



Effective Health Care Program

Comparative Effectiveness Review
Number 152

Treatment of Nonmetastatic Muscle-Invasive Bladder Cancer



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Treatment of Nonmetastatic Muscle-Invasive Bladder Cancer

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Preface

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

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 email 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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Key Informants

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

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

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In designing the 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,

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Treatment of Nonmetastatic Muscle-Invasive Bladder Cancer

Structured Abstract

Objectives. Although the standard treatment for nonmetastatic muscle-invasive bladder cancer is cystectomy and neoadjuvant chemotherapy, there is interest in bladder-preserving therapy as an alternative, and there is uncertainty about the need for and optimal extent of lymph node dissection and optimal chemotherapy regimens and timing of administration.

Data Sources. Electronic databases (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); references lists; and clinical trials registries.

Review methods. We selected randomized controlled trials, nonrandomized controlled clinical trials, and nonrandomized cohort studies with concurrent comparators that evaluated bladder-preserving therapies against one another or versus radical cystectomy, that evaluated the effectiveness of lymph node dissection or effects of extent of dissection, and that compared neoadjuvant or adjuvant chemotherapy versus another chemotherapy regimen or versus no chemotherapy. The quality of included studies was assessed, data were extracted, and results were summarized qualitatively.

Results. One randomized controlled trial with methodological limitations 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%) (strength of evidence: insufficient). Cohort studies of bladder-preserving treatments versus radical cystectomy had methodological shortcomings and reported inconsistent results, precluding reliable conclusions (strength of evidence: insufficient).

Cohort studies suggested that lymph node dissection was associated with lower risk of mortality than no lymph node dissection and that more extensive lymph node dissection with cystectomy might be more effective than less extensive lymph node dissection at improving survival, but studies had methodological limitations, there was some inconsistency in results, and there was variability in the lymph node dissection techniques evaluated (strength of evidence: low).

Six randomized controlled trials consistently found neoadjuvant chemotherapy with cisplatin-based combination regimens to be associated with decreased risk, or a trend toward decreased risk, of mortality versus no neoadjuvant chemotherapy, including three trials that evaluated current regimens (cisplatin, methotrexate, and vinblastine; methotrexate, vinblastine, doxorubicin, and cisplatin) (strength of evidence: moderate). Four trials found adjuvant chemotherapy to be associated with decreased risk of mortality versus no adjuvant

chemotherapy, but no trial reported a statistically significant effect and there was some inconsistency in findings (strength of evidence: low). One trial and two cohort studies found no clear differences between neoadjuvant and adjuvant use of methotrexate, vinblastine, doxorubicin, and cisplatin in survival (strength of evidence: low).

Evidence on harms, effectiveness of treatments for muscle-invasive bladder cancer in patient subgroups (including older patients, patients with comorbidities, and patients with renal dysfunction), and comparative effectiveness of different chemotherapy regimens was too limited to reach reliable conclusions.

Conclusions. Neoadjuvant chemotherapy with cisplatin-based regimens improved 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-preserving therapies versus radical cystectomy and define patient subgroups in which such therapies may be an option.

Contents

Executive Summary	ES-1
Introduction	1
Background.....	1
Nature and Burden of Nonmetastatic Muscle-Invasive Bladder Cancer	1
Interventions and Outcomes for Muscle-Invasive Bladder Cancer	2
Rationale for Evidence Review	3
Scope of Review and Key Questions.....	3
Key Questions.....	4
Methods	7
Topic Development and Refinement	7
Searching for the Evidence	7
Study Selection	8
Population and Condition of Interest	8
Interventions, Comparisons, and Study Designs of Interest	8
Outcomes of Interest	9
Timing and Setting of Interest	9
Data Extraction and Data Management	9
Assessment of the Risk of Bias of Individual Studies	9
Assessing Applicability	10
Data Synthesis.....	10
Grading the Strength of Evidence for Each Key Question	10
Peer Review and Public Commentary	11
Results	12
Results of Literature Searches	12
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?.....	13
Key Points.....	13
Detailed Synthesis.....	13
Key Question 1a. Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?	16
Key Points.....	16
Detailed Synthesis.....	16
Key Question 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?.....	16
Key Points.....	16
Detailed Synthesis.....	16

