Comparative Effectiveness Review
Number 152

Effective Health Care Program

# Treatment of Nonmetastatic Muscle-Invasive Bladder Cancer

## *Executive Summary*

## Background

### Nature and Burden of Nonmetastatic Muscle-Invasive Bladder Cancer

Bladder cancer is the 4th most commonly diagnosed cancer in men and the 10th most commonly diagnosed cancer in women in the United States.[1] In 2013, the American Cancer Society estimated that there would be 72,570 new cases of bladder cancer that year (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] Bladder cancer occurs primarily in men age 60 and older, and roughly twice as frequently in white compared with black men,[2] although the number of deaths due to bladder cancer is similar for men of both races, presumably due to delayed diagnosis in black men.

Bladder cancer remains 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, taking into account diagnostic testing, management, and long-term followup.[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.

### Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare.ahrq.gov/reports/final.cfm**.

Bladder cancers that have not invaded the bladder smooth-muscle layer (staged according to the TNM [tumor, node, metastasis] classification as stages Tis, Ta, and T1) are grouped as non–muscle-invasive bladder cancers. Stage classification T2 cancers are muscle

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invasive, and higher stage cancers invade beyond the muscle layer into surrounding fat (stage classification T3 bladder cancer). Stage T4a cancers, which involve the prostate, vaginal wall, or uterus, are still considered localized because the bladder is contiguous with these structures. Stage T4b cancer, in which the tumor has spread to the pelvis or abdominal wall; bladder cancer involving the lymph nodes (N >0); and metastatic bladder cancer (stage M1) are considered nonlocalized. They are not amenable to potentially curative treatments and are outside the scope of this review. Approximately 25 percent of newly diagnosed bladder cancers present as stage 2 or higher tumors.[5] Once bladder cancer invades muscle, it can quickly progress and metastasize, and is associated with a poor prognosis.

## Interventions and Outcomes for 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 patient's age and general health, and other factors. A variety of molecular and other biomarkers—p53, mTOR pathway genes, MRE11, BRCA1, ERCC1, MDR1, ET-1, and others—have also been evaluated for their prognostic value and to potentially inform selection of treatments.[6]

For nonmetastatic muscle-invasive bladder cancer, the gold standard treatment option is radical cystectomy combined with neoadjuvant (administered prior to cystectomy) systemic chemotherapy with combination gemcitabine and cisplatin.[7] Other commonly used chemotherapeutic regimens are methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC); cisplatin, methotrexate, and vinblastine (CMV); and gemcitabine plus carboplatin. These treatments are approved by the U.S. Food and Drug Administration (FDA) and clinically available in the United States. Other chemotherapy regimens and adjuvant (administered after cystectomy) systemic chemotherapy have also been evaluated. Selection of therapy is complicated by the fact that patients with bladder cancer are often older and have multiple medical comorbidities. Therefore, factors such as performance status and renal function must be considered in relation to treatment effectiveness and adverse effects. For example, medically frail patients with baseline renal insufficiency may not be ideal candidates for cisplatin-based therapy because of potential renal toxicity.

Regional lymph node dissection in conjunction with cystectomy or partial cystectomy is recommended because it can be used to diagnose clinically nonevident lymph node metastases and may be associated with improved cancer-specific survival, but it may be underused.[7-10] Similarly, cystectomy appears to be underused for nonmetastatic muscle-invasive bladder cancer,[11] in part because removal of the urinary bladder necessitates reconstruction with a urinary diversion, and there is interest in bladder-sparing options that combine maximal transurethral resection of bladder tumor (TURBT), chemotherapy, and/or radiation therapy. Several modalities of radiation therapy have been evaluated, including external beam radiation therapy and interstitial radiation therapy (brachytherapy). These alternative treatments are generally recommended only for carefully selected, well-informed patients because of the need for continued surveillance and invasive diagnostic procedures, and the risk of eventual cystectomy.[7] The comparative effectiveness of these treatments or their combinations is uncertain.

## Rationale for Evidence Review

Systematic reviews of the comparative effectiveness of treatment options for muscle-invasive bladder cancer have primarily focused on the effectiveness of neoadjuvant and adjuvant chemotherapy in patients undergoing radical cystectomy. A systematic review that also evaluates the effectiveness of bladder-preserving therapies and regional lymph node dissection, and includes recently published evidence focusing on treatments used in current practice, may be useful for developing updated clinical guidelines for muscle-invasive bladder cancer.

## Scope and Key Questions

This topic was nominated for review by the American Urological Association and focuses on treatment of nonmetastatic muscle-invasive bladder cancer. 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, and health outcomes we examined.

**Key Question 1**. For patients with nonmetastatic muscle-invasive bladder cancer, what is the effectiveness of bladder-preserving treatments (chemotherapy, external beam or interstitial radiation therapy, partial cystectomy, and/or maximal transurethral resection of bladder tumor) for decreasing mortality or improving other outcomes (e.g., recurrence, metastasis, quality of life, functional status) compared with cystectomy alone or cystectomy in combination with chemotherapy?

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 patient characteristics, such as age, sex, race/ethnicity, performance status, or medical comorbidities such as chronic kidney disease?

c. What is the comparative effectiveness of various combinations of agents and/or radiation therapy used for bladder-preserving chemotherapy?

d. What is the effectiveness of different bladder-preserving treatments (chemotherapy, external beam or interstitial radiation therapy, partial cystectomy, and/or maximal transurethral resection of bladder tumor) compared with one another?

**Key Question 2**. For patients with clinically nonmetastatic muscle-invasive bladder cancer that is treated with cystectomy, does regional lymph node dissection improve outcomes compared with cystectomy alone?

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 extent of the regional lymph node dissection (e.g., as measured by the number of lymph nodes removed or the anatomic extent of dissection)?

**Key Question 3**. For patients with nonmetastatic muscle-invasive bladder cancer that is treated with cystectomy, does neoadjuvant or adjuvant chemotherapy improve outcomes compared with cystectomy alone?

a. What is the comparative effectiveness of various combinations of agents used for neoadjuvant or adjuvant chemotherapy?

b. Does the comparative effectiveness of various combinations of agents used for neoadjuvant or adjuvant chemotherapy differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?

