06)	8
Tumor stage Ta	0.86 (0.76 to 0.92)	0.85 (0.75 to 0.91)	0.01 (-0.09 to 0.12); <0.0001 (p=1.0)	2	No data	No data	--	--
T1	0.86 (0.68 to 0.95)	0.82 (0.64 to 0.92)	0.04 (-0.16 to 0.23); <0.0001 (p=1.0)	2	No data	No data	--	--

	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
Tumor grade G1	0.81 (0.68 to 0.90)	0.81 (0.68 to 0.90)	0.0 (-0.15 to 0.15); <0.0001 (p=1.0)	2	No data	No data	--	--
G2	0.89 (0.73 to 0.96)	0.86 (0.70 to 0.94)	0.03 (-0.13 to 0.19); <0.0001 (p=1.0)	2	No data	No data	--	--

[a] Based on Fisher's exact test

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

	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	0.44 (0.28 to 0.61); 0.66 (p=0.02)	7	T1 vs. Ta	0.28 (0.17 to 0.39)	p=0.002
T1	0.72 (0.57 to 0.84)	8	≥T2 vs. T1	0.14 (0.03 to 0.26)	--
≥T2	0.87 (0.73 to 0.94)	8	Ta vs. CIS	-0.16 (-0.44 to 0.11)	--
CIS	0.61 (0.30 to 0.85)	5	--	--	--
Tumor grade G1	0.38 (0.23 to 0.55); 0.63 (p=0.02)	8	G2 vs. G1	0.20 (0.08 to 0.32)	p<0.0005
G2	0.58 (0.42 to 0.73)	8	G3 vs. G2	0.25 (0.14 to 0.36)	--
G3	0.83 (0.70 to 0.91)	8	--	--	--
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	0.530.40 to 0.66)	3	≥T2 vs. T1	0.59 (-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	0.66 (0.56 to 0.75); <0.0001 (p=1.0)	4	T1 vs. Ta	0.24 (0.08 to 0.40)	p=0.73
T1	0.900.68 to 0.97)	3	≥T2 vs. T1	0.10 (-0.03 to 0.23)	
≥T2	1.0 (0.86 to 1.0)	3	Ta vs. CIS	-0.34 (-0.43 to -0.25)	
CIS	1.0 (0.77 to 1.0)	2			
Tumor grade G1	0.52 (0.38 to 0.65); <0.0001 (p=1.0)	4	G2 vs. G1	0.28 (0.10 to 0.45)	p=0.004
G2	0.80 (0.66 to 0.89)	4	G3 vs. G2	0.17 (0.05 to 0.29)	
G3	0.97 (0.89 to 0.99)	4			
Quantitative BTA					
Tumor stage Ta	0.54 (0.36 to 0.72); <0.0001 (p=1.0)	3	T1 vs. Ta	0.26 (0.11 to 0.41)	p=0.08

	Sensitivity (95% CI); τ^2 (p value)	Number of Studies	Comparison	Difference in Sensitivity	Overall Difference Across Categories: p value for chi-square
T1	0.80 (0.66 to 0.89)	3	≥T2 vs. T1	0.12 (0.02 to 0.23)	
≥T2	0.93 (0.80 to 0.98)	3	Ta vs. CIS	-0.14 (-0.53 to 0.24)	
CIS	0.69 (-0.27 to 0.93)	2			
Tumor grade G1	0.52 (0.36 to 0.68); 0.09 (p=0.43)	3	G2 vs. G1	0.11 (-0.08 to 0.29)	p=0.02
G2	0.63 (0.47 to 0.76)	3	G3 vs. G2	0.28 (0.12 to 0.43)	
G3	0.91 (0.78 to 0.96)	3			
Qualitative BTA					
Tumor stage Ta	0.47 (0.38 to 0.56); 0.36 (p=0.001)	14	T1 vs. Ta	0.30 (0.22 to 0.38)	p<0.0001
T1	0.770.68 to 0.84)	13	≥T2 vs. T1	0.16 (0.08 to 0.24)	
≥T2	0.93(0.86 to 0.96)	13	Ta vs. CIS	-0.21 (-0.37 to -0.06)	
CIS	0.68 (0.50 to 0.82)	8			
Tumor grade G1	0.370.27 to 0.49)	15	G2 vs. G1	0.26 (0.17 to 0.35)	p<0.0001
G2	0.63 (0.52 to 0.73)	15	G3 vs. G2	0.20 (0.13 to 0.28)	
G3	0.84 (0.76 to 0.89)	15			
Immunocyt					
Tumor stage Ta	0.73 (0.49 to 0.88); 0.88 (p=0.10)	4	T1 vs. Ta	0.05 (-0.10 to 0.20)	p=0.86
T1	0.78 (0.52 to 0.92)	4	≥T2 vs. T1	0.09 (-0.09 to 0.27)	
≥T2	0.87(0.62 to 0.96)	4	Ta vs. CIS	-0.27 (-0.47 to -0.07)	
CIS	1.0 (0.85 to 1.0)	3			
Tumor grade G1	0.71 (0.45 to 0.88); 0.87 (p=0.21)	4	G2 vs. G1	0.10 (-0.06 to 0.26)	p=0.51
G2	0.81(0.53 to 0.94)	4	G3 vs. G2	0.03 (-0.13 to 0.19)	
G3	0.83 (0.57 to 0.95)	4			

Table 6. Summary of bacillus Calmette–Guérin study characteristics and result

Author, Year	Population	Intervention	Results/Followup
BCG vs. MMC; BCG vs. MMC+BCG; BCG+MMC vs. MMC			
Di Stassi, 2003[132]	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 Chemical 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 FU 43 vs. 42 vs. 45 months
Friedrich, 2007[131]	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 FU 2.9 years
Gardmark, 2007[134] Lundholm, 1996[129] Malmstrom, 1999[135]	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 FU 39 months; Also 10 year followup

Author, Year	Population	Intervention	Results/Followup
Gulpinar, 2012[138]	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 TUR B. MMC 40, single dose at surgery followed by 6 weekly instillations beginning at least 15 days from TUR	Recurrence: 5/26 vs. 9/25 Progression: 1/26 vs. 1/25 Cystectomy: 1/26 vs. 1/25 Median FU 41months
Jarvinen, 2009[137] Rintala, 1991[126]	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 FU 28 months; Also median FU 8.5 years
Jarvinen, 2012[143] Rintala, 1995[145] (Jarvinen, 2012[143], Rintala, 1995[145] and Rintala, 1996[144] 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 FU 33 months; Also median FU 7.2 years
Kaasinen, 2003[139]	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 FU 56 months

Author, Year	Population	Intervention	Results/Followup
Krege, 1996[92]	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 FU 20 months
Lamm, 1995[124]	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 FU 913 days
Mangiarotti, 2008[130]	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 Chemical 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 FU 66 months
Mohsen, 2010[141]	At least 2 histologically verified recurrent stage Ta or T1 during the preceding 1.5 years	A. BCG $5x10^8$ CFU, 6 weekly instillations then monthly for months 3-12 B. 40 mg, 4 weekly instillations then monthly for months 2-13	Recurrence: 16/27 vs. 9/29 Cystectomy: 2/27 vs. 1/29 Mean FU 24 months
Ojea, 2007[128]	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 FU 57 vs. 61 vs. 53 months

Author, Year	Population	Intervention	Results/Followup
Oosterlinck, 2011[140]	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 FU 4.7 years
Rintala, 1996[144] (Jarvinen, 2012[143], Rintala, 1995[145] and Rintala, 1996[144] 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 FU 34 months
Witjes, 1996[133] Witjes, 1993[125]	Histologically proven papillary pTa-pT1 transitional cell transitional cell carcinoma of the bladder with or without CIS	A. BCG 50 mg (Tice), 6 weekly instillations with a B. BCG RIVM), 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 Chemical 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 FU 32 months
Witjes, 1998b[142]	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 Chemical cystitis: 37/90 vs. 29/92 Systemic side effects: 21/90 vs. 20/92 Fever: 11/90 vs. 3/92 Median FU 32 months

Author, Year	Population	Intervention	Results/Followup
BCG vs. Epirubicin; BCG vs. Epirubicin + BCG			
Ali-El-Dein, 1999[156]	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 Chemical 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 FU 30 months
Bilen, 2000[157]	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 Fu 18 months
Cai, 2008[155]	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 FU 15 months
Cheng, 2005[150]	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 FU 23 months for recurrence, 47 months for progression, 61 months for survival

Author, Year	Population	Intervention	Results/Followup
De Reijke, 2005[153]	Patients with biopsy proven primary, secondary or concurrent carcinoma in-situ (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 Chemical 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 FU 67 months
Melekos, 1993[83]	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 Chemical 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
Melekos, 1996[151]	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 Chemical cystitis: 39/58 vs. 23/61 Hematuria: 14/58 vs. 10/61 Median FU 43 months
Hinotsu, 2011[152]	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 FU 2 years

Author, Year	Population	Intervention	Results/Followup
Sylvester, 2010[149] Van Der Meijden, 2001[154]	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 Chemical cystitis: 111/263 vs. 82/265 Hematuria: 93/263 vs. 45/264 DC instillations: 190/265 vs. 201/265 Median FU 4 years; Also median FU 9 years
BCG vs. Gemcitabine; BCG vs. BCG + Gemcitabine			
Cho, 2009[163]	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 FU 32 and 34 months
Di Lorenzo, 2010[160]	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 FU 15 months
Gontero, 2013[162]	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

Author, Year	Population	Intervention	Results/Followup
Porena, 2010[161]	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 FU 44 months
BCG vs. Interferon alpha-2a; BCG vs. Interferon alpha-2b + BCG			
Jimenez-Cruz, 1997[164]	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. INF 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 FU 21 vs. 18 months
Kaasinen, 2000[165]	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. INF 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 FU 56 months

Author, Year	Population	Intervention	Results/Followup
Nepple, 2010[166]	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. INF 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
BCG vs. Doxorubicin			
Hinotsu, 2006[146]	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 FU 667 days
Lamm, 1991[147]	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[148]	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 FU 3 years

Author, Year	Population	Intervention	Results/Followup
BCG vs. Thiotepa			
Martinez-Pineiro, 1990[148]	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 FU 3 years
BCG vs. Epirubicine + Interferon alpha-2b			
Duchek, 2010[158] Hemdan, 2014[159]	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 + INF 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-yr Recurrence: 50/126 vs. 75/124 No difference in progression-free survival (p=NR) Cystectomy: 9/126 vs. 13/124 DC instillations: 11/126 vs. 2/124 No difference in urinary symptoms (p=NR) Followup 24 months; Also median FU 6.9 years
BCG vs. Observation			
Herr, 1995[82] Herr, 1988[86] Herr, 1997[87] Cookson, 1997[88] Pinsky, 1985[89]	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 FU 72 months; Also median FU 108 vs. 140 months
Koga, 2010[81]	Histologically-confirmed Ta, T1 transitional cell carcinoma or CIS of bladder	All patients received 8 weekly instillations of BCG 80 mg prior to randomization A. BCG 80 mg, instillations at 3, 6 and 9 months B. Control	Overall mortality: 2/24 vs. 2/27 Bladder cancer mortality: 0/24 vs. 1/27 Recurrence: 1/24 vs. 7/27 Progression: 0/24 vs. 1/27 Median FU 27 vs. 29 months