Key Question 1c. What is the comparative effectiveness of various combinations of agents and/or radiation therapy used for bladder-preserving chemotherapy?	17
Key Points	17
Detailed Synthesis.....	17
Key Question 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?	17
Key Points	17
Detailed Synthesis.....	17
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?	18
Key Points	18
Detailed Synthesis.....	18
Key Question 2a. Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?	19
Key Points	19
Detailed Synthesis.....	19
Key Question 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)?	19
Key Points	19
Detailed Synthesis.....	19
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?	22
Key Points	22
Detailed Synthesis.....	23
Key Question 3a. What is the comparative effectiveness of various combinations of agents used for neoadjuvant or adjuvant chemotherapy?	26
Key Points	26
Detailed Synthesis.....	26
Key Question 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?	26
Key Points	26
Detailed Synthesis.....	26
Key Question 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?.....	27
Key Points	27
Detailed Synthesis.....	27
Key Question 3d. Does the comparative effectiveness of neoadjuvant or adjuvant chemotherapy differ according to dosing frequency and/or the timing of its administration relative to radical cystectomy?.....	28
Key Points	28

Detailed Synthesis.....	28
Key Question 4. What are the comparative adverse effects of treatments for nonmetastatic muscle-invasive bladder cancer?	29
Key Points	29
Detailed Synthesis.....	29
Key Question 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?	31
Key Points	31
Detailed Synthesis.....	31
Discussion	73
Key Findings and Strength of Evidence	73
Findings in Relationship to What Is Already Known.....	78
Applicability	79
Implications for Clinical and Policy Decisionmaking	79
Limitations of the Review Process	80
Limitations of the Evidence Base	80
Research Gaps.....	80
Conclusions.....	80
References	82
Abbreviations	87
Tables	
Table A. Summary of evidence	ES-13
Table 1. Bladder cancer tumor staging	2
Table 2. Characteristics of studies on bladder-preserving treatments	32
Table 3. Summary of results for studies of bladder-preserving treatments	35
Table 4. Characteristics of studies on lymph node dissection with radical cystectomy	39
Table 5. Summary of results for studies of lymph node dissection	45
Table 6. Characteristics of studies on adjuvant and neoadjuvant chemotherapy	52
Table 7. Summary of results for adjuvant and neoadjuvant chemotherapy studies.....	60
Table 8. Summary of evidence	74
Figures	
Figure A. Analytic framework.....	ES-4
Figure 1. Analytic framework.....	6
Figure 2. Literature flow diagram.....	12
Appendixes	
Appendix A. Search Strategies	
Appendix B. PICOTS	
Appendix C. Included Studies	
Appendix D. Excluded Studies	
Appendix E. Evidence Tables	
Appendix F. Risk of Bias Ratings	

Appendix G. Strength of Evidence

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. 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 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)?

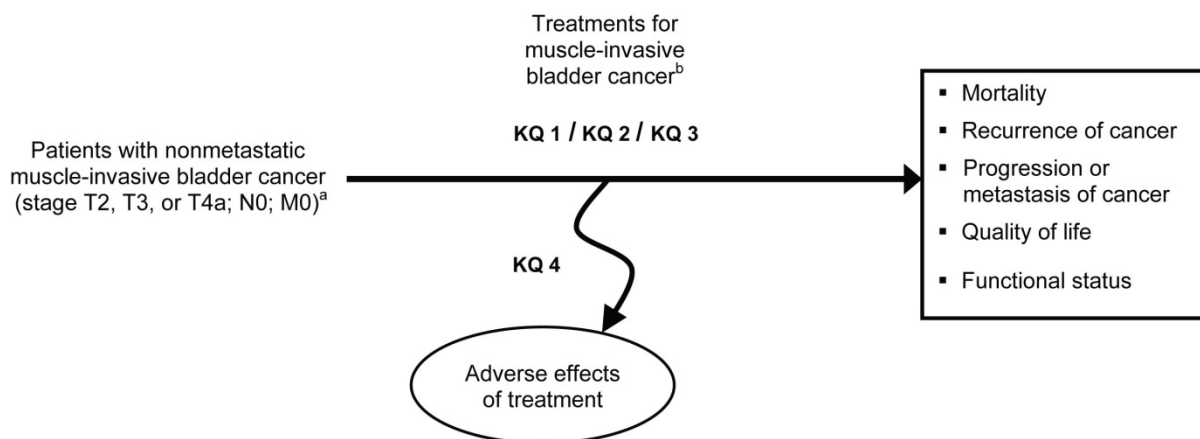
Key Question 3. For patients with nonmetastatic muscle-invasive bladder cancer that is treated with cystectomy, does neoadjuvant or adjuvant chemotherapy improve outcomes compared with cystectomy alone?