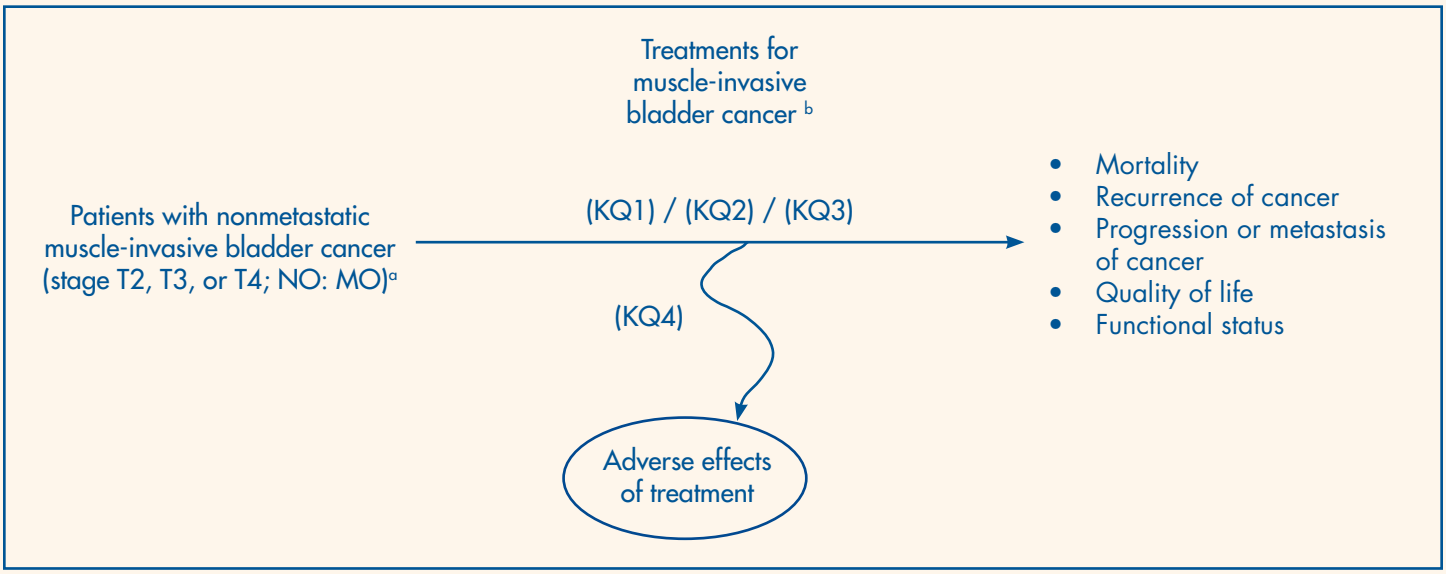
c. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, race/ethnicity, performance status, or medical comorbidities such as chronic kidney disease?

d. Does the comparative effectiveness of neoadjuvant or adjuvant chemotherapy differ according to dosing frequency and/or the timing of its administration relative to cystectomy?

**Key Question 4**. What are the comparative adverse effects of treatments for nonmetastatic muscle-invasive bladder cancer?

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

**Figure A. Analytic framework**




[a]Questions on diagnostic testing and identification of patients with muscle-invasive bladder cancer are addressed in a complementary review of non–muscle-invasive bladder cancer (Chou R, Buckley D, Fu R, Gore J, Gustafson K, Griffin J, Grusing S, Selph S. Emerging Approaches to Diagnosis and Treatment of Non–Muscle-Invasive Bladder Cancer. Comparative Effectiveness Review No. 153. [Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2012-00014-I.] AHRQ Publication No. 15-EHC017-EF. Rockville, MD: Agency for Healthcare Research and Quality. To be published. www.effectivehealthcare.ahrq.gov/reports/final.cfm.).
[b]Treatments include bladder-preserving chemotherapy and/or radiation therapy, partial cystectomy, maximal transurethral resection of bladder tumor (KQ 1); regional lymph node dissection (KQ 2); neoadjuvant or adjuvant chemotherapy (KQ 3).
KQ = Key Question. Cancer stages shown are the TNM (tumor, node, metastastis) classification.

## 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] 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 to October 2014), Cochrane Central Register of Controlled Trials (through September 2014), Cochrane Database of Systematic Reviews (through September 2014), Health Technology Assessment (through Third Quarter 2014), National Health Sciences Economic Evaluation Database (through Third Quarter 2014), and Database of Abstracts of Reviews of Effects (through Third Quarter 2014) to capture both published and gray literature. We searched for unpublished studies in clinical trial registries (ClinicalTrials.gov, Current Controlled Trials, ClinicalStudyResults.org and the World Health Organization International Clinical Trials Registry Platform) and regulatory documents (Drugs@FDA.gov and FDA Medical Devices Registration and Listing). Reference lists of relevant studies and previous systematic reviews were hand-searched for additional studies. Scientific information packets were solicited from drug and device manufacturers and via a notice published in the Federal Register.

Literature search updates were performed while the draft report was posted for public comment. Literature identified during the update search was assessed using the same process of dual review as used for studies identified during the initial searches. Pertinent new literature meeting inclusion criteria was incorporated before the final submission of the report.

### Study Selection

We developed criteria for inclusion and exclusion of studies based on the Key Questions and populations, interventions, comparators, outcomes, timing, and settings (PICOTS) approach, in accordance with the AHRQ Methods Guide.[12]

Inclusion and exclusion criteria are summarized below. Abstracts were reviewed by two investigators, and all citations deemed appropriate for inclusion by at least one of the reviewers were retrieved. Two investigators independently reviewed all full-text articles for inclusion. Discrepancies were resolved by discussion and consensus.

**Population and Condition of Interest**. For all Key Questions, we included studies of adults with node-negative nonmetastatic muscle-invasive bladder cancer. This includes TNM staging of T2, T3, or T4a, N0, and M0.

**Interventions, Comparators, and Study Designs of Interest**. For Key Questions 1 and 4, we included studies of bladder-preserving chemotherapy, radiation therapy (external beam or interstitial radiation therapy), partial cystectomy, or maximal TURBT compared with radical cystectomy alone, radical cystectomy in combination with chemotherapy, or other included bladder-preserving approaches.

For Key Question 2, we included studies of regional lymph node dissection in conjunction with radical cystectomy or partial cystectomy compared with radical cystectomy without lymph node dissection, and studies of more extensive versus more limited regional lymph node dissection.

For Key Questions 3 and 4, we included studies of radical cystectomy plus neoadjuvant and/or adjuvant chemotherapy versus radical cystectomy alone. We focused on chemotherapeutic regimens recommended in clinical practice guidelines[7] and currently used in clinical practice: carboplatin and gemcitabine, cisplatin and gemcitabine, CMV, and MVAC. However, we also included trials of other cisplatin-based combination regimens. We excluded trials that evaluated chemotherapy with a single agent.

For Key Questions 1, 3, and 4, we included randomized controlled trials (RCTs), nonrandomized controlled clinical trials, and nonrandomized cohort studies with concurrent comparators when RCTs were not available. 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**. Clinical outcomes evaluated were mortality, recurrence of bladder cancer, progression or metastasis of bladder cancer, quality of life, and functional status. For harms (Key Question 4), we included studies reporting complications or adverse effects related to treatment with chemotherapy, radiation therapy, and radical cystectomy, with or without regional lymph node dissection.

**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

We extracted the following information into evidence tables: study design; setting; inclusion and exclusion criteria; dose and duration of treatment for experimental and control groups; duration of followup; number of subjects screened, eligible, and enrolled; population characteristics (including age, race/ethnicity, sex, stage of disease, and functional status); results; adverse events; withdrawals due to adverse events; and sources of funding. We calculated relative risks and associated 95% confidence intervals (CIs) based on the information provided (sample sizes and incidence of outcomes in each intervention group). We noted discrepancies between calculated and reported results when present. 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 RCTs and observational studies using criteria adapted from those developed by the U.S. Preventive Services Task Force.[13] These criteria were applied in conjunction with the approach recommended in the AHRQ Methods Guide[12] for medical interventions.

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] We rated the quality of each RCT 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 with allocated treatments; the use of intent-to-treat analysis; and avoidance of selective outcomes reporting.[13]

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 (defined as a minimum of age, sex, tumor stage, and tumor grade).[13]

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 category of medium risk of bias 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. 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.