Author, Year	Population	Intervention	Results/Followup
Lamm, 2000[80] Lerner, 2007[91]	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	All patients received 6 weekly instillations of BCG 81 mg prior to randomization A. BCG 81 mg, 3 weekly instillations at 3 and 6 months and every 6 months to 3 years B. Control	Overall mortality: 81/192 vs. 93/192 Recurrence: 108/192 vs. 142/192 Progression: 87/192 vs. 102/192 Median FU 120 months
Melekos, 1990[84]	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 FU 29 vs. 30 months
Melekos, 1993[83]	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
Pagano, 1991[85] Pagano, 1990[90]	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 FU 21 months
Palou, 2001[79]	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	All patients received 6 weekly instillations of BCG 81 mg prior to randomization A. BCG 81 mg, 6 weekly instillations every 6 months for 2 years B. Control	Overall mortality: 11/66 vs. 8/61 Bladder cancer mortality: 3/66 vs. 2/61 Cystectomy: 5/66 vs. 3/61 Median FU 78 months

BCG, bacillus Calmette-Guérin; CFU, Colony Forming Unit; CIS, carcinoma in situ; cm, centimeter; DC, dendritic cells; EAU guidelines, European Association of Urology Guidelines; FU, followup; G1, Grade 1; G2, Grade 2; G3, Grade 3; INF, Interferon; mg, milligram; MMC, Mitomycin C; MU, Million units; NMIBC, Non-Muscle Invasive Bladder Cancer; NR, Not Reported; 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, sex, stage of disease, functional status)
Addeo, 2010[170]	Italy Number centers not reported 2003 - 2005	A: MMC, 40 mg (in 50 mL normal saline). Total 5 installations: 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.	36 months (median) for each group Followup method not specified.	Age (mean), years: 67.9 vs. 64.9 Age (median), years: 70 vs. 66.5 Male: 85.5% vs. 85.2% Race: 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[93] Study One (followup of Niijima, 1983[97])	Japan 33 centers 1980 - 1985	A: Doxorubicin, 30 mg (in 30 mL saline). Total 8 installations. (n = 149) B: Doxorubicin, 20 mg (in 40 mL saline). Total 8 installations. (n = 148) C: MMC: 20 mg (in 40 mL saline). Total 8 installations. (n = 139) D: No adjuvant treatment. TUR alone. (n = 139) For A, B, and C: First installation within 1 week of TURBT. Twice weekly X 4 weeks	5 years (maximum), overall. Followup with cystoscopy and urinary cytology.	Age (average), yrs: 62.3 vs. 62.9 vs. 62.9 vs. 62.9 Male: 82.6% vs. 75.7% vs. 74.8% vs. 74.1% Race: 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%

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Akaza, 1987[93] Study Two	Japan Number centers not reported 1982 - 1985	A: Doxorubicin, 30 mg (in 30 mL saline). Total 21 installations over 2 years. (n = 151) B: Doxorubicin, 20 mg (in 40 mL saline). Total 21 installations over 2 years. (n = 158) C: MMC: 20 mg (in 40 mL saline). Total 21 installations over 2 years. (n = 150) D: No adjuvant treatment. TUR alone. (n = 148) For A, B, and C: First installation 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	3.5 years (maximum), overall. Followup with cystoscopy and urinary cytology.	Age (average), yrs: 63.1 vs. 62.1 vs. 62.3 vs. 62.0 Male): 80.1% vs. 82.3% vs. 82.0% vs. 81.1% Race: 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%

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Akaza, 1992[94] Study Two (followup of sub-group of Akaza, 1987[93])	Japan Number centers not reported 1982 - 1990	A: Doxorubicin, 30 mg (in 30 mL saline). Total 21 installations over 2 years. (n = 44) B: Doxorubicin, 20 mg (in 40 mL saline). Total 21 installations over 2 years. (n = 42) C: MMC: 20 mg (in 40 mL saline). Total 21 installations over 2 years. (n = 41) D: No adjuvant treatment. TUR alone. (n = 31) For A, B, and C: First installation 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	6.6 years (median), overall. Followup 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: 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[169]	Italy Number centers not reported 1987 - 1989	A: MMC, 40 mg (in 50 mL saline). Total 8 installations: weekly dose X 8 weeks. (n = 141) B: Interferon alfa-2b, 50 million units (in 50 mL normal saline). Total 8 installations: weekly dose X 8 weeks. (n = 146)	42 months (maximum). Followup with cystoscopy and urine cytology.	Age (median), years: 64 vs. 63 Male: 87.9% vs. 84.9% Race: 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%

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
De Nunzio, 2011[95]	Italy Single center 2000 - 2009	A: MMC, 40 mg (in 50 mL saline). Single installation within 24 hours of TURBT. (n = 97) B: TURBT only. No adjuvant therapy. (n = 105)	90 months vs. 85 months (median). Followup with cystoscopy and urine cytology.	Age (median), years: 60.8 vs. 61.5 Male: 62.9% vs. 68.6% Race: 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
Giannopoulos, 2003[117]	Greece Multi-center 1997 - 2001	A: Interferon-gamma 1b, 15 million units (in 50 mL normal saline). Total 20 installations: First installation 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 installations: First installation 2 weeks after TURBT; then once a week X 7, then once biweekly X 4, then once monthly X 8. (n = 63)	26.5 months vs. 24 months (median). Followup with 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: 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

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Gustafson, 1991[96]	SwedenNumber centers not reportedStudy 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 installations: First installation approximately 2 weeks after TURBT; installations 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 installations: Same protocol as A. (n = 20)C: TURBT only. No adjuvant therapy. (n = 21)	47 months vs. 45 months vs. 35 months (mean).Followup with cystoscopy.	Age (mean), years: 67 (overall) Male: "Four to one", male/female (overall) Race: 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

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Huland, 1990[167]	Germany Six centers 1983 - 1985	A: MMC (20 mg/20 mL). Total 42 installations: 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 installations: 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 installations: Every week X 20 weeks. (n = 75) D: Doxorubicin (50 mg/50 mL). Total 42 installations: 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: Installations started 4 to 6 weeks after discharge from hospital.	26.7 months vs. 27.4 months vs. 26.7 months vs. 30.2 months (mean). Followup with 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: 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
Krege, 1996[92]	Germany, Multicenter, number not reported 1985-1992	A. MMC 20 mg (in 50 mL saline). Total 38 installations: 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)	20 months, overall (mean) Followup method not specified.	Age (mean), years: 65 (not specified by group) Male: 84% vs. 75% Race: 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

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Liu, 2006[168]	China Number centers not reported 1997 - 1998	A: Epirubicin, 80 mg (in 40 mL normal saline). Single installation within 6 hours of TURBT. (n = 14) B: Epirubicin, 40 mg. Total 16 - 18 installations: Every week for 6 ~ 8 weeks, then every month for 10 months. (n = 15) C: MMC, 40 mg. Total 16 - 18 installations: Every week for 6 ~ 8 weeks, then every month for 10 months. (n = 15)	5 years (all patients). Followup with cystoscopy and urine cytology.	Age (mean), years: 62.2 (overall) Male: Not reported Race: 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
Niijima, 1983[97] (see Akaza, 1987[93])	Japan 33 centers 1980 - 1985	A: Doxorubicin, 30 mg (in 30 mL saline). Total 8 installations. (n = 149) B: Doxorubicin, 20 mg (in 40 mL saline). Total 8 installations. (n = 148) C: MMC: 20 mg (in 40 mL saline). Total 8 installations. (n = 139) D: No adjuvant treatment. TURBT alone. (n = 139) For A, B, and C: First installation within 1 week of TURBT. Twice weekly X 4 weeks	5 years (maximum), overall. Followup with cystoscopy and urinary cytology.	Age (average), yrs: 62.3 vs. 62.9 vs. 62.9 vs. 62.9 Male: 82.6% vs. 75.7% vs. 74.8% vs. 74.1% Race: 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%

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Solsona, 1999[98]	Spain Number centers not reported 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)	94 months vs. 93 months (median). Followup with cystoscopy and urine cytology.	Age (mean), years: 62.2 vs. 59.9 Male: 91.2% vs. 92.2% Race: 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.
Tolley, 1996[99] (followup Tolley, 1988[222])	United Kingdom 17 centers 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 installations: First within 24 hours of TURBT, then every 3 months x 1 year. (n = 146) C: TURBT only. No adjuvant therapy. (n = 157)	7 years (median) for groups A and B; not reported for group C. Followup with 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: 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

cm, centimeters; G1, Grade 1; G2, Grade 2; G3, Grade 3; mg, milligrams; mL, milliliters; 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[170]	A: MMC, 40 mg (in 50 mL normal saline). Total 5 installations: 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[93] Study One (followup of Niijima, 1983[97])	A: Doxorubicin, 30 mg (in 30 mL saline). Total 8 installations. B: Doxorubicin, 20 mg (in 40 mL saline). Total 8 installations. C: MMC: 20 mg (in 40 mL saline). Total 8 installations. D: No adjuvant treatment. TURBT alone. For A, B, and C: First installation 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, $p < 0.05$		

Author, year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Akaza, 1987[93] Study Two	A: Doxorubicin, 30 mg (in 30 mL saline). Total 21 installations over 2 years. B: Doxorubicin, 20 mg (in 40 mL saline). Total 21 installations over 2 years. C: MMC: 20 mg (in 40 mL saline). Total 21 installations over 2 years. D: No adjuvant treatment. TURBT alone. For A, B, and C: First installation 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[94] Study Two (followup of sub-group of Akaza, 1987[93])	A: Doxorubicin, 30 mg (in 30 mL saline). Total 21 installations over 2 years. B: Doxorubicin, 20 mg (in 40 mL saline). Total 21 installations over 2 years. C: MMC: 20 mg (in 40 mL saline). Total 21 installations over 2 years. D: No adjuvant treatment. TURBT alone. For A, B, and C: First installation 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"	

Author, year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Boccardo, 1994[169]	A: MMC, 40 mg (in 50 mL saline). Total 8 installations: weekly dose X 8 weeks. (n = 141) B: Interferon alfa-2b, 50 million units (in 50 mL normal saline). Total 8 installations: 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)	
De Nunzio, 2011[95]	A: MMC, 40 mg (in 50 mL saline). Single installation 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	