- 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



^aQuestions 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.)

^bTreatments 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, metastasis) 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 guidelines⁷ 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 Guide¹² 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).

Table A. Summary of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
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.
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.

Table A. Summary of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
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.
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.

Table A. Summary of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
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.
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 life⁴² 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 Cystectomy for Muscle Invasive Urothelial Cancer. <https://clinicaltrials.gov/show/NCT01224665>. Accessed April 22, 2015.

Introduction

Background

Nature and Burden of Nonmetastatic Muscle-Invasive Bladder Cancer

Bladder cancer is the fourth most commonly diagnosed cancer in men and tenth most commonly diagnosed cancer in women in the United States.¹ The American Cancer Society estimates there will be 74,690 new cases of bladder cancer in the United States in 2014 (about 56,390 men and 18,300 women), and about 15,580 deaths due to bladder cancer (about 11,170 men and 4,410 women).¹

The lifetime probability of developing bladder cancer in the United States is approximately 3.8 percent in men and 1.2 percent in women, although 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 with black men,² though the number of deaths due to bladder cancer is similar, 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 in the United States on a per capita basis, taking into account diagnostic testing, management, and long term followup.⁴ The most common risk factor for bladder cancer is 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, Ta, and T1) are grouped as non-muscle-invasive bladder cancers. Stage classification T2 cancers are muscle-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 (M1) are considered nonlocalized and are outside the scope of this review. Approximately 25 percent of newly diagnosed bladder cancers present as stage 2 or higher tumors.⁶ Once bladder cancer invades muscle, it can quickly progress and metastasize, and is associated with a poor prognosis.

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 cancer has started to grow into the connective tissue beneath the bladder lining
	T2	The cancer has grown through the connective tissue into the muscle
	T2a	The cancer has grown into the superficial muscle
	T2b	The cancer has grown into the deeper muscle
	T3:	The cancer has grown through the muscle into the fat layer
	T3a	The cancer in the fat layer can only be seen under a microscope
	T3b	The cancer in the fat layer can be seen on tests, or felt by a doctor during an examination under anesthetic
	T4:	The cancer has spread outside the bladder
	T4a	The cancer has spread to the prostate, womb (uterus), or vagina
T4b	The cancer has spread to the wall of the pelvis or abdomen	
N stages (lymph nodes)	N0	No cancer in any lymph nodes
	N1	There is cancer in one lymph node in the pelvis
	N2	There is cancer in more than one lymph node in the pelvis
	N3	There is cancer in one or more lymph nodes in the groin
M stages (metastasized)	M0	There are no signs of distant spread
	M1	The cancer has spread to distant parts of the body
1973 WHO grading urothelial papilloma	Grade 1 (G1)	Well differentiated
	Grade 2 (G2)	Moderately differentiated
	Grade 3 (G3)	Poorly differentiated
2004 WHO grading	-	Flat lesions
	-	Hyperplasia (flat lesion without atypia or papillary)
	-	Reactive atypia (flat lesion with atypia)
	-	Atypia of unknown significance
	-	Urothelial dysplasia
	-	Urothelial carcinoma <i>in situ</i>
	-	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, 2013.⁷ American Cancer Society, 2014.⁸ EUA Guidelines (Babjuk 2013).⁹

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, including p53, mTOR pathway genes, pRb, MRE11, BRCA1, ERCC1, MDR1, ET-1, and others, have also been evaluated for their prognostic value and to potentially inform selection of treatments.¹⁰

For nonmetastatic muscle-invasive bladder cancer, the gold standard treatment option is radical cystectomy combined with neoadjuvant (administered prior to chemotherapy) systemic chemotherapy with a cisplatin-based regimen (methotrexate, vinblastine, doxorubicin, and cisplatin [MVAC], cisplatin, methotrexate, and vinblastine [CMV], or gemcitabine and cisplatin).¹¹ The components of these treatment regimens are US Food and Drug Administration

approved and clinically available in the United States, though the combinations do not have a specific bladder cancer indication. 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; an alternative chemotherapeutic regimen with potentially less renal toxicity is gemcitabine and carboplatin.