## Applicability

We recorded factors important for understanding the applicability of studies, such as whether the publication adequately described the study sample, the country in which the study was conducted, the characteristics of the patient sample (e.g., age, sex, race/ethnicity, risk factors for bladder cancer, presenting symptoms, and medical comorbidities), and tumor characteristics (e.g., stage and grade, primary or recurrent, unifocal or multifocal lesions). We recorded the characteristics of the diagnostic tests (e.g., specific test evaluated and cutoffs used) and interventions (e.g., treatment dose, duration, and interval), and the magnitude of effects on clinical outcomes.[12] 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

We synthesized data qualitatively for the comparisons and outcomes addressed by each Key Question, based on the risk of bias, consistency, precision, and directness. We did not perform meta-analysis due to the small number of RCTs and the heterogeneity of the populations and interventions included.

## 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, which was based on 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 or undetected).

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

## Results

Database searches resulted in 3,921 potentially relevant articles. After dual review of abstracts and titles, 295 articles were selected for full-text dual review and 39 studies (in 41 publications) were determined to meet inclusion criteria and were included in this review.

### Key Question 1. Effectiveness of Bladder-Preserving Treatments Compared With Cystectomy Alone or in Combination With Chemotherapy

One RCT, seven retrospective cohort studies, and one nonrandomized controlled clinical trial compared bladder-sparing therapy versus radical cystectomy either alone or in combination with chemotherapy in patients with nonmetastatic muscle-invasive bladder cancer.

- One RCT with high risk of bias found no difference between bladder-preserving external beam radiation therapy (60 Gray) versus radical cystectomy plus external beam radiation therapy (40 Gray) in median

survival duration (18 vs. 20 months; p = 0.21), but increased risk of local or regional recurrence (35.8% vs. 6.8%) (strength of evidence [SOE]: insufficient).

- There was insufficient evidence from cohort studies and a nonrandomized controlled clinical trial to evaluate effects of bladder-preserving therapies versus radical cystectomy on risk of overall or bladder-specific mortality (7 studies) or local or regional recurrence (3 studies) because of methodological shortcomings in the studies, inconsistent results, and imprecise estimates (SOE: insufficient).
- No study evaluated effects of bladder-sparing therapy versus radical cystectomy on quality of life (SOE: insufficient).

### Key Question 1a. Tumor Characteristics

- No study evaluated how estimates of effectiveness of bladder-sparing therapy versus radical cystectomy vary in subgroups defined by tumor characteristics, such as stage, grade, size, or molecular or genetic markers (SOE: insufficient).

### Key Question 1b. Patient Characteristics

- No study evaluated how estimates of effectiveness of bladder-sparing therapy versus radical cystectomy vary in subgroups defined by patient characteristics, such as age, sex, race/ethnicity, performance status, or comorbidities, including chronic kidney disease (SOE: insufficient).

### Key Question 1c. Various Combinations of Agents and/or Radiation Therapy Used for Bladder-Preserving Chemotherapy

- No study compared the effectiveness of different combinations of chemotherapeutic agents and/or radiation treatment (SOE: insufficient).

### Key Question 1d. Different Bladder-Preserving Treatments Compared With One Another

- One RCT found external beam radiation therapy with synchronous chemotherapy to be associated with lower likelihood of 2-year locoregional recurrence (33% vs. 46%; hazard ratio [HR], 0.68; 95% CI, 0.48 to 0.95) and 5-year metastasis (HR, 0.72; 95% CI, 0.53 to 0.99); it also found trends toward decreased risk of overall (52% vs. 65%; HR, 0.82; 95% CI, 0.63 to 1.09) and bladder–cancer-specific mortality (42% vs. 51%; HR, 0.77; 95% CI, 0.57 to 1.05) versus radiation therapy alone (SOE: low).
- There was insufficient evidence from one cohort study with serious methodological limitations to determine the comparative effectiveness of bladder-preserving radiation therapy versus maximal TURBT (SOE: insufficient).

### Key Question 2. Regional Lymph Node Dissection Versus Cystectomy Alone

- Three cohort studies found regional lymph node dissection to be associated with lower risk of mortality than no lymph node dissection; two cohort studies examined the same population-based database, and one did not perform statistical adjustment for potential confounders (SOE: low).

### Key Question 2a. Tumor Characteristics

- One study found that effects of lymph node dissection on reducing risk of all-cause and bladder–cancer-specific mortality appeared to be stronger for lower stage tumors than for higher stage tumors, but for all-cause mortality there was no clear pattern suggesting differential effectiveness according to tumor stage (SOE: low).

### Key Question 2b. Extent of Regional Lymph Node Dissection

Eight retrospective cohort studies evaluated effects of the extent of lymph node dissection on clinical outcomes.

- Eleven cohort studies found that more extensive lymph node dissection was associated with improved all-cause or bladder–cancer-specific mortality versus less extensive lymph node dissection, but studies had methodological limitations, there was variability in the lymph node dissection techniques evaluated, and there was some inconsistency in results (SOE: low).
- Six cohort studies found that more extensive lymph node dissection was associated with lower risk of bladder cancer recurrence or progression, but most studies had serious methodological limitations and there was some inconsistency in results (SOE: low).

### Key Question 3. Improvement in Outcomes With Neoadjuvant or Adjuvant Chemotherapy Compared With Cystectomy Alone

Six trials (reported in eight publications) evaluated neoadjuvant chemotherapy (NAC) and four trials evaluated adjuvant chemotherapy (AC) for muscle-invasive bladder cancer.

*Neoadjuvant Chemotherapy*

- Six trials found NAC to be associated with decreased risk or a trend toward decreased risk of mortality versus no NAC. Three trials evaluated standard chemotherapy regimens (CMV and MVAC), and three trials used cisplatin-based regimens not commonly used in clinical practice (cisplatin and doxorubicin or cisplatin and methotrexate) (SOE: moderate).
- Three trials found NAC (CMV, MVAC, or cisplatin and methotrexate) to be associated with lower risk of disease progression versus no NAC; the largest trial and the only one to show a statistically significant effect found neoadjuvant CMV to be associated with lower likelihood of metastasis or death versus no NAC after 4 years (45% vs. 53%; HR, 0.79; CI, 0.66 to 0.93) (SOE: low).
- Three trials found that NAC was not superior to no NAC in risk of locoregional bladder cancer recurrence (SOE: moderate).

*Adjuvant Chemotherapy*

- Four trials found that AC was associated with decreased risk of mortality versus no AC, but no trial reported a statistically significant effect and there was some inconsistency in findings (SOE: low).
- One trial found that AC was not superior to no AC in risk of bladder cancer progression (SOE: insufficient).
- There was insufficient evidence to determine effects of AC versus no AC on risk of locoregional recurrence because of imprecise estimates and inconsistency between studies (SOE: insufficient).

**Key Question 3a. Various Combinations of Agents**

- Evidence from three cohort studies of neoadjuvant or adjuvant MVAC versus cisplatin and gemcitabine was too unreliable to evaluate comparative effectiveness because of serious methodological limitations (SOE: insufficient).