Author, year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Giannopoulos, 2003[117]	A: Interferon-gamma 1b, 15 million units (in 50 mL normal saline). Total 20 installations: First installation 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 installations: First installation 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[96]	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 installations: First installation approximately 2 weeks after TURBT; installations 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 installations: 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)	

Author, year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Huland, 1990[167]	A: MMC (20 mg/20 mL). Total 42 installations: 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 installations: 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 installations: Every week X 20 weeks. (n = 75) D: Doxorubicin (50 mg/50 mL). Total 42 installations: 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: Installations 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)	
Krege, 1996[92]	A. MMC 20 mg (in 50 mL saline). Total 38 installations: 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)		

Author, year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Liu, 2006[168]	A: Epirubicin, 80 mg (in 40 mL normal saline). Single installation within 6 hours of TURBT. (n = 14) B: Epirubicin, 40 mg. Total 16 - 18 installations: Every week for 6 ~ 8 weeks, then every month for 10 months. (n = 15) C: MMC, 40 mg. Total 16 - 18 installations: 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		
Niijima, 1983[97]	A: Doxorubicin, 30 mg (in 30 mL saline). Total 8 installations. B: Doxorubicin, 20 mg (in 40 mL saline). Total 8 installations. C: MMC: 20 mg (in 40 mL saline). Total 8 installations. D: No adjuvant treatment. TURBT alone. For A, B, and C: First installation 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		

Author, year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Solsona, 1999[98]	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)	
Tolley, 1996[99] (followup Tolley, 1988[222])	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 installations: 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)

CI, Confidence Interval; cm, centimeters; G1, Grade 1; G2, Grade 2; G3, Grade 3; HR, hazard ratio; mg, milligrams; mL, milliliters; NNT, number needed to treat; T1, Tumor stage 1; 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, sex, stage of disease, functional status)
Akaza, 1987[93] [Study One] (followup of Niijima, 1983[97])	Japan 33 centers 1980 - 1985	A: Doxorubicin, 30 mg (in 30 mL saline). Total 8 installations: First within 1 week of TURBT, twice weekly X 4 weeks. (n = 149) B: Doxorubicin, 20 mg (in 40 mL saline). Total 8 installations: First within 1 week of TURBT, twice weekly X 4 weeks. (n = 148) C: MMC: 20 mg (in 40 mL saline). Total 8 installations: First within 1 week of TURBT, twice weekly X 4 weeks. (n = 139) D: No adjuvant treatment. TURBT alone. (n = 139)	5 years, maximum; Not reported as median/mean, nor for each group. Followup 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: Not reported Smoking status: Not reported Recurrent bladder cancer: 29.5% vs. 31.1% vs. 33.8% vs. 35.3% Stage: Not reported ("no differences") Grade: Not reported ("no differences") 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%

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Akaza, 1987[93] [Study Two]	Japan Number centers not reported. 1982 - 1985	A: Doxorubicin, 30 mg (in 30 mL saline). Total 21 installations. (n = 151) B: Doxorubicin, 20 mg (in 40 mL saline). Total 21 installations. (n = 158) C: MMC: 20 mg (in 40 mL saline). Total 21 installations. (n = 150) D: No adjuvant treatment. TURBT alone. (n = 148) For A, B, and C: First installation 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.	3.5 years, maximum; Not reported as median/mean, nor for each group. Followup 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: Not reported Smoking status: Not reported Recurrent bladder cancer: None (primary only) Stage: Not reported ("no differences") Grade: Not reported ("no differences") 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%

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Akaza, 1992[94] [Study Two] (followup of Akaza, 1987[93])	Japan Number centers not reported. 1982 - 1990	A: Doxorubicin, 30 mg (in 30 mL saline). Total 21 installations. (n = 44) B: Doxorubicin, 20 mg (in 40 mL saline). Total 21 installations. (n = 42) C: MMC: 20 mg (in 40 mL saline). Total 21 installations. (n = 41) D: No adjuvant treatment. TURBT alone. (n = 31) For A, B, and C: First installation 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.	Median, overall: 2,366 days (6.5 years); range: 480-2,817 days. Not reported for each group. Followup cystoscopy and urinary cytology.	Only reported overall; Not reported by treatment group Age: ≤ 50 yrs: 13.3%; ≤ 60 yrs: 17.7%; < 70 yrs: 35.4%; ≥ 70 yrs: 33.5% Male: 84.8% Race: 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

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Ali-El-Dein, 1997[100] (Journal of Urology)	Egypt Single center 1991 - 1995	A: Epirubicin, 50 mg (in 50 mL normal saline). Total 18 installations: 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 installations: 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 installations: 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)	30.1 months (mean) for all groups. Followup with cysto-urethroscopy, urine cytology, and flow cytometry.	Age: Not reported Male: 81.4%,overall; not reported by group Race: Not reported Smoking status: 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% 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: Not reported

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Cheng, 2005[101]	Hong Kong Single site 1986 - 1991	A: Doxorubicin, 50 mg (in 50 mL saline). Total 12 installations: 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)	Median followup (Overall; not reported by groups): Recurrence: 45 months Progression: 128 months Mortality overall: 131.5 months Followup with cystoscopy and urine cytology.	Age (mean), years: 65.5 vs. 62.1 Male: 71.7% vs. 86.1% Race: Not reported Smoking status: 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% Grade: G1: 34.8% vs. 41.7%; G2: 32.6% vs. 19.4%; G3: 23.9% vs. 16.7%; Not reported: 8.7% vs. 22.2% Functional Status: Not reported Size (cm): 0.1 - 1.0: 21.7% vs. 25.0%; 1.1 - 3.0: 43.5% vs. 27.8%; 3.1 - 10.0: 23.9% vs. 22.2%; Not reported: 10.9% vs. 25.0% Multiplicity: Single: 50.0% vs. 72.2%; Multiple: 43.5% vs. 8.3%; Not reported: 6.5% vs.19.4%

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Eto, 1994[171]	Japan 21 centers 1990 - 1992	A: Epirubicin, 30 mg (in 30 mL physiological saline). Total 19 installations: 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 installations: 2 times/week for 4 weeks, then 1 time/month for 11 months. (n = 54)	674 days vs. 606 days (mean). Followup with cystoscopy and urine cytology.	Age (median), years: 65 vs. 67 Male: 85.0% vs. 87.0% Race: Not reported Smoking status: 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% Grade: G1: 33.3% vs. 20.4%; G2: 48.3% vs. 66.7%; G3: 11.7% vs. 7.4%; Unknown: 6.7% vs. 5.6% Functional Status: Not reported Size: < 1 cm: 45% vs. 50%; 1- 3 cm: 40% vs. 46%; 3-5 cm: 13% vs. 4%; > 5 cm: 17% vs. 0% Number of tumors: 1: 47% vs. 63%; 2-4: 38% vs. 22%; ≥ 5: 12% vs. 11%

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Gustafson, 1991[96]	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 installations: First installation approximately 2 weeks after TURBT; installations 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 installations: Same protocol as A. (n = 20) C: TURBT only. No adjuvant therapy. (n = 21)	47 months vs. 45 months vs. 35 months (mean). Followup with cystoscopy.	Age (mean), years: 67 (overall) Male: "Four to one", male/female (overall) Race: 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

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Huland, 1990[167]	Germany Six centers1983 - 1985	A: MMC (20 mg/20 mL). Total 42 installations: 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 installations: 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 installations: First at 4-6 weeks after hospital discharge, then every week X 20 weeks. (n = 75)D: Doxorubicin (50 mg/50 mL). Total 42 installations: 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)	26.7 months vs. 27.4 months vs. 26.7 months vs. 30.2 months (mean).Followup with 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: Not reportedSmoking status: Not reportedRecurrent 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%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%Functional Status: Not reported

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Kurth, 1997[102]	Europe (multinational)21 centers1979 - 1983	A: Doxorubicin, 50 mg (in 50 mL normal saline). Total 15 installations: 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)	Median followup (Overall; not reported by groups):Recurrence: 3.4 yearsProgression: 5 yearsMortality from malignancy: 7.2 yearsMortality overall: 10.7 years(maximum followup 14 years).Followup with cystoscopy.	Age: < 50 yrs: 8% vs. 7%; 50-59 yrs: 21% vs. 28%; 60-69 yrs: 28% vs. 35%; 70-79 yrs: 39% vs. 24%; ≥ 80 yrs: 4% vs. 7%; Unknown: 1% vs. 0%Male: 80% vs. 90%Race: Not reportedSmoking status: Not reportedRecurrent bladder cancer: 30.2% vs. 34.7%; Unknown: 1% vs. 0% Stage: T0: 0% vs. 0%; Ta: 50% vs. 58%; T1: 45% vs. 40%; Tis: 4% vs. 1%; Unknown: 1% vs. 0% Grade: G0: 8% vs. 15%; G1: 43% vs. 40%; G2: 33% vs. 36%; G3: 12% vs. 1%; Unknown: 4% vs. 5% Functional Status: Not reported
Martinez-Pineiro, 1990[148]	Spain Number of centers not reported 1980-1988	A. Thiotepa 50 mg (in 50 ml saline). (n = 56) B. Doxorubicin 50 mg (in 50 ml saline). Total 16 installations. (n = 53) A and B: First treatment within 14 days of TURBT, then weekly X 4 weeks, then monthly X 11 months.	34 months vs. 40 months Range (months): (6-78) vs. (5-97) Followup with cystoscopy and urinary cytology.	Age (Median), years: 64 vs. 62 Male: 84% vs. 89% Race: Not reported Smoking: Not reported Stage: Ta: 41% vs. 40%; T1: 59% vs. 60% Grade: G1: 32% vs. 45%; G2: 43% vs. 34%; G3: 25% vs. 21% Associated Tis: 9% vs. 11% Multiplicity: Single: 57% vs. 58%; Multiple: 43% vs. 42%