Regional lymph node dissection in conjunction with cystectomy or partial cystectomy is recommended because it can diagnose clinically nonevident lymph node metastases and may be associated with improved cancer-specific survival, but may be underutilized.¹¹⁻¹⁴ Similarly, cystectomy appears to be underused for non-metastatic muscle-invasive bladder cancer relative to recommendations from clinical practice guidelines,¹⁵ 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. Maximal TURBT refers to a procedure involving resection of all visible tumors into deep muscle or perivesical fat, with at least 1 cm resected margin of normal mucosa.¹⁶ Several modalities of radiation therapy have been evaluated, including external beam radiation therapy and interstitial radiation therapy (brachytherapy). These alternative treatments are generally only recommended for carefully selected, well-informed patients due to the need for continued surveillance and invasive diagnostic procedures, and the risk of eventual cystectomy.¹¹ The comparative effectiveness of these treatments or their combinations is an important clinical issue.

Rationale for Evidence Review

Systematic reviews on 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, the effectiveness of regional lymph node dissection, and includes recently published evidence focusing on treatments used in current practice may be useful for developing updated clinical guideline for muscle-invasive bladder cancer.

Scope of Review 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 1) shows the scope of this review, including the target population, interventions, and health outcomes we examined.

Key Questions

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 non-metastatic 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?

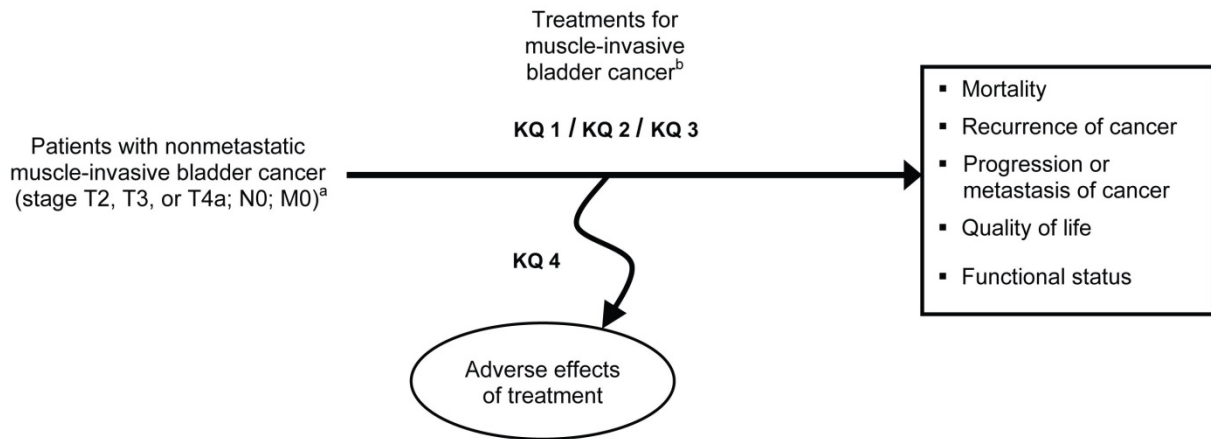
- a. What is the comparative effectiveness of various combinations of agents used for neoadjuvant or adjuvant chemotherapy?
- b. Does the comparative effectiveness of various combinations of agents used for neoadjuvant or adjuvant chemotherapy differ according to tumor characteristics, such as histology, 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 1. 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

^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]

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”).¹⁷ All methods were determined a priori.

Topic Development and Refinement

AHRQ initially received this topic as a nomination via the Effective Healthcare Website (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 Pacific Northwest 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 8 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 it was posted on the AHRQ Web site on July 21, 2014 (www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1940). The protocol was also registered in the PROSPERO international database of prospectively registered systematic reviews.