**Key Question 3b. Various Combinations of Agents According to Tumor Characteristics**

Six studies (in 7 publications) were included.

- Four trials found no clear differences in estimates of effectiveness of NAC versus no NAC in subgroups based on tumor stage or grade (SOE: low).
- Two trials found no clear differences in estimates of effectiveness of AC versus no AC in subgroups based on nodal status or tumor stage (SOE: low).

**Key Question 3c. Patient Characteristics**

Five trials evaluated the effect of patient characteristics on the comparative effectiveness of neoadjuvant or adjuvant chemotherapy.

- Five trials found no clear differences in estimates of effectiveness of NAC versus no NAC in subgroups based on patient age (SOE: low).
- One trial found no interaction between sex or performance status on effectiveness of NAC versus no NAC but found NAC to be more effective than no NAC in patients with better renal function (SOE: low).

**Key Question 3d. Dosing Frequency and/or Timing of Administration Relative to Radical Cystectomy**

Four studies were included for this Key Question.

- One trial and two cohort studies found that neither adjuvant nor neoadjuvant MVAC was superior for overall or bladder–cancer-specific survival (SOE: low).
- There was insufficient evidence from one small cohort study of adjuvant versus neoadjuvant gemcitabine plus cisplatin, which had methodological shortcomings, to determine effects on bladder cancer recurrence (SOE: insufficient).
- One trial found that neither administration of adjuvant cisplatin plus gemcitabine on day 2 or on day 15 was superior for 5-year survival (SOE: low).

**Key Question 4. Comparative Adverse Effects of Treatments**

Seven studies were included for this Key Question.

***Bladder-Preserving Therapies Versus Radical Cystectomy***

- There was insufficient evidence from four studies of bladder-sparing therapies versus radical cystectomy to determine comparative risk of harms because of poor reporting of harms data and methodological limitations in the studies (SOE: insufficient).

***More Versus Less Extensive Regional Lymph Node Dissection***

- One cohort study found extended lymph node dissection to be associated with longer operative time than standard lymph node dissection (median, 330 vs. 277 minutes) (SOE: insufficient).

***Neoadjuvant Chemotherapy***

- In three trials, NAC was not associated with increased risk of surgical complications or perioperative deaths versus no NAC (SOE: moderate).

- In two trials, NAC was associated with grade 3 or 4 hematological adverse events (SOE: low).

***Adjuvant Chemotherapy***

- Harms were poorly reported in three trials of AC versus no AC (SOE: insufficient).

***Adjuvant Chemotherapy Versus Neoadjuvant Chemotherapy***

- One trial found no difference between neoadjuvant versus adjuvant MVAC in risk of mortality related to chemotherapy toxicity (SOE: low).

**Key Question 4a. Patient Characteristics**

- No trial evaluated how estimates of harms associated with NAC or AC vary in subgroups defined by patient characteristics such as age, sex, race/ethnicity, performance status, or comorbidities.

## Discussion

### Key Findings and Strength of Evidence

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

We found limited evidence with which to evaluate the effectiveness of bladder-preserving therapies for muscle-invasive bladder cancer versus radical cystectomy. The only RCT of bladder-preserving therapy had important methodological limitations, used lower doses of radiation therapy than in current practice, and may have used outdated surgical techniques, as patients were treated in the early 1980s.[14] It found no difference between bladder-preserving external beam radiation therapy (60 Gray) versus radical cystectomy plus radiation therapy (40 Gray) in median survival duration, although bladder-preserving treatment was associated with increased risk of local or regional recurrence (35.8% vs. 6.8%) (SOE: low). Cohort studies and one nonrandomized controlled clinical trial of bladder-preserving treatments versus radical cystectomy had methodological shortcomings and reported inconsistent results, precluding reliable conclusions (SOE: insufficient). Although a potential advantage of bladder-preserving therapy is on subsequent quality of life, no study evaluated quality of life. Harms were also poorly reported (SOE: insufficient). The most commonly evaluated bladder-preserving therapy was radiation therapy, with or without systemic chemotherapy. Only one study evaluated bladder-preserving therapy with maximal TURBT.[15] It reported high 5-year mortality rates, with no clear differences between radiation therapy and maximal TURBT, and did not attempt to adjust for potential confounders.

Some evidence from cohort studies suggests that more extensive lymph node dissection with cystectomy might be more effective than less extensive lymph node dissection at improving survival (SOE: low). However, studies had methodological limitations (including failure to adequately adjust for confounders and comparisons of patients who underwent different lymph node dissection techniques in different countries); there was variability in the lymph node dissection techniques evaluated; and there was some inconsistency in results. More extensive lymph node dissection was associated with longer operative times in one study (SOE: low),[16] but other harms were poorly reported.

Evidence was somewhat stronger on the effects of NAC and AC in patients with muscle-invasive bladder cancer. Six RCTs consistently found NAC associated with decreased risk or a trend toward decreased risk of mortality versus no NAC (SOE: moderate). Three trials evaluated currently recommended chemotherapy regimens (CMV and MVAC),[17-19] and three trials evaluated other cisplatin-based combination regimens (cisplatin with methotrexate or doxorubicin).[20-22] There was limited evidence that there was no clear difference in the effectiveness of NAC in subgroups based on tumor or patient characteristics. Compared with evidence on NAC, evidence on benefits of AC was not as strong. Although four trials found AC to be associated with decreased risk of mortality versus no AC, no trial reported a statistically significant effect and there was some inconsistency in findings (SOE: low). Three cohort studies compared effects of NAC or AC with MVAC versus cisplatin and gemcitabine but had serious methodological limitations, including failure to adjust for confounders, precluding reliable conclusions (SOE: insufficient).[23-25] One trial and two cohort studies found no clear differences between neoadjuvant and adjuvant MVAC in overall or bladder–cancer-specific survival (SOE: low).[25-27] Although NAC was not associated with an increased risk of complications related to cystectomy, chemotherapy was associated with an increased risk of hematological adverse events (SOE: low). Although cisplatin is nephrotoxic, renal adverse events were not well reported.[28] No study compared benefits or harms of cisplatin-based versus carboplatin-based chemotherapy regimens.