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Matsumura, 1992[104]	Japan Number centers not reported (multicenter) 1987 - 1989	A: Doxorubicin, 20 mg (in 40 mL physiological saline). Total 21 installations over 2 years after TURBT: Timing of first dose not specified; installations 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 installations over 2 weeks before TURBT: specific schedule not reported. (n = 75) C: No adjuvant treatment. TURBT alone. (n = 83)	240 days, overall. (n = 284) 720 days (maximum), overall, not reported by group. (n = 156) Followup methods not reported.	Age: ≤ 49 yrs: 7.1% vs. 4.0% vs.12.1%; 50-59 yrs: 15.1% vs. 20.0% vs. 13.3%; 60-69 yrs: 34.1% vs. 32.0% vs. 31.3%; ≥ 70 yrs: 42.9% vs. 44.0% vs. 42.2% Male: 81.7% vs. 78.7% vs. 84.3% Race: Not reported Smoking status: 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% Grade: G0: 2.4% vs. 8.0% vs. 2.4%; G1: 33.3% vs. 34.7% vs. 32.5%; G2: 36.5% vs. 30.7% vs. 36.1%; G3: 4.0% vs. 4.0% vs. 0.0%; Unknown: 23.8% vs. 22.7% vs. 28.9% Functional Status: Not reported Size: ≈ 1 cm: 52.4% vs. 49.3% vs. 55.4%; ≈ 3 cm: 34.1% vs. 42.7% vs. 33.7%; ≈ 5 cm: 7.1% vs. 6.7% vs. 7.2%; > 5 cm: 0.8% vs. 1.3% vs. 1.2%; Unknown: 5.6% vs. 0.0% vs. 2.4% Multiplicity: Single: 26.2% vs. 22.7% vs. 24.1%; 2-4: 58.7% vs. 46.7% vs. 54.2%; ≥ 5: 11.9% vs. 25.3% vs. 18.1%; Unknown: 2.4% vs. 2.7% vs. 2.4%

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Niijima, 1983[97] (see Akaza, 1987[93])	Japan 33 centers 1980 - 1985	A: Doxorubicin, 30 mg (in 30 mL saline). Total 8 installations. (n = 149) B: Doxorubicin, 20 mg (in 40 mL saline). Total 8 installations. (n = 148) C: MMC: 20 mg (in 40 mL saline). Total 8 installations. (n = 139) D: No adjuvant treatment. TURBT alone. (n = 139) For A, B, and C: First installation within 1 week of TURBT. Twice weekly X 4 weeks	5 years (maximum), overall. Followup with cystoscopy and urinary cytology.	Age (average), yrs: 62.3 vs. 62.9 vs. 62.9 vs. 62.9 Male: 82.6% vs. 75.7% vs. 74.8% vs. 74.1% Race: 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%

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Obata, 1994[105]	Japan 62 centers 1985 - 1987	A: Doxorubicin, 20 mg (in 40 mL physiological saline). Total 19 installations over 1 year, after TURBT: Timing of first dose not specified; installations twice a week X 4 weeks, then once a month X 11 months. (n = 90) B: No adjuvant treatment. TURBT alone. (n = 76)	Until January, 1991. Not reported as mean/median nor by group. Method of followup not reported.	Age: ≤ 49 yrs: 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: Not reported Smoking status: 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% Grade: G0: 0.0% vs. 0.0%; G1: 31.1% vs. 48.7%; G2: 64.4% vs. 46.1%; Gx: 3.3% vs. 3.9% Functional Status: Not reported Size: < 1 cm: 51.1% vs. 57.9%; 1-3 cm: 36.7% vs. 32.9%; > 3 cm: 8.9% vs. 5.7%; Unknown: 3.3% vs. 3.9% Multiplicity: Single: 16.7% vs. 11.8%; 2-4: 56.7% vs. 68.4%; ≥ 5: 24.4% vs. 18.4%; Unknown: 1.1% vs. 1.3%
Okamura, 2002[106]	JapanNumber centers not reported1994 - 1998	A: Doxorubicin, 30 mg (in 30 mL normal saline). Single intravesical installation within 6 hours of TURBT. (n = 81)B: TURBT only. No adjuvant therapy. (n = 79)	40.8 months (median) all patients. Followup with cystoscopy and urine cytology.	Age (mean), years: 59.7 vs. 61.9 Male: Not reportedRace: Not reportedSmoking status: Not reportedRecurrent bladder cancer: 7.4% vs. 2.5% Stage: pTa: 95.1% vs. 93.7%; pT1: 4.9% vs. 6.3% Grade: G1: 50.6% vs. 45.6%; G2: 46.9% vs. 49.4%; G3: 2.5% vs. 5.1% Functional Status: All patients had Eastern Cooperative Oncology Group performance status ≤ 2

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Shuin, 1994[172]	Japan 23 centers 1990 - 1993	A: Epirubicin, 30 mg (in 40 mL saline). Total 17 installations: 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 installations: Timing of first not specified; every 2 weeks X 3 months, then every 4 weeks for remainder of 1 year.	Overall duration of study was 43 months. Mean/median followup durations not reported. Followup method not described.	Age: < 40 years: 6% vs. 3% Age: 40-49 years: 3% vs. 9% Age: 50-59 years: 9% vs. 24% Age: 60-69 years: 25% vs. 21% Age: ≥ 70: 56% vs. 42% Male: 81% vs. 82% Race: Not reported Smoking status: Not reported Recurrent bladder cancer: All (recurrent only) Stage Ta: 69% vs. 64% Stage T1: 25% vs. 27% Stage unknown: 6% vs. 9% Grade G1: 50% vs. 39% Grade G2: 59% vs. 61% Functional status: Not reported

cm, centimeters; G1, Grade 1 ; G2, Grade 2; G3, Grade 3; Gx, Grade unknown; mg, milligrams; mL, milliliters; pTa, Tumor stage a determined by pathology pTa, Tumor stage determined by pathology; T1, Tumor stage 1; Ta, Tumor stage a; Tis, Carcinoma in situ; TURBT, Transurethral resection of bladder tumor

Table 10. Summary of doxorubicin study results

Author, year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Akaza, 1987[93] [Study One] (followup of Niijima, 1983[97])	A: Doxorubicin, 30 mg (in 30 mL saline). Total 8 installations: First within 1 week of TURBT, twice weekly X 4 weeks. (n = 149) B: Doxorubicin, 20 mg (in 40 mL saline). Total 8 installations: First within 1 week of TURBT, twice weekly X 4 weeks. (n = 148) C: MMC: 20 mg (in 40 mL saline). Total 8 installations: 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		
Akaza, 1987[93] [Study Two]	A: Doxorubicin, 30 mg (in 30 mL saline). Total 21 installations. (n = 151) B: Doxorubicin, 20 mg (in 40 mL saline). Total 21 installations. (n = 158) C: MMC: 20 mg (in 40 mL saline). Total 21 installations. (n = 150) D: No adjuvant treatment. TURBT alone. (n = 148) For A, B, and C: First installation 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, $p < 0.05$		

Author, year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Akaza, 1992[94] [Study Two] (followup of Akaza, 1987[93])	A: Doxorubicin, 30 mg (in 30 mL saline). Total 21 installations. (n = 44) B: Doxorubicin, 20 mg (in 40 mL saline). Total 21 installations. (n = 42) C: MMC: 20 mg (in 40 mL saline). Total 21 installations. (n = 41) D: No adjuvant treatment. TURBT alone. (n = 31) For A, B, and C: First installation 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"	

Author, year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Ali-El-Dein, 1997[100] (Journal of Urology)	A: Epirubicin, 50 mg (in 50 mL normal saline). Total 18 installations: 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 installations: 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 installations: 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[101]	A: Doxorubicin, 50 mg (in 50 mL saline). Total 12 installations: 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%

Author, year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Eto, 1994[171]	A: Epirubicin, 30 mg (in 30 mL physiological saline). Total 19 installations: 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 installations: 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[96]	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 installations: First installation approximately 2 weeks after TURBT; installations 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 installations: 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)	

Author, year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Huland, 1990[167]	A: MMC (20 mg/20 mL). Total 42 installations: 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 installations: 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 installations: First at 4-6 weeks after hospital discharge, then every week X 20 weeks. (n = 75) D: Doxorubicin (50 mg/50 mL). Total 42 installations: 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)	

Author, year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Kurth, 1997[102]	A: Doxorubicin, 50 mg (in 50 mL normal saline). Total 15 installations: 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[148]	A. Doxorubicin 50 mg (in 50 ml saline). Total 16 installations. (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

Author, year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Matsumura, 1992[104]	A: Doxorubicin, 20 mg (in 40 mL physiological saline). Total 21 installations over 2 years after TURBT: Timing of first dose not specified; installations 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 installations 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[97]	A: Doxorubicin, 30 mg (in 30 mL saline). Total 8 installations. B: Doxorubicin, 20 mg (in 40 mL saline). Total 8 installations. C: MMC: 20 mg (in 40 mL saline). Total 8 installations. D: No adjuvant treatment. TURBT alone. For A, B, and C: First installation 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, $p < 0.10$		

Author, year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Obata, 1994[105]	A: Doxorubicin, 20 mg (in 40 mL physiological saline). Total 19 installations over 1 year, after TURBT: Timing of first dose not specified; installations 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[106]	A: Doxorubicin, 30 mg (in 30 mL normal saline). Single intravesical installation 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[172]	A: Epirubicin, 30 mg (in 40 mL saline). Total 17 installations: 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 installations: 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 ;mg, milligrams; mL, milliliters; 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, sex, stage of disease, functional status)
Ali-El-Dein, 1997[100] (Journal of Urology)	Egypt Single center 1991 - 1995	A: Epirubicin, 50 mg (in 50 mL normal saline). Total 18 installations: 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 installations: 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 installations: 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)	30.1 months (mean) for all groups. Followup with cysto-urethroscopy, urine cytology, and flow cytometry.	Age: Not reported Male: 81.4%,overall; not reported by group Race: Not reported Smoking status: 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% 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: Not reported

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Ali-El-Dein, 1997[107] (British Journal of Urology)	Egypt Single center 1992 - 1996	A: Epirubicin, 50 mg (in 50 mL normal saline). Single installation immediately after TURBT. (n = 55) B: Epirubicin, 50 mg (in 50 mL normal saline). Total 18 installations: 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)	32.2 months (mean) for all groups. Followup with cysto-urethroscopy, 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: Not reported Smoking status: 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% 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% Functional Status: Not reported Size: < 3 cm: 65% vs. 71% vs. 63%; ≥ 3 cm: 35% vs. 29% vs. 37%
Berrum-Svennung, 2008[108]	Sweden 13 centers 1998 - 2004	A: Epirubicin, 50 mg (in 50 mL saline). Single installation within 6 hours after TURBT. (n = 155) B: Placebo. Saline, 50 mL. Single installation within 6 hours after TURBT. (n = 152)	2 years, overall; Not reported as median/mean, nor for each group. Followup with cystoscopy.	Age (median), years: 74 vs. 71 Age (mean), years: 71 vs. 69 Male: 69.7% vs. 77.6% Race: Not reported Smoking status: 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 Size, median (mm): 10 vs. 10 Size, mean (mm): 13 vs. 13 Number of tumors: Single: 56.1% vs. 61.2%; Multiple: 43.9% vs. 38.8%