Searching for the Evidence

A research librarian experienced in conducting literature searches for CERs searched in Ovid MEDLINE (January 1990–October 2014), Cochrane Central Register of Controlled Trials (through September 2014), Cochrane Database of Systematic Reviews (through September 2014), Health Technology Assessment (through 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 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. Scientific information packets were solicited from drug and device manufacturers and via a

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

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 PICOTS approach, in accordance with the AHRQ Methods Guide.¹⁷ 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 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, M0. Patients staged clinically could have occult metastasis.

Interventions, Comparisons, 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 transurethral resection of bladder tumor (TURBT) compared with radical cystectomy alone, radical cystectomy in combination with chemotherapy, or to the 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, or 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 guidelines¹¹ and currently used in clinical practice: cisplatin and gemcitabine; cisplatin, methotrexate and vinblastine (CMV); methotrexate, vinblastine, doxorubicin and cisplatin (MVAC); and carboplatin and gemcitabine. 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) and nonrandomized controlled clinical trials and nonrandomized cohort studies with concurrent comparators (referred to simply as “cohort studies” throughout this report) 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. We restricted

inclusion to studies published in or after 1990, given changes in surgical techniques and other medical practices over time.

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 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

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. When data were available, we calculated relative risks and associated 95% confidence intervals (CI) based on the 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. See Appendix E for evidence tables containing extracted data.

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.¹⁸ These criteria were applied in conjunction with the approach recommended in the AHRQ Methods Guide for medical interventions.¹⁷

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.¹⁷ 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 to allocated treatments; the use of intent-to-treat analysis; and avoidance of selective outcomes reporting.¹⁸

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).¹⁸

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 high risk of bias studies are at least as likely to reflect flaws in the study design as the differences between the compared interventions. We did not exclude studies rated as having high risk of bias a priori, but they were considered the least reliable when synthesizing the evidence, particularly when discrepancies between studies were present.

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

Assessing Applicability

We recorded factors important for understanding the applicability of studies, such as whether the publication adequately described the study sample, the country in which the study was conducted, the characteristics of the patient sample (e.g., age, sex, race/ethnicity, risk factors for bladder cancer, presenting symptoms, and medical comorbidities), tumor characteristics (e.g., stage and grade, primary or recurrent, unifocal or multifocal lesions), the characteristics of the diagnostic tests (e.g., specific test evaluated and cutoffs used) and interventions (e.g., treatment dose, duration and interval) used, and the magnitude of effects on clinical outcomes.¹⁷ 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. The funding source was also recorded.

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,¹⁷ based on the overall quality of each body of evidence, 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)

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.¹⁷ 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 table.