| Table A. Summary of evidence | | | |
|---|---|---|---|
| **Key Question** | **Outcome** | **Strength-of-Evidence Grade** | **Conclusion** |
| 1. For patients with nonmetastatic muscle-invasive bladder cancer, what is the effectiveness of bladder-preserving treatments (chemotherapy, external beam or interstitial radiation therapy, partial cystectomy, and/or maximal transurethral resection of bladder tumor) for decreasing mortality or improving other outcomes (e.g., recurrence, metastasis, quality of life, functional status) compared with cystectomy alone or cystectomy in combination with chemotherapy? | Mortality | Insufficient | One RCT with high risk of bias found no difference between bladder-preserving external beam radiation therapy (60 Gray) vs. radical cystectomy plus radiation therapy (40 Gray) in median survival duration (18 vs. 20 months; p = 0.21). |
| | Local recurrence | Low | One RCT with high risk of bias found increased risk of local or regional recurrence (35.8% vs. 6.8%) for bladder-preserving external beam radiation therapy vs. radical cystectomy. |
| | Overall mortality, bladder–cancer-specific mortality | Insufficient | There was insufficient evidence from cohort studies and a nonrandomized controlled clinical trial to evaluate effects of bladder-preserving therapies vs. radical cystectomy on risk of overall or bladder-specific mortality (7 studies) because of methodological shortcomings in the studies, inconsistent results, and imprecise estimates. |
| | Recurrence | Insufficient | There was insufficient evidence from 3 cohort studies to evaluate effects of bladder-preserving therapies vs. radical cystectomy on risk of local or regional recurrence because of methodological shortcomings in the studies and inconsistent results. |
| | Quality of life | Insufficient | No study evaluated effects of bladder-sparing therapy vs. radical cystectomy on quality of life. |
| 1a. Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers? | Effectiveness | Insufficient | No study evaluated how estimates of effectiveness of bladder-sparing therapy vs. radical cystectomy vary in subgroups defined by tumor characteristic, such as stage, grade, size, or molecular or genetic markers. |
| 1b. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, race/ethnicity, performance status, or medical comorbidities such as chronic kidney disease? | Effectiveness | Insufficient | No study evaluated how estimates of effectiveness of bladder-sparing therapy vs. radical cystectomy vary in subgroups defined by patient characteristics, such as age, sex, race/ethnicity, performance status, or comorbidities (including chronic kidney disease). |
| 1c. What is the comparative effectiveness of various combinations of agents and/or radiation therapy used for bladder-preserving chemotherapy? | Effectiveness | Insufficient | No study compared the effectiveness of different combinations of chemotherapeutic agents and/or radiation treatment. |

| Table A. Summary of evidence (continued) | | | |
|---|---|---|---|
| **Key Question** | **Outcome** | **Strength-of-Evidence Grade** | **Conclusion** |
| 1d. What is the effectiveness of different bladder-preserving treatments (chemotherapy, external beam or interstitial radiation therapy, partial cystectomy, and/or maximal transurethral resection of bladder tumor) compared with one another? | Mortality | Low | One randomized trial found external beam radiation therapy with synchronous chemotherapy to be associated with trends toward decreased risk of overall (52% vs. 65%; HR, 0.82; 95% CI, 0.63 to 1.09) and bladder–cancer-specific mortality (42% vs. 51%; HR, 0.77; 95% CI, 0.57 to 1.05) vs. radiation therapy alone. |
| | Recurrence | Low | One randomized trial found external beam radiation therapy with synchronous chemotherapy to be associated with lower likelihood of 2-year locoregional recurrence (33% vs. 46%; HR, 0.68; 95% CI, 0.48 to 0.95) and 5-year metastasis (HR, 0.72; 95% CI, 0.53 to 0.99) vs. radiation therapy alone. |
| 2. For patients with clinically nonmetastatic muscle-invasive bladder cancer that is treated with cystectomy, does regional lymph node dissection improve outcomes compared with cystectomy alone? | Mortality | Low | Three cohort studies found regional lymph node dissection to be associated with lower risk of mortality than no lymph dissection; 2 cohort studies examined the same population-based database, and 1 did not perform statistical adjustment for potential confounders. |
| 2a. Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers? | Mortality | Low | One study found increased risk of 10-year cancer-specific mortality and overall mortality for all stages of bladder cancer for patients who underwent no lymph node dissection. |
| 2b. Does the comparative effectiveness differ according to the extent of the regional lymph node dissection (e.g., as measured by the number of lymph nodes removed or the anatomic extent of dissection)? | Mortality | Low | Eleven cohort studies found more extensive lymph node dissection to be associated with improved all-cause or bladder–cancer-specific mortality vs. less extensive lymph node dissection, but studies had methodological limitations, there was variability in the lymph node dissection techniques evaluated, and there was some inconsistency in results. |
| | Recurrence, progression | Low | Six cohort studies found that more extensive lymph node dissection was associated with lower risk of bladder cancer recurrence or progression, but most studies had serious methodological limitations and there was some inconsistency in results. |

| Table A. Summary of evidence (continued) | | | |
|---|---|---|---|
| **Key Question** | **Outcome** | **Strength-of-Evidence Grade** | **Conclusion** |
| 3. For patients with nonmetastatic muscle-invasive bladder cancer that is treated with cystectomy, does neoadjuvant or adjuvant chemotherapy improve outcomes compared with cystectomy alone? | Neoadjuvant chemotherapy: mortality | Moderate | Six trials found NAC to be associated with decreased risk, or a trend toward decreased risk, of mortality vs. no NAC. Three trials evaluated standard chemotherapy regimens (CMV and MVAC), and 3 trials used cisplatin-based regimens not commonly used in clinical practice (cisplatin and doxorubicin or cisplatin and methotrexate). |
| | Neoadjuvant chemotherapy: likelihood of metastasis or death | Low | Three trials found NAC (CMV, MVAC, or cisplatin and methotrexate) to be associated with lower risk of disease progression; the largest trial and the only one to show a statistically significant effect found neoadjuvant CMV to be associated with lower likelihood of metastasis or death versus no NAC after 4 years (45% vs. 53%; HR, 0.79; 95% CI, 0.66 to 0.93). |
| | Neoadjuvant chemotherapy: recurrence | Moderate | Three trials found that NAC was not superior to no NAC in risk of locoregional bladder cancer recurrence. |
| | Adjuvant chemotherapy: mortality | Low | Four trials found AC to be associated with decreased risk of mortality vs. no AC, but no trial reported a statistically significant effect and there was some inconsistency in findings. |
| | Adjuvant chemotherapy: progression | Insufficient | One trial found that AC was not superior to no AC in risk of bladder cancer progression. |
| | Adjuvant chemotherapy: recurrence | Insufficient | There was insufficient evidence to determine effects of AC vs. no AC on risk of locoregional recurrence because of imprecise estimates and inconsistency between studies. |
| 3a. What is the comparative effectiveness of various combinations of agents used for neoadjuvant or adjuvant chemotherapy? | Effectiveness | Insufficient | Evidence from 3 cohort studies of neoadjuvant or adjuvant MVAC vs. cisplatin and gemcitabine was too unreliable to evaluate comparative effectiveness because of serious methodological limitations. |
| 3b. Does the comparative effectiveness of various combinations of agents used for neoadjuvant or adjuvant chemotherapy differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers? | Neoadjuvant chemotherapy: effectiveness | Low | Four trials found no clear differences in estimates of effectiveness of NAC vs. no NAC in subgroups based on tumor stage or grade. |
| | Adjuvant chemotherapy: effectiveness | Low | Two trials found no clear differences in estimates of effectiveness of AC vs. no AC in subgroups based on nodal status or tumor stage. |