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Eto, 1994[171]	Japan 21 centers 1990 - 1992	A: Epirubicin, 30 mg (in 30 mL physiological saline). Total 19 installations: 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 installations: 2 times/week for 4 weeks, then 1 time/month for 11 months. (n = 54)	674 days vs. 606 days (mean). Followup with cystoscopy and urine cytology.	Age (median), years: 65 vs. 67 Male: 85.0% vs. 87.0% Race: Not reported Smoking status: 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% Grade: G1: 33.3% vs. 20.4%; G2: 48.3% vs. 66.7%; G3: 11.7% vs. 7.4%; Unknown: 6.7% vs. 5.6% Functional Status: Not reported Size: < 1 cm: 45% vs. 50%; 1- 3 cm: 40% vs. 46%; 3-5 cm: 13% vs. 4%; > 5 cm: 17% vs. 0% Number of tumors: 1: 47% vs. 63%; 2-4: 38% vs. 22%; ≥ 5: 12% vs. 11%
Gudjónsson, 2009[109]	Sweden Multi-center 1997 - 2004	A: Epirubicin, 80 mg (in 30 mL saline). Single installation within 24 hours of TURBT. (n = 102) B: TURBT only. No adjuvant therapy. (n = 117)	3.9 years (median), for all patients). 3.6 years (median) for patients without recurrence. Followup with cystoscopy and urine cytology.	Age (median), years: 71 vs. 72 Age (mean), years: 70 vs. 70 Male: 72.5% vs. 69.3% Race: Not reported Smoking status: 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% Grade: G1: 53.9% vs. 48.7%; G2: 39.2% vs. 44.4%; Unknown: 6.9% vs. 6.8% Functional Status: Not reported Number of tumors: 1: 44% vs. 46%; 2-3: 21% vs. 27%; ≥ 4: 33% vs. 26%

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Igawa, 1996[110]	JapanNumber centers not reported.Study years not reported.	A: Epirubicin, 20 mg (in 40 mL saline). Total 24 installations: First installation within 2 weeks of TURBT, once a month X 24 months. (n = 43)B: TURBT only. No adjuvant therapy. (n = 32)	20 months (median), all patients, (range 3-42).Followup with cystoscopy.	Population characteristics not reported according to treatment status.
Liu, 2006[168]	China Number centers not reported 1997 - 1998	A: Epirubicin, 80 mg (in 40 mL normal saline). Single installation within 6 hours of TURBT. (n = 14) B: Epirubicin, 40 mg. Total 16 - 18 installations: Every week for 6 ~ 8 weeks, then every month for 10 months. (n = 15) C: MMC, 40 mg. Total 16 - 18 installations: Every week for 6 ~ 8 weeks, then every month for 10 months. (n = 15)	5 years (all patients). Followup with cystoscopy and urine cytology.	Age (mean), years: 62.2 (overall) Male: Not reported Race: 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

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Melekos, 1992[111]	Greece Number centers not reported. Study years not reported.	A: Epirubicin, 50 mg (in 5 mL sterile saline). Total minimum 6 installations for all patients: First installation 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 installations). (n = 43) B: TURBT only. No adjuvant therapy. (n = 22)	Duration of followup not reported. Followup with cystoscopy and urine cytology.	Age (mean), years: 66.2 vs. 67.4 Male: 83.7% vs. 86.4% Race: Not reported Smoking status: 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% Grade: G1: 44.2% vs. 45.5%; G2: 44.2% vs. 41.0%; G3: 11.6% vs. 13.6% Functional Status: Not reported Multiplicity: Single: 69.8% vs. 72.7%; Multiple: 30.2% vs. 27.3%
Melekos, 1993[83]	Greece Number of centers not reported. Study years not reported.	A. Epirubicin, 50 mg (in 50 ml saline). Total installations 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)	50 months, overall. Followup with cystoscopy and urine cytology.	Age (mean), years: 66 vs. 68 Male: 84% vs. 84% Race: Not reported Smoking: Not reported Stage: Ta: 63% vs. 66%; T1: 37% vs 34% Grade: G1: 46% vs 41%; G2: 37% vs 44%; G3:16% vs 16% Tis: 4% vs 6% Functional Status: Not reported

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Oosterlinck, 1993[112]	Europe 36 centers 1986 - 1989	A: Epirubicin, 80 mg (in 50 mL physiological solution). Single installation minimum for each patient, within 6 hours after TURBT. For recurrence, repeat TURBT and repeat installation for each recurrence until maximum of 3 additional installations. (n = 194) B: Placebo. Sterile water, 50 mL. Single installation minimum for each patient, within 6 hours after TURBT. For recurrence, repeat TURBT and repeat installation for each recurrence until maximum of 3 additional installations. (n = 205)	2 years (average), overall. 4.5 years (maximum), overall. Followup with cystoscopy and urine cytology.	Reported for randomized groups (205 vs. 215) Age: Not reported % Male: Not reported Race: Not reported Smoking status: 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% Grade: G1: 38.0% vs. 50.7%; G2: 47.8% vs. 40.9%; G3: 11.7% vs. 7.0%; Gx: 2.4% vs. 1.4% Functional Status: Not reported Size: < 1 cm: 26.3% vs. 30.2%; < 3 cm: 58.5% vs. 54.0%; > 3 cm: 11.7% vs. 13.9%; Unknown: 3.4% vs. 2.3%
Rajala, 1999[114]	Finland 18 centers 1991 - 1994	A: Interferon-α-2b, 50 million units (in 100 mL physiological saline). Single intravesical installation immediately after TURBT. (n = 66) B: Epirubicin, 100 mg (in 100 mL physiological saline). Single intravesical installation immediately after TURBT. (n = 68)C: TURBT only. No adjuvant therapy. (n = 66)	2 years overall. Followup with cystoscopy and urine cytology.	Age: Not reported Male: 81.8% vs. 70.6% vs. 65.2 Race: Not reported Smoking status: 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% Grade: G1: 43.9% vs. 50.0% vs. 57.6%; G2: 43.9% vs. 26.8% vs. 31.8%; G3: 12.1% vs. 13.2% vs. 10.6% Functional Status: NR Multiplicity: Single tumor: 77.3% vs. 76.5% vs. 71.2%; Multiple tumors: 22.7% vs. 23.5% vs. 28.8%

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Rajala, 2002[113]	Finland 18 centers 1991 - 1994	A: Interferon-α-2b, 50 million units (in 100 mL physiological saline). Single intravesical installation immediately after TURBT. (n = 66) B: Epirubicin, 100 mg (in 100 mL physiological saline). Single intravesical installation immediately after TURBT. (n = 68) C: TURBT only. No adjuvant therapy. (n = 66)	72 months (median) all patients. Followup with 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: Not reported Smoking status: 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% Grade: G1: 43.9% vs. 50.0% vs. 57.6%; G2: 43.9% vs. 26.8% vs. 31.8%; G3: 12.1% vs. 13.2% vs. 10.6% Functional Status: Not reported Multiplicity: Single tumor: 77.3% vs. 76.5% vs. 71.2%; Multiple tumors: 22.7% vs. 23.5% vs. 28.8%
Saika, 2010[115]	Japan 25 centers 1995 - 2001	A. Epirubicin, 20 mg (in 40 mL physiological saline). Total 2 installations: 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 installations: 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)	44 months vs. 46 months vs. 42 months (median). Followup with cystoscopy.	Based on eligible patents (n = 257): Age (median), years: 69 vs. 69 vs. 71 Male: 81% vs. 89% vs. 88% Race: Not reported Smoking status: Not reported 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: Not reported

Author, Year	Setting and Study Years	Interventions (number analyzed for recurrence)	Duration of Followup and Method	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)
Shuin, 1994[172]	Japan 23 centers 1990 - 1993	A: Epirubicin, 30 mg (in 40 mL saline). Total 17 installations: 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 installations: Timing of first not specified; every 2 weeks X 3 months, then every 4 weeks for remainder of 1 year.	Overall duration of study was 43 months. Mean/median followup durations not reported. Followup method not described.	Age: < 40 years: 6% vs. 3% Age: 40-49 years: 3% vs. 9% Age: 50-59 years: 9% vs. 24% Age: 60-69 years: 25% vs. 21% Age: ≥ 70: 56% vs. 42% Male: 81% vs. 82% Race: Not reported Smoking status: Not reported Recurrent bladder cancer: All (recurrent only)Stage Ta: 69% vs. 64% Stage T1: 25% vs. 27% Stage unknown: 6% vs. 9% Grade G1: 50% vs. 39% Grade G2: 59% vs. 61% Functional status: Not reported

cm, centimeters; G1, Grade 1; G2, Grade 2; G3, Grade 3; Gx, Grade unknown; mg, milligrams; mL, milliliters; mm, millimeters; 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[100] (Journal of Urology)	A: Epirubicin, 50 mg (in 50 mL normal saline). Total 18 installations: 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 installations: 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 installations: 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[107] (British Journal of Urology)	A: Epirubicin, 50 mg (in 50 mL normal saline). Single installation immediately after TURBT. (n = 55) B: Epirubicin, 50 mg (in 50 mL normal saline). Total 18 installations: 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	

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Berrum-Svennung, 2008[108]	A: Epirubicin, 50 mg (in 50 mL saline). Single installation within 6 hours after TURBT. (n = 155) B: Placebo. Saline, 50 mL. Single installation 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[171]	A: Epirubicin, 30 mg (in 30 mL physiological saline). Total 19 installations: 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 installations: 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[109]	A: Epirubicin, 80 mg (in 30 mL saline). Single installation 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[110]	A: Epirubicin, 20 mg (in 40 mL saline). Total 24 installations: First installation 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	

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Liu, 2006[168]	A: Epirubicin, 80 mg (in 40 mL normal saline). Single installation within 6 hours of TURBT. (n = 14) B: Epirubicin, 40 mg. Total 16 - 18 installations: Every week for 6 ~ 8 weeks, then every month for 10 months. (n = 15) C: MMC, 40 mg. Total 16 - 18 installations: 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[111]	A: Epirubicin, 50 mg (in 5 mL sterile saline). Total minimum 6 installations for all patients: First installation 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 installations). (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	

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Melekos, 1993[83]	A. Epirubicin, 50 mg (in 50 mL saline). Total installations 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[112]	A: Epirubicin, 80 mg (in 50 mL physiological solution). Single installation minimum for each patient, within 6 hours after TURBT. For recurrence, repeat TURBT and repeat installation for each recurrence until maximum of 3 additional installations. (n = 194) B: Placebo. Sterile water, 50 mL. Single installation minimum for each patient, within 6 hours after TURBT. For recurrence, repeat TURBT and repeat installation for each recurrence until maximum of 3 additional installations. (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.	