Peer Review and Public Commentary

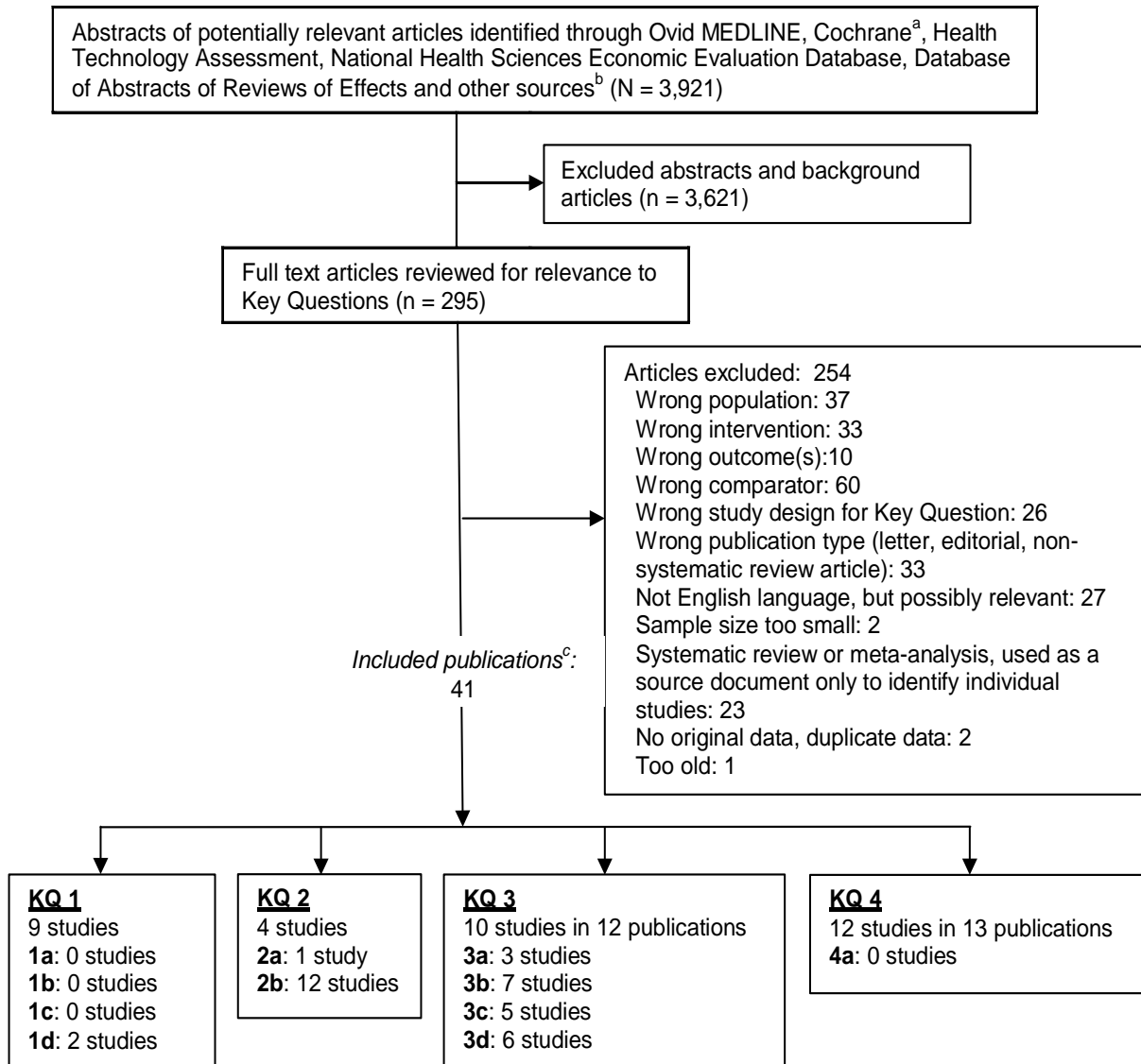
Experts in urology, urologic surgery, urologic oncology, and medical and radiation oncology, were invited to provide peer review of the draft report. The AHRQ Task Order Officer and an Evidence-based Practice Center Associate Editor also provided comments and editorial review. The draft report was posted on the AHRQ Web site for 3 weeks to obtain 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 3,921 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. Data extraction and quality assessment tables for all included studies per Key Question are available in Appendixes E and F.

Figure 2. Literature flow diagram



^aCochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.

^bOther sources include prior reports, reference lists of relevant articles, systematic reviews, etc.

^cSome studies have multiple publications and some are included for more than one Key Question.

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?

Key Points

- One high risk of bias randomized controlled trial (RCT) 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 (seven studies) or local or regional recurrence (three studies), due to 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).

Detailed Synthesis

One RCT,¹⁹ seven retrospective cohort studies,²⁰⁻²⁶ and one nonrandomized controlled clinical trial²⁷ compared bladder-sparing therapy versus radical cystectomy either alone or in combination with chemotherapy in patients with clinically nonmetastatic muscle-invasive bladder cancer (Tables 2, 3; Appendix E). Tumor stage was reported in seven studies.^{19, 21-26} In addition to muscle-invasive bladder cancer, three studies included some patients with T1 tumors (proportion 2.3% to 24%),²⁴⁻²⁶ including one study restricted to patients with T1 and T2 cancers.²⁵ One study was restricted to T2 tumors.²³ No study reported the proportion of patients undergoing radical cystectomy found to have lymph node metastasis based on pathological staging, or described whether such patients were excluded from analyses.

The interventions evaluated in the studies varied. The RCT evaluated bladder-sparing radical external beam radiation therapy with 60 Gray versus preoperative external beam radiation therapy with 40 Gray followed by radical cystectomy.¹⁹ In three cohort studies, the bladder-sparing therapy was radical external beam radiation therapy with at least 55 Gray, though the