| Table A. Summary of evidence (continued) | | | |
|---|---|---|---|
| **Key Question** | **Outcome** | **Strength-of-Evidence Grade** | **Conclusion** |
| 3c. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, race/ethnicity, performance status, or medical comorbidities such as chronic kidney disease? | Subgroup—patient age: effectiveness | Low | Five trials found no clear interaction between age and estimates of effectiveness of NAC vs. no NAC. |
| | Subgroups—sex, performance status, renal function: effectiveness | Low | One trial found no interaction between sex or performance status on effectiveness of NAC vs. no NAC, but found NAC to be more effective than no NAC in patients with better renal function. |
| 3d. Does the comparative effectiveness of neoadjuvant or adjuvant chemotherapy differ according to dosing frequency and/or the timing of its administration relative to cystectomy? | Adjuvant vs. neoadjuvant MVAC: overall survival, bladder–cancer-specific survival | Low | One trial and 2 cohort studies found that neither adjuvant nor neoadjuvant MVAC was superior for overall or bladder–cancer-specific survival. |
| | Adjuvant vs. neoadjuvant gemcitabine plus cisplatin: recurrence | Insufficient | There was insufficient evidence from 1 small cohort study with methodological shortcomings of adjuvant vs. neoadjuvant gemcitabine plus cisplatin to determine effects on bladder cancer recurrence. |
| | Adjuvant cisplatin plus gemcitabine on day 2 vs. day 15: 5-year survival | Low | One trial found that neither administration of adjuvant cisplatin plus gemcitabine on day 2 nor day 15 was superior for 5-year survival. |

| Table A. Summary of evidence (continued) | | | |
|---|---|---|---|
| **Key Question** | **Outcome** | **Strength-of-Evidence Grade** | **Conclusion** |
| 4. What are the comparative adverse effects of treatments for nonmetastatic muscle-invasive bladder cancer? | Bladder-sparing therapies vs. radical cystectomy: adverse events | Insufficient | There was insufficient evidence from 4 studies of bladder-sparing therapies vs. radical cystectomy to determine comparative risk of harms because of poor reporting of harms data and methodological limitations in the studies. |
| | Extended lymph node dissection vs. standard lymph node dissection: operative time | Insufficient | One cohort study found extended lymph node dissection to be associated with longer operative time than standard lymph node dissection (median, 330 vs. 277 minutes). |
| | Neoadjuvant chemotherapy vs. no neoadjuvant chemotherapy: surgical complications, perioperative deaths | Low | In 3 trials, NAC was not associated with increased risk of surgical complications or perioperative deaths vs. no NAC. |
| | Neoadjuvant chemotherapy: grade 3 or 4 hematological adverse events | Low | In 2 trials, NAC was associated with grade 3 or 4 hematological adverse events. |
| | Adjuvant chemotherapy vs. no adjuvant chemotherapy: adverse events | Insufficient | Harms were poorly reported in 3 trials of AC vs. no AC. |
| | Neoadjuvant vs. adjuvant MVAC: mortality related to chemotherapy toxicity | Low | One trial found no difference between neoadjuvant vs. adjuvant MVAC in risk of mortality related to chemotherapy toxicity. |
| 4a. How do adverse effects of treatment vary by patient characteristics, such as age, sex, race/ethnicity, performance status, or medical comorbidities such as chronic kidney disease? | Effectiveness | Insufficient | No trial evaluated how estimates of harms associated with NAC or AC vary in subgroups defined by patient characteristics, such as age, sex, race/ethnicity, performance status, or comorbidities. |

AC = adjuvant chemotherapy; CI = confidence interval; CMV = cisplatin, methotrexate, vinblastine; HR = hazard ratio; MVAC = methotrexate, vinblastine, doxorubicin, cisplatin; NAC = neoadjuvant chemotherapy.

## Findings in Relationship to What Is Already Known

Our findings regarding bladder-preserving therapy are consistent with findings from a recent review conducted to inform an International Consultation on Urological Diseases/European Association of Urology guideline on radical cystectomy and bladder-preserving therapy,[29] which concluded that open radical cystectomy remains the standard of treatment for muscle-invasive bladder cancer. However, that review also concluded that bladder-preserving therapy is a valid alternative to radical cystectomy in selected patients, based largely on cross-study comparisons of survival rates in series of patients who underwent radical cystectomy or bladder preservation using multiple modalities.

Our findings are consistent with systematic reviews that found lymph node dissection to be associated with better outcomes than no lymph node dissection, and more extensive lymph node dissection to be associated with better outcomes than less extensive dissection. Like our review, prior reviews found serious methodological shortcomings in the evidence,[30,31] precluding strong conclusions.

Our findings are also consistent with prior systematic reviews that found platinum-based NAC to be associated with improved survival versus no NAC,[32-34] despite some differences between the methods used to conduct the reviews. For example, prior reviews included studies of patients who received cisplatin monotherapy, which is not used in clinical practice, as well as noncisplatin combination regimens, whereas we restricted our analysis to patients who received cisplatin combination regimens and carboplatin/gemcitabine. Prior reviews support our decision to exclude trials of cisplatin monotherapy, as benefits were not observed in this subgroup of trials.[33] Other differences in the methods used in prior reviews include access to and analysis of individual patient data, unpublished data, and trials published only as abstracts.[33] Our findings are consistent with systematic reviews that found less definitive evidence that AC is more effective than no AC than was found for NAC versus no NAC.[34,35] Although one review based on individual patient data found AC to be associated with reduced risk of mortality versus no AC (HR, 0.75; 95% CI, 0.60 to 0.96), it noted methodological issues that could have biased estimates, including early stopping of trials, nonreceipt of allocated treatments, and nonreceipt of salvage chemotherapy.[35]

## Applicability

Some issues could impact the applicability of our findings. The only RCT of bladder-sparing therapy was conducted in the early 1980s and used doses of radiation therapy that are lower than employed in current practice.[14] Surgical techniques may have also been outdated. Among the available cohort studies, few evaluated currently recommended trimodality regimens (radiation therapy, cisplatin-based chemotherapy, and TURBT).[36]

Techniques for lymph node dissection varied, as did methods and definitions used to define the extent of regional lymph node dissection. Some studies were conducted in Europe, where techniques for lymph node dissection may vary from U.S. surgical practices.

For chemotherapy regimens, few trials evaluated currently recommended cisplatin-based chemotherapy regimens (MVAC, CMV, cisplatin and gemcitabine). No trial evaluated adjuvant or neoadjuvant therapy with carboplatin versus cisplatin, which may be used in clinical practice in patients with baseline renal dysfunction.

We also identified issues that could limit applicability of our findings to specific populations of interest. Although bladder-preserving therapies might be of interest for older patients or patients with substantial comorbidities in whom the risk of radical cystectomy might be increased, there was insufficient evidence to determine the effectiveness of bladder-sparing therapy in these populations. For patients with renal dysfunction, carboplatin may be considered because it is less nephrotoxic than cisplatin, but there were insufficient data to evaluate the effectiveness of cisplatin-based versus carboplatin-based regimens in patients with underlying renal dysfunction.

## Implications for Clinical and Policy Decisionmaking

Our review has implications for clinical and policy decisionmaking. Consistent with a European guideline7 that recommends radical cystectomy as first-line therapy for muscle-invasive bladder cancer, we found no evidence that bladder-sparing therapies are more effective than radical cystectomy and some studies suggesting that bladder-sparing therapies are less effective. However, research indicates that radical cystectomy continues to be underused in patients with muscle-invasive bladder cancer.[11]

We found evidence to support regional lymph node dissection with radical cystectomy, and some evidence to support more extensive lymph node dissection. However, some evidence suggests that lymph node dissection is not always performed in patients undergoing radical cystectomy for muscle-invasive bladder cancer.[37]

Our review also supports recommendations for NAC in patients undergoing radical cystectomy using cisplatin-based combination regimens. Although we found limited evidence of no difference between NAC versus AC, evidence showing effectiveness was more limited for AC than for NAC.