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Rajala, 1999[114]	A: Interferon-α-2b, 50 million units (in 100 mL physiological saline). Single intravesical installation immediately after TURBT. (n = 66) B: Epirubicin, 100 mg (in 100 mL physiological saline). Single intravesical installation 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[113]	A: Interferon-α-2b, 50 million units (in 100 mL physiological saline). Single intravesical installation immediately after TURBT. (n = 66) B: Epirubicin, 100 mg (in 100 mL physiological saline). Single intravesical installation 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)		

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Saika, 2010[115]	A. Epirubicin, 20 mg (in 40 mL physiological saline). Total 2 installations: 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 installations: 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).	
Shuin, 1994[172]	A: Epirubicin, 30 mg (in 40 mL saline). Total 17 installations: 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 installations: 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; mg, milligrams; mL, milliliters; NS, not significant; TURBT, Transurethral resection of bladder tumor

Table 13. 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	3 trials, RR 0.90, 95% CI 0.72 to 1.11, I^2=0%	3 trials, RR 0.68, 95% CI 0.37 to 1.24,I^2=0%	5 trials, RR 0.63, 95% CI 0.50 to 0.79, I^2=40%	6 trials, RR 0.50, 95% CI 0.32 to 0.77, I^2=69%
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	6 trials, RR 0.68, 95% CI 0.53 to 0.88, I2=75%	4 trials, RR 0.71, 95% CI 0.39 to 1.29, 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	8 trials, RR 0.80, 95% CI 0.74 to 0.88, I^2 = 42%	5 trials, RR 1.03, 95% CI 0.72 to 1.46, I^2 = 0.0%
Epirubicin	No evidence	No evidence	9 trials, RR 0.66, 95% CI 0.56 to 0.77, I^2 = 54%	8 trials, RR 0.72, 95% CI 0.44 to 1.17, I^2 = 26%
Gemcitabine	1 trial, RR 0.50, 95% CI 0.13 to 2.00	1 trial, RR 1.00, 95% CI 0.06 to 15.81	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	No evidence	No evidence	2 trials, RR 0.34, 95% CI 0.16 to 0.72 and RR 0.58, 95% CI 0.37 to 0.93	No evidence

BCG, bacillus Calmette Guérin; CI, confidence interval; I^2, I-squared value; RR, risk ratio

Table 14. 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%	9 trials, RR 0.97, 95% CI 0.78 to 1.16, I^2=68%	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; I^2, I-squared value; MMC, Mitomycin C; RR, risk ratio

Table 15. Study characteristics for trials comparing doses, duration, and timing of administration

Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration of Followup and Cystoscopic Followup Method
BCG Trials				
Gruenwald, 1997[178] 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[152] 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
Irie, 2003[181] 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
Martinez-Pineiro, 2002[185] 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: NR
Martinez-Pineiro, 2005[186] 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: NR

Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration of Followup and Cystoscopic Followup Method
Morales, 1992[189] 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
Oddens, 2013[191] 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[128] 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[193] Bassi, 1992[223] (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: NR Method: NR

Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration of Followup and Cystoscopic Followup Method
Sengiku, 2013[196] 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
Witjes, 1993[125] Witjes, 1996[133] The Netherlands Multicenter 1987-1990	Histologically proven papillary pTa-pT1 transitional cell transitional cell carcinoma of the bladder with or without CIS	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.	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[174] 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
Ersoy, 2013[176] 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.

Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration of Followup and Cystoscopic Followup Method
Friedrich, 2007[131] 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
Huland, 1990[167] 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 installations. 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 installations. 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 installations. Every week X 20 weeks. D: Doxorubicin, 50 mg/50 ml. Total 42 installations. Every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year. For all groups: Installations 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[195] 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

Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration of Followup and Cystoscopic Followup Method
Tolley, 1996[99] 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
Doxorubicin Trials				
Akaza, 1987[93] 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 installation 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 NR Method: Cystoscopy and urinary cytology studies at 12-week intervals throughout study period
Flamm, 1990[177] 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
Matsumara, 1992[104] 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: NR

Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration of Followup and Cystoscopic Followup Method
Niijima, 1983[97] 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 installation within 1 week of TURBT. Twice weekly X 4 weeks (Total: 8 doses)	707/575	Duration: 5 years, maximum; Mean/Median NR Method: Cystoscopy and urinary cytology studies at 12-week intervals during the observation period.
Rubben, 1988[194] 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[199] 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

Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration of Followup and Cystoscopic Followup Method
Epirubicin Trials				
Ali-El-Dein, 1997[100] (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 installation 7 to 14 days after TURBT. Retained intravesically for 2 hours; Installations 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[107] (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.

Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration of Followup and Cystoscopic Followup Method
Hendricksen, 2008[179] 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[182] 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[183] 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

Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration of Followup and Cystoscopic Followup Method
Liu, 2006[168] 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 installation within 6 hours of TURBT. B: Epirubicin, 40 mg, intravesical installation every week for 6 ~ 8 weeks, then every month for 10 months. C: MMC, 40 mg, intravesical installation 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[187] 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[188] 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
Nomata, 2002[190] 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, s/p 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

Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration of Followup and Cystoscopic Followup Method
Okamura, 1998[192] 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[115] 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[197] 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
Turkeri, 2010[198] 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
Thiotepa Trials				
Koontz, 1981[121] (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

Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration of Followup and Cystoscopic Followup Method
Koontz, 1981[121] (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
Interferon alpha-2b Trials				
Hoeltl, 1991[180] 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
Giannakopoulos, 1998[123] Greece Unclear if single or multicenter Study years NR	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 (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 installation after histological verification of stage and grade; 48 - 72 hours after TURBT. Retained intravesically for 1 hour; patient position changed every 15 minutes. Installations 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.

Author, Year Setting Study Years	Inclusion Criteria	Interventions	Number Randomized/ Analyzed	Duration of Followup and Cystoscopic Followup Method
Malmström, 2002[184] Europe Multicenter Study years: NR	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 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: MMC, 40 mg (in 40 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 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[175] 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

ECOG = Eastern Cooperative Oncology Group; MMC = Mitomycin C; NMIBC = non-muscle-invasive bladder cancer; TCC = transitional cell carcinoma; TURBT = transurethral resection of the bladder tumor

Table 16. Results summary for trials comparing dosages, duration and timing of administration

Author, year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
BCG Trials					
Gruenwald, 1997[178] 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)
Hinotsu, 2011[152] 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)

Author, year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Irie, 2003[181] 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)	NR	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)
Martinez-Pineiro, 2002[185] 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)

Author, year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Martinez-Pineiro, 2005[186] 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[189] 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)

Author, year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Oddens, 2013[191] 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
Ojea, 2007[128] 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%

Author, year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Pagano, 1995[193] Bassi, 1992[223] (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
Sengiku, 2013[196] 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

Author, year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Witjes, 1993[125] Witjes, 1996[133] The Netherlands Multicenter 1987-1990	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.	Progression: 5% (7) vs. 6% (8)	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)		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)

Author, year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
MMC Trials					
Au, 2001[174] 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% (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 Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Ersoy, 2013[176] 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): NR vs. 34.8 (28.5-41.1)		NR
Friedrich, 2007[131] 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%

Author, year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Huland, 1990[167] Germany Multicenter 1983 - 1985	A: MMC, 20 mg/20 ml. Total 42 installations. 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 installations. 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 installations. Every week X 20 weeks. D: Doxorubicin, 50 mg/50 ml. Total 42 installations. Every 2 weeks X 1 year, then every 4 weeks X 1 year, then every 3 months X 1 year. For all groups: Installations 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%
Schwaibold, 1997[195] 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

Author, year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Tolley, 1996[99] 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.

Author, year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Doxorubicin Trials					
Akaza, 1987[93] 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 installation 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[177] 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%

Author, year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Matsumara, 1992[104] 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[97] 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 installation 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"

Author, year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Rubben, 1988[194] 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%
Ueda, 1992[199] 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)

Author, year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Epirubicin Trials					
Ali-El-Dein, 1997[100] (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 installation 7 to 14 days after TURBT. Retained intravesically for 2 hours; Installations 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 installations: 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)
Ali-El-Dein, 1997[107] (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.

Author, year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Hendricksen, 2008[179] 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[182] 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)

Author, year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Kuroda, 2004[183] 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%

Author, year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Liu, 2006[168] China Unclear if single or multicenter 1997 - 1998	A: Epirubicin, 80 mg (in 40 ml normal saline). Single intravesical installation within 6 hours of TURBT. B: Epirubicin, 40 mg, intravesical installation every week for 6 ~ 8 weeks, then every month for 10 months. C: MMC, 40 mg, intravesical installation 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
Masters, 1999[187] 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)

Author, year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Mitsumori, 2004[188] 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)

Author, year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Nomata, 2002[190] 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) Gross hematuria (grade 1-3): 42% (23/55) vs. 36% (25/70)
Okamura, 1998[192] 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 Gross hematuria: 0.7% overall Withdrawal due to adverse events: 1.4% (2/138) Local toxicity: No difference between groups
Saika, 2010[115] 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)

Author, year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Serretta, 2010[197] 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
Turkeri, 2010[198] 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

Author, year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Thiotepa Trials					
Koontz, 1981[121] (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)
Koontz, 1981[121] (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)

Author, year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Interferon alpha-2b Trials					
Hoeltl, 1991[180] 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
Giannakopoulos, 1998[123] Greece Unclear if single or multicenter Study years NR	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 installation after histological verification of stage and grade; 48 - 72 hours after TURBT. Retained intravesically for 1 hour; patient position changed every 15 minutes. Installations 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.

Author, year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Malmström, 2002[184] Europe Multicenter Study years: NR	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: MMC, 40 mg (in 40 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 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%)

Author, year Setting Study Years	Interventions	Progression	Recurrence	Mortality	Adverse Events
Multiple Drugs					
Bouffioux, 1995[175] 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

MMC = Mitomycin C; TURBT = transurethral resection of the bladder tumor

Table 17. 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, sex, stage of disease, functional status)
Babjuk, 2005[202]	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	24 months, followup with 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[206]	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	12 months, followup cystoscopy 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[207] (also Denzinger 2007a, Denzinger 2007b)	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	Mean 21 months, followup cystoscopy method not reported	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% 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

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, sex, stage of disease, functional status)
Geavlete, 2010[208]	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	6 weeks, followup with white light cystoscopy	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
Geavlete, 2011[209]	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	2 years, followup with 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[211]	DenmarkTwo centersStudy 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 BCB (10 in arm A and 11 in arm B)	12 months, followup with white light cystoscopy	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
Karaolides, 2012[212]	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	18 months, followup with white light cystoscopy	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

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, sex, stage of disease, functional status)
Kriegmair, 2002[213]	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	10 to 14 days, followup cystoscopy 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[215] Italy	Italy Two centers 2009-2010	A: Narrow band imaging cystoscopy and TURBT (n=76) B: White light cystoscopy and TURBT (n=72) Additional treatments not reported	1 year, followup with 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[216]	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	12 months, followup cystoscopy 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[217] (also Daniltchenko, 2005[203])	Germany Two centers 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	60 months (median 42 vs. 39 months), followup 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
Schumacher, 2010[218]	SwedenMulticenter2002-2005	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	12 months, followup with 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

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, sex, stage of disease, functional status)
Stenzl, 2010[219] (also Grossman 2012[210]) US, Canada, and Europe RCT	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	9 months, followup with 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[220]	Italy Two centers 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	12 months, followup with 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

HAL = hexaminolevulinate; TURBT = transurethral resection of the bladder tumor

Table 18. Fluorescent cystoscopy results summary

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
5-ALA fluorescent cystoscopy				
Babjuk, 2005[202]	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	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)	Progression through 15 months: 8.3% (5/60) vs. 8.1% (5/62)	
Filbeck, 2002[207] (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) All patients received intravesical prophylaxis based on AUA guidelines according to number of tumors, stage, and grade	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 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)	Patients with T1 high grade lesions on initial cystoscopy (multifocal, concomitant CIS, >3 cm, n=21 and 25) 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)	Patients with T1 high grade lesions on initial cystoscopy (multifocal, concomitant CIS, >3 cm, n=21 and 25) Bladder cancer-specific survival after cystectomy: No difference (data not reported)

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Kriegmair, 2002[213]	A: White light and 5-ALA fluorescent cystoscopy with TURBT (n=52) B: White light cystoscopy with TURBT (n=49) Additional treatments not reported	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)		
Riedl, 2001[217] (also Daniltchenko, 2005[203])	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	Recurrence, through end of followup: 59% (30/51) vs. 75% (38/51)	Progression: 7.8% (4/51) vs. 18% (9/51), p=0.04	
Schumacher, 2010[218]	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	Recurrence-free at 12 months (n=141 and 138): 55% vs. 56% for all patients (p=0.69, 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)
Stenzl, 2011[220]	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	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)	

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
HAL fluorescent cystoscopy				
Dragoescu, 2011[206]	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	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)		
Geavlete, 2010[208]	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	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		
Geavlete, 2011[209]	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	Recurrence at 3 months: 7.2% (9/125) vs. 16% (18/114), p=0.003Recurrence at 6 months: 12% (15/125) vs. 22% (25/114), p=0.003Recurrence at 12 months: 22% (27/125) vs. 32% (37/114), p=0.005Recurrence at 24 months, overall: 31% (39/125) vs. 46% (52/114), p=0.001	Progression: 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)	

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Hermann, 2011[211]	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 BCB (10 in arm A and 11 in arm 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[212]	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	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)	Progression to MIBC: 0% (0/41) vs. 4.4% (2/45)	
O'Brien, 2013[216]	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	Recurrence at 3 months: 20% (17/86) vs. 17% (14/82), p=0.7 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 MMC)		Mortality: 5.4% (7/129) vs. 0.8% (1/120)

Author, Year	Interventions (number analyzed for recurrence)	Recurrence	Progression	Mortality
Stenzl, 2010[219] (also Grossman 2012[210])US, Canada, and EuropeRCT	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	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-free through long-term followup (median 53 vs. 55 months): 38% (97/255) vs. 32% (83/261), p=0.14	Progression to muscle invasion through 9 months: 1.8% (5/271) vs. 1.8% (5/280)	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 monthsBladder cancer mortality at long-term followup: 2.2% (6/271) vs. 2.9% (8/280) known bladder cancer deaths
Narrow band imaging cystoscopy				
Naselli, 2012[215] Italy	A: Narrow band imaging cystoscopy and TURBT (n=76) B: White light cystoscopy and TURBT (n=72) Additional treatments not reported	Recurrence at 3 months: 3.9% (3/76) vs. 17% (12/72), unadjusted OR 0.24 (95% CI 0.07 to 0.81), adjusted OR 0.26 (95% CI 0.07 to 0.75) Recurrence through 1 year: 32% (24/76) vs. 51% (37/72), unadjusted OR 0.62 (95% CI 0.41 to 0.92), adjusted OR 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		

HAL = hexaminolevulinate; 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 19) 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 0.58 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, though 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 for quantitative NMP22. 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 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[220] 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 13, 14). Versus 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 (RRs 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 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).[100,171,172]

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, performance status, or comorbidities on estimates of effectiveness of intravesical therapies was not available.

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 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 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 (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). 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).[200]

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.[224-226] 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[227,228] 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.[220] 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,[229,230] 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.[231-233] Like our review, a 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.[234] Our findings are also consistent with prior systematic reviews that found BCG associated with decreased risk of bladder cancer versus epirubicin,[235] that the evidence on intravesical gemcitabine is limited,[236] and that the optimal dose and duration of intravesical therapy cannot be determined based on the available evidence.[237]

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, 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 20 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.

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,[13,238] 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.[239-241] 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.”[241] 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.[242,243] 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.[221]

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 (six 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 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, 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 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 19. Summary of evidence by key question

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 0.70 (95% CI 0.62 to 0.77) and specificity 0.81 (95% CI 0.75 to 0.87), based on 15 studies, for a positive likelihood ratio of 3.75 (95% CI 2.73 to 5.16) and negative likelihood ratio of 0.37 (95% CI 0.28 to 0.48)
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 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)
Qualitative BTA: Sensitivity and specificity	Moderate	Sensitivity was 0.64 (95% CI 0.57 to 0.72, 17 studies) and specificity 0.80 (95% CI 0.75 to 0.84, 17 studies), for a positive likelihood ratio of 3.26 (95% CI 2.61 to 4.08) and negative likelihood ratio of 0.44 (95% CI 0.36 to 0.54)
Quantitative BTA: Sensitivity and specificity	Low	Sensitivity was 0.66 (95% CI 0.53 to 0.77) and specificity 0.72 (95% CI 0.59 to 0.83), based on three studies, for a positive likelihood ratio of 2.38 (95% CI 1.69 to 3.35) and negative likelihood ratio of 0.47 (95% CI 0.36 to 0.62)
FISH: Sensitivity and specificity	Low	Sensitivity was 0.69 (95% CI 0.53 to 0.82) and specificity 0.89 (95% CI 0.73 to 0.96), based on six studies, for a positive likelihood ratio of 6.10 (95% CI 2.37 to 15.7) and negative likelihood ratio of 0.35 (95% CI 0.21 to 0.56)

Key Question Outcome	Strength of Evidence Grade	Conclusion
Immunocyt: Sensitivity and specificity	Low	Sensitivity was 0.77 (95% CI 0.57 to 0.90) and specificity 0.77 (95% CI 0.71 to 0.82), based on four studies, for a positive likelihood ratio of 5.59 (95% 3.32 to 9.40) and negative likelihood ratio of 0.47 (95% CI 0.32 to 0.69)
CxBladder: Sensitivity and specificity	Low	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)
Quantitative NMP22 versus qualitative BTA: Sensitivity and specificity	Moderate	Based on 5 studies, there was no difference between quantitative NMP22 versus qualitative BTA in sensitivity (0.72, 95% CI 0.67 to 0.77 vs. 0.71, 95% CI 0.65 to 0.76, for a difference of 0.01, 95% CI -0.05 to 0.08) or specificity (0.78, 95% CI 0.65 to 0.87 vs. 0.78, 95% CI 0.65 to 0.87, for a difference of 0.002, 95% CI -0.05 to 0.08)
Other head-to-head urinary biomarkers	Insufficient	comparisons of urinary biomarkers was too sparse to draw reliable conclusions regarding diagnostic accuracy
Various urinary biomarkers plus cytology versus the urinary biomarker alone: Sensitivity and specificity	Moderate	Ten studies found sensitivity of various urinary biomarkers plus cytology associated with higher sensitivity than the urinary biomarker alone (0.84, 95% CI 0.76 to 0.90 vs. 0.69, 95% CI 0.58 to 0.78, for a difference of 0.15, 95% CI 0.09 to 0.21), with no difference in specificity
a. 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?		
Effects of tumor stage: Sensitivity	High	Across urinary biomarkers, sensitivity increased with higher tumor stage. Evidence was most robust for quantitative NMP22 (eight studies) and qualitative BTA (14 studies). Sensitivity for CIS tumors was intermediate between Ta and T1
Effects of tumor grade: Sensitivity	High	Across urinary biomarkers, sensitivity increased with higher tumor grade. Evidence was most robust for quantitative NMP22 (eight studies) and qualitative BTA (15 studies)
Effects of tumor size: Sensitivity	Low	Two studies found sensitivity was higher for larger (>1 cm or >2 cm) 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 Outcome	Strength of Evidence Grade	Conclusion
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	Insufficient	No studies
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	Low	There was no difference in risk of all-cause mortality vs. no intravesical therapy (3 trials, RR 0.90, 95% CI 0.72 to 1.11, I^2=0%)
Bladder cancer-specific mortality	Low	The effect on bladder cancer-specific mortality was not statistically significant (3 trials, RR 0.68, 95% CI 0.37 to 1.24,I^2=0%) vs. no intravesical therapy
Recurrence	Moderate	BCG was associated with decreased risk of bladder cancer recurrence (5 trials, RR 0.63, 95% CI 0.50 to 0.79, I^2=40%)
Progression	Moderate	BCG was associated with decreased risk of bladder cancer progression (6 trials, RR 0.50, 95% CI 0.32 to 0.77, I^2=69%) versus no intravesical therapy
MMC vs. no intravesical therapy		
All-cause mortality	Low	There was no difference in risk of all cause-mortality (1 trial, HR 1.17, 95% CI 0.89 to 1.53) vs. no intravesical therapy
Bladder cancer-specific mortality	Low	The effects on bladder cancer-specific mortality were not statistically significant (1 trial, HR 0.71, 95% CI 0.34 to 1.46) vs. no intravesical therapy
Recurrence	Moderate	MMC was associated with decreased risk of bladder cancer recurrence vs. no intravesical therapy (6 trials, RR 0.68, 95% CI 0.53 to 0.88, I2=75%)
Progression	Low	The effects on bladder cancer progression were not statisticaly significant (4 trials, RR 0.71, 95% CI 0.39 to 1.29, 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
Bladder cancer-specific mortality	Low	Doxorubicin was associated with no clear effects on bladder cancer-specific mortality (1 trial) vs. no intravesical therapy

Key Question Outcome	Strength of Evidence Grade	Conclusion
Recurrence	Moderate	Doxorubicin was associated with decreased risk of bladder cancer recurrence vs. no intravesical therapy (8 trials, RR 0.80, 95% CI 0.74 to 0.88, I^2 = 42%)
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 0.66, 95% CI 0.56 to 0.77, I^2 = 54%) vs. no intravesical therapy
Progression	Low	Epirubicin was associated with a non statistically significant effect on bladder cancer progression (8 trials, RR 0.72, 95% CI 0.44 to 1.17, I^2 = 26%)
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 were very imprecise (RR 1.00, 95% CI 0.06 to 15.81)
Recurrence	Low	One trial found no difference between gemcitabine versus 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 (IFN-alpha) was associated with and no difference in risk of bladder-cancer specific mortality (1 trial, RR 1.00, 95% CI 0.15 to 6.75)
Recurrence	Low	Interferon-alpha was associated with a non statistically significant difference 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%)
Progression	Low	Interferon-alpha (IFN-alpha) was associated with decreased risk of bladder cancer progression (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 (IFN-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)
Progression	Low	Interferon-gamma (IFN-gamma) was associated with no difference in risk of bladder cancer progression (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 versus no intravesical therapy in two trials (RR 0.34, 95% CI 0.16 to 0.72 and RR 0.58, 95% CI 0.37 to 0.93)
a. What is the comparative effectiveness of various chemotherapeutic or immunotherapeutic agents, as monotherapy or in combination?		
BCG versus MMC		
All-cause mortality	Moderate	There was no difference in risk of all-cause (7 trials, RR 0.94, 95% CI 0.83 to 1.06, I^2=0%)
Bladder cancer- specific mortality	Moderate	There was no difference in risk of bladder cancer-specific mortality (5 trials, RR 0.77, 95% CI 0.54 to 1.10, I^2=0%

Key Question Outcome	Strength of Evidence Grade	Conclusion
Recurrence	Low	There were no differences between BCG versus MMC in risk of bladder cancer recurrence (9 trials, RR 0.97, 95% CI 0.78 to 1.16, I^2=68%)
Progression	Moderate	There was no difference in risk of or progression (7 trials, RR 0.88, 95% CI 0.66 to 1.17, I^2=18%)
BCG 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		
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 versus doxorubicin (2 trials, RR 0.31, 95% CI 0.16 to 0.6 and RR 0.75, 95% CI 0.6 to 0.88), but there were no difference in risk of all-cause mortality (2 trials, RR 0.40, 95% CI 0.1 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)
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%)
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%)
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%)
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 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		

Key Question Outcome	Strength of Evidence Grade	Conclusion
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, though 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)
Recurrence	Insufficient	Evidence from three trials was insufficient to determine 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)
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)
Quality of life	Low	There were no differences in risk of quality of life (1 trial)
BCG 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)
BCG vs. alternating BCG and interferon alpha-2b		
Recurrence	Low	BCG was associated with reduced risk of bladder cancer recurrence (1 trial, RR 0.42, 95% CI 0.30 to 0.59)
BCG 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 .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, progression	Low	One trial found reduced risk of bladder cancer recurrence (RR 0.38, 95% CI 0.19 to 0.76) but the difference in risk of progression was not statistically significant (RR 0.42, 95 5CI 0.19 to 0.76)
MMC vs. doxorubicin		
Recurrence, progression	Low	There was no difference in risk of bladder cancer recurrence (4 trials, RR 1.02, 95% CI 0.86 to 1.21, I^2=30%), but MMC was associated with decreased risk of bladder cancer progression (3 trials, RR 0.48, 95% CI 0.26 to 0.90, I^2 = 53%)
MMC vs. epirubicin		
Recurrence	Low	There was no difference in risk of bladder cancer recurrence in one trial (RR 1.16, 95% CI 0.52 to 2.58)
MMC vs. gemcitabine		

Key Question Outcome	Strength of Evidence Grade	Conclusion
Recurrence, progression	Low	In one 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	MMC was associated with no difference 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 one trial (RR 1.61, 95% CI 0.97 to 2.67)
Doxorubin 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 difficerence 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).
Progression, noncancer mortality, cancer-specific mortality	Insufficient	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.
Epirubicin vs. interferon-alpha		
Recurrence	Low	Epirubicin was associated with decreased risk of bladder cancer recurrence in one trial (RR 0.67, 95% CI 0.49 to 0.91)
b. 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 policy
c. 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	Insufficient	No studies
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 Outcome	Strength of Evidence Grade	Conclusion
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, though there was some inconsistency between trials. Standard therapy was associated with increased risk of local and systemic adverse events versus lower dose BCG
Maintenance vs. induction BCG: Recurrence, progression, adverse events	Low	Two trials found more prolonged courses of BCG associated with decreased risk of bladder cancer recurrence versus 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 T1G3 or multiple Ta-T1/G1-G3 tumors found no difference between 1 versus 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 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 vs. nonoptimized administration: Recurrence, adverse events	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
Doxorubicin eight weeks vs. two 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 week) or long (two 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

Key Question Outcome	Strength of Evidence Grade	Conclusion
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 versus 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
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 one trial of patients with higher-risk NMIBC. There were no differences in risk of local adverse events
Epirubicin more versus 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 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
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 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 versus no additional maintenance therapy. There were no clear differences in local or systemic adverse events
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	Strength of Evidence Grade	Conclusion
Mortality, recurrence, progression	Low	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
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
a. Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?	Insufficient	No studies
b. Does the comparative effectiveness differ according to the treatment used (i.e., specific chemotherapeutic or immunotherapeutic agents and/or TURBT)?	Insufficient	No studies
c. Does the comparative effectiveness differ according to the length of surveillance intervals?	Insufficient	No studies
d. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, or ethnicity?	Insufficient	No studies
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 versus white light cystoscopy in risk of mortality (three trials, RR 1.27, 95% CI 0.56 to 2.87, I^2=41%)
Recurrence	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, eight trials, RR 0.56, 95% CI 0.34 to 0.94, I^2=72%), intermediate-term (3 months to <1 year, four trials, RR 0.71, 95% CI 0.53 to 0.95, I^2=26%), and long-term followup (≥1 year, 11 trials, RR 0.80, 95% CI 0.67 to 0.94, I^2=58%), but findings were inconsistent and potentially susceptible to performance bias (due to failure to blind the initial cystoscopy) and publication bias

Key Question Outcome	Strength of Evidence Grade	Conclusion
Progression	Moderate	There was no difference between fluorescent versus white light cystoscopy in risk of progression to muscle invasive bladder cancer (six trials, RR 0.83, 95% CI 0.53 to 1.28, 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% 0.07 to 0.81) in one trial
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 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
Fluorescent vs. white light cystoscopy: False positives	Low	There were no clear differences between fluorescent cystoscopy versus white light cystoscopy in risk of false-positives in two trials
Fluorescent vs. white light cystoscopy: Renal and genitourinary adverse events	Low	There were no clear differences between fluorescent cystoscopy versus white light cystoscopy in risk of renal and genitourinary adverse events in two trials
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 of reported chemical 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 for local adverse events, insufficient for systemic adverse events	Evidence on harms 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
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%), chemical 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

Key Question Outcome	Strength of Evidence Grade	Conclusion
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%) versus MMC
BCG vs. BCG plus MMC given sequentially		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)
Discontinuation of therapy	Low	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%)
BCG plus MMC given sequentially vs. MMC		
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 chemical cystitis (1 trial, RR 1.30, 95% CI 0.88 to 1.93)
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)
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 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
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)
Discontinuation of therapy	Insufficient	Results were mixed for discontinuation of intravesical therapy (2 trials, data not pooled)
Systemic adverse events	Low	BCG was associated with increased risk chemical 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 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%)
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), chemical 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%)

Key Question Outcome	Strength of Evidence Grade	Conclusion
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)
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)
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 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 1319)
Systemic adverse events	Low	There was no difference in risk of fever (1 trial, RR 4.82, 95% CI 0.25 to 94)
BCG 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), cystitis (1 trial, RR 18, 95% CI 1.11 to 306)
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 versus doxorubicin on risk of local adverse events, based on inconsistent results from four trials
MMC vs. epirubicin		
Local adverse events	Low	One small trial found no difference between MMC versus epirubicin 80 mg in risk of urinary symptoms
MMC vs. interferon-alpha		
Local adverse events	Low	One trial found MMC associated with greater risk of hematuria versus interferon-alpha (RR 2.00, 95% CI 1.09 to 3.65) and no difference in risk of dysuria or urinary frequency
Systemic adverse events	Low	One trial found MMC associated with decreased risk of fever (RR 0.13, 95% CI 0.03 to 0.55)
MMC vs. gemcitabine		

Key Question Outcome	Strength of Evidence Grade	Conclusion
Local adverse events	Low	One trial found MMC 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
Systemic adverse events	Low	One trial found no difference in risk of fever
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?		
Adverse effects	Insufficient	No studies

BCG, bacillus Calmette–Guérin; CI, confidence interval; IFN, interferon; MMC, mitomycin C; RR, relative risk; TURBT, transurethral resection of bladder tumor

Table 20. Post-test probability of bladder cancer using different biomarkers

Urinary Biomarker	Pretest Probability of Bladder Cancer	Positive Likelihood Ratio	Post-Test Probability of HCC Following a Positive Test	Negative Likelihood Ratio	Post-Test Probability of HCC Following a Negative Test
Quantitative NMP22	5%	3.75 (2.73 to 5.16)	16%	0.37 (0.28 to 0.48)	1,9%
	20%		48%		8.5%
Qualitative NMP22	5%	4.89 (3.23 to 7.40)	20%	0.48 (0.33 to 0.71)	2.5%
	20%		55%		11%
Qualitative BTA	5%	3.26 (2.61 to 4.08)	15%	0.44 (0.36 to 0.54)	2.3%
	20%		45%		9.9%
Quantitative BTA	5%	2.38 (1.69 to 3.35)	11%	0.47 (0.36 to 0.62)	2.4%
	20%		37%		10%
FISH	5%	6.10 (2.37 to 15.7)	24%	0.35 (0.21 to 0.56)	1.8%
	20%		60%		8.0%
Immunocyt	5%	5.59 (3.32 to 9.40)	23%	0.47 to 0.69)	2.4%
	20%		58%		10%

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 is associated with a high rate of adverse events.

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Abbreviations

Abbreviation	Term
AHRQ	Agency for Healthcare Research and Quality
BCG	bacillus Calmette-Guèrin
CER	Comparative Effectiveness Review
CI	Confidence interval
ECOG	Eastern Cooperative Oncology Group
EMDA	Electromotive drug administration
EPC	Evidence-based Practice Center
FDA	US Food and Drug Administration
HAL	Hexaminolevulinate
IFN	Interferon
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
RCT	Randomized controlled trial
ROC	Receiver operating characteristic
SIP	Scientific information packet
SRC	Scientific Research Center
TEP	Technical Expert Panel
TOO	Task Order Officer
TURBT	Transurethral resection of the bladder tumor
U.S.	United States
WHO	World Health Organization