## Limitations

The review process had some limitations. We were unable to perform meta-analysis because of variability in the bladder-preserving therapies, lymph node dissection methods, and chemotherapy regimens evaluated, as well as in other factors, such as the patient populations evaluated. Therefore, we synthesized the evidence qualitatively. Although pooling may not have been suitable, a potential disadvantage of qualitative synthesis is the inability to detect potential effects of interventions in individual studies because of lack of statistical power. Because we did not perform meta-analysis, we were also unable to assess for publication bias using formal graphical or statistical methods. However, such methods are not recommended when the number of studies is small, as in our review, since they can be misleading.[38,39] We excluded non–English language articles and did not search for studies published only as abstracts. However, results of systematic reviews that were not restricted to English language and that included unpublished studies reported findings that were similar to those of our review.[33,35] We also did not have access to individual patient data, but findings of systematic reviews with access to such data reported findings similar to those of our review.[33,35]

The evidence base had a number of important limitations that made it difficult to draw strong conclusions. For assessing the effects of bladder-sparing therapy versus radical cystectomy on clinical outcomes and the effects of extent of lymph node dissection, almost all of the evidence was restricted to observational studies. Furthermore, the observational studies had important limitations, including failure to adequately adjust for potential confounders. Some observational studies had serious methodological limitations because of how the comparison groups were selected. For example, two studies that compared effects of the extent of lymph node dissection on clinical outcomes evaluated patients who underwent more extensive lymph node dissection in one country with patients who underwent less extensive lymph node dissection in another country.[40,41]

Although RCTs were available on the effects of NAC and AC, all trials had methodological shortcomings. In addition, variability in the chemotherapy regimens evaluated—with few trials evaluating regimens recommended in current guidelines—complicates interpretation of findings.

Other limitations of the evidence base include poor or suboptimal reporting of harms, little evidence with which to determine how patient and tumor characteristics impact estimates of effectiveness, and limited evidence directly comparing the effectiveness of different bladder-sparing treatments and chemotherapy regimens.

## Research Gaps

Additional research is needed to more reliably address all of the Key Questions evaluated in this review. Well-conducted studies that compare effects of bladder-sparing therapies versus radical cystectomy in clearly defined patient groups would help to clarify situations in which bladder-sparing therapy is an acceptable alternative. Research is also needed to understand the role of maximal TURBT as a potential option for bladder-preserving therapy. Research on bladder-preserving therapies should also address effects on quality of life[42] and harms, which have been poorly studied to date.

Randomized trials that evaluate more versus less extensive regional lymph node dissection using standardized definitions and techniques are needed, and they should also more fully address comparative harms. Trials that compare currently recommended cisplatin-based and carboplatin-based chemotherapy regimens would be helpful for clarifying their relative effectiveness, particularly for patients with renal dysfunction, in whom cisplatin might be associated with higher risk. A number of ongoing trials are evaluating non–cisplatin-based chemotherapy regimens,[34] and a trial of more versus less extensive lymph node dissection is also in progress.[43]

## Conclusions

NAC with cisplatin-based regimens improves survival in patients with muscle-invasive bladder cancer, and extended lymph node dissection during cystectomy might be more effective than standard lymph node dissection for improving survival. More research is needed to clarify the effectiveness of bladder-sparing therapies versus radical cystectomy and to define patient subgroups for which such therapies are a potential option.

## References


1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013 Jan;63(1):11-30. PMID: 23335087.
2. U.S. Cancer Statistics Working Group. United States Cancer Statistics: 1999–2009 Incidence and Mortality Web-Based Report. Centers for Disease Control and Prevention and National Cancer Institute. Atlanta: 2013. www.cdc.gov/uscs.
3. National Cancer Institute Surveillance Research Program. Surveillance Epidemiology and End Results. Browse the SEER Cancer Statistics Review 1975-2009 (Vintage 2009 Populations). http://seer.cancer.gov/csr/1975_2009_pops09/browse_csr.php?section=27&page=sect_27_table.01.html. Accessed October 16, 2014.
4. James AC, Gore JL. The costs of non-muscle invasive bladder cancer. Urol Clin North Am. 2013 May;40(2):261-9. PMID: 23540783.
5. Konety BR, Joyce GF, Wise M. Bladder and upper tract urothelial cancer. J Urol. 2007 May;177(5):1636-45. PMID: 17437776.
6. Ru Y, Dancik GM, Theodorescu D. Biomarkers for prognosis and treatment selection in advanced bladder cancer patients. Curr Opin Urol. 2011 Sep;21(5):420-7. PMID: 21814055.
7. Stenzl A, Witjes JA, Compérat E. Guidelines on Bladder Cancer Muscle-invasive and Metastatic. European Association of Urology (EAU); 2012.
8. Bruins HM, Huang GJ, Cai J, et al. Clinical outcomes and recurrence predictors of lymph node positive urothelial cancer after cystectomy. J Urol. 2009 Nov;182(5):2182-7. PMID: 19758623.
9. Stein JP, Cai J, Groshen S, et al. Risk factors for patients with pelvic lymph node metastases following radical cystectomy with en bloc pelvic lymphadenectomy: concept of lymph node density. J Urol. 2003 Jul;170(1):35-41. PMID: 12796639.
10. Wright JL, Lin DW, Porter MP. The association between extent of lymphadenectomy and survival among patients with lymph node metastases undergoing radical cystectomy. Cancer. 2008 Jun;112(11):2401-8. PMID: 18383515.
11. Gore JL, Litwin MS, Lai J, et al. Use of radical cystectomy for patients with invasive bladder cancer. JNCI. 2010 Jun 2;102(11):802-11. PMID: 20400716.
12. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at www.effectivehealthcare.ahrq.gov.
13. U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Procedure Manual. 2008. www.uspreventiveservicestaskforce.org/uspstf08/methods/procmanual.htm. Accessed April 4, 2014.
14. Sell A, Jakobsen A, Nerstrom B, et al. Treatment of advanced bladder cancer category T2 T3 and T4a. A randomized multicenter study of preoperative irradiation and cystectomy versus radical irradiation and early salvage cystectomy for residual tumor. DAVECA protocol 8201. Danish Vesical Cancer Group. Scand J Urol Nephrol Suppl. 1991;138:193-201. PMID: 1785004.
15. Holmang S, Hedelin H, Anderstrom C, et al. Long-term followup of all patients with muscle invasive (stages T2, T3 and T4) bladder carcinoma in a geographical region. J Urol. 1997 Aug;158(2):389-92. PMID: 9224309.
16. Brossner C, Pycha A, Toth A, et al. Does extended lymphadenectomy increase the morbidity of radical cystectomy? BJU Int. 2004 Jan;93(1):64-6. PMID: 14678370.
17. International Collaboration of Trialists. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. International collaboration of trialists. [Erratum appears in Lancet. 1999 Nov 6;354(9190):1650]. Lancet. 1999 Aug 14;354(9178):533-40. PMID: 10470696.
18. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. [Erratum appears in N Engl J Med. 2003 Nov 6;349(19):1880]. N Engl J Med. 2003 Aug 28;349(9):859-66. PMID: 12944571.
19. Kitamura H, Tsukamoto T, Shibata T, et al. Randomised phase III study of neoadjuvant chemotherapy with methotrexate, doxorubicin, vinblastine and cisplatin followed by radical cystectomy compared with radical cystectomy alone for muscle-invasive bladder cancer: Japan Clinical Oncology Group Study JCOG0209. Ann Oncol. 2014 Jun;25(6):1192-8. PMID: 24669010.
20. Rintala E, Hannisdahl E, Fossa SD, et al. Neoadjuvant chemotherapy in bladder cancer: a randomized study. Nordic Cystectomy Trial I. Scand J Urol Nephrol. 1993;27(3):355-62. PMID: 8290916.
21. Sherif A, Rintala E, Mestad O, et al. Neoadjuvant cisplatin-methotrexate chemotherapy for invasive bladder cancer -- Nordic cystectomy trial 2. Scand J Urol Nephrol. 2002;36(6):419-25. PMID: 12623505.
22. Sengelov L, von der Maase H, Lundbeck F, et al. Neoadjuvant chemotherapy with cisplatin and methotrexate in patients with muscle-invasive bladder tumours. Acta Oncol. 2002;41(5):447-56. PMID: 12442921.
23. Fairey AS, Daneshmand S, Quinn D, et al. Neoadjuvant chemotherapy with gemcitabine/cisplatin vs. methotrexate/vinblastine/doxorubicin/cisplatin for muscle-invasive urothelial carcinoma of the bladder: a retrospective analysis from the University of Southern California. Urol Oncol. 2013 Nov;31(8):1737-43. PMID: 23141776.
24. Pal SK, Ruel NH, Wilson TG, et al. Retrospective analysis of clinical outcomes with neoadjuvant cisplatin-based regimens for muscle-invasive bladder cancer. Clin Genitourin Cancer. 2012 Dec;10(4):246-50. PMID: 22981208.
25. Yeshchina O, Badalato GM, Wosnitzer MS, et al. Relative efficacy of perioperative gemcitabine and cisplatin versus methotrexate, vinblastine, adriamycin, and cisplatin in the management of locally advanced urothelial carcinoma of the bladder. Urology. 2012 Feb;79(2):384-90. PMID: 22196406.

26. Millikan R, Dinney C, Swanson D, et al. Integrated therapy for locally advanced bladder cancer: final report of a randomized trial of cystectomy plus adjuvant M-VAC versus cystectomy with both preoperative and postoperative M-VAC. J Clin Oncol. 2001 Oct 15;19(20):4005-13. PMID: 11600601.

27. Wosnitzer MS, Hruby GW, Murphy AM, et al. A comparison of the outcomes of neoadjuvant and adjuvant chemotherapy for clinical T2-T4aN0-N2M0 bladder cancer. Cancer. 2012 Jan 15;118(2): 358-64. PMID: 21717438.

28. Pabla N, Dong Z. Cisplatin nephrotoxicity: mechanisms and renoprotective strategies. Kidney Int. 2008;73:994-1007. PMID: 18272962.

29. Gakis G, Efstathiou J, Lerner SP, et al. ICUD-EAU International Consultation on Bladder Cancer 2012: Radical cystectomy and bladder preservation for muscle-invasive urothelial carcinoma of the bladder. Eur Urol. 2013 Jan;63(1):45-57. PMID: 22917985.

30. Bruins HM, Veskimae E, Hernandez V, et al. The impact of the extent of lymphadenectomy on oncologic outcomes in patients undergoing radical cystectomy for bladder cancer: a systematic review. Eur Urol. 2014 Dec;66(6):1065-77. Epub 2014 Jul 26. PMID: 25074764.

31. Mandel P, Tilki D, Eslick GD. Extent of lymph node dissection and recurrence-free survival after radical cystectomy: a meta-analysis. Urol Oncol. 2014 Nov;32(8):1184-90. Epub 2014 Jul 11. PMID: 25027683.

32. Winquist E, Kirchner TS, Segal R, et al. Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: a systematic review and meta-analysis. J Urol. 2004 Feb;171(2 Pt 1):561-9. PMID: 14713760.

33. Advanced Bladder Cancer Overview Collaboration. Neoadjuvant chemotherapy for invasive bladder cancer. Cochrane Database Syst Rev. 2004;CD005246. PMID: 15846746.

34. Meeks JJ, Bellmunt J, Bochner BH, et al. A systematic review of neoadjuvant and adjuvant chemotherapy for muscle-invasive bladder cancer. Eur Urol. 2012 Sep;62(3):523-33. PMID: 22677572.

35. Vale CL. Adjuvant chemotherapy for invasive bladder cancer (individual patient data). Cochrane Database Syst Rev. 2006;(2):CD006018. PMID: 16625650.

36. Mitin T, Shipley WU, Efstathiou JA, et al. Trimodality therapy for bladder conservation in treatment of invasive bladder cancer. Curr Urol Rep. 2013 Apr;14(2):109-15. PMID: 23341373.

37. Konety BR, Joslyn SA, O'Donnell MA. Extent of pelvic lymphadenectomy and its impact on outcome in patients diagnosed with bladder cancer: analysis of data from the Surveillance, Epidemiology and End Results Program data base. J Urol. 2003 Mar;169(3):946-50. PMID: 12576819.

38. Song F, Khan KS, Dinnes J, et al. Asymmetric funnel plots and publication bias in meta-analyses of diagnostic accuracy. Int J Epidemiol. 2002 Feb;31(1):88-95. PMID: 11914301.

39. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol. 2005 Sep;58(9):882-93. PMID: 16085191.

40. Dhar NB, Klein EA, Reuther AM, et al. Outcome after radical cystectomy with limited or extended pelvic lymph node dissection. J Urol. 2008 Mar;179(3):873-8; discussion 8. PMID: 18221953.

41. Zehnder P, Studer UE, Skinner EC, et al. Super extended versus extended pelvic lymph node dissection in patients undergoing radical cystectomy for bladder cancer: a comparative study. J Urol. 2011 Oct;186(4):1261-8. PMID: 21849183.

42. Parkinson JP, Konety BR. Health related quality of life assessments for patients with bladder cancer. J Urol. 2004 Dec;172(6 Pt 1):2130-6. PMID: 15538218.

43. Southwest Oncology Group Trial. S1011 Standard of Extended Pelvic Lymphadenectomy in Treating Patients Undergoing Surgery for Invasive Bladder Cancer. A Phase III Surgical Trial to Evaluate the Benefit of a Standard Versus an Extended Pelvic Lymphadenectomy Performed at Time of Radical Csytectomy for Muscle Invasive Urothelial Cancer. https://clinicaltrials.gov/show/NCT01224665. Accessed April 22, 2015.

## Full Report

This executive summary is part of the following document: Chou R, Selph S, Buckley D, Gustafson K, Griffin J, Grusing S, Gore J. Treatment of Nonmetastatic Muscle-Invasive Bladder Cancer. Comparative Effectiveness Review No. 152. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2012-00014-1.) AHRQ Publication No. 15-EHC015-EF. Rockville, MD: Agency for Healthcare Research and Quality; June 2015. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

AHRQ Pub. No. 15-EHC015-1-EF
June 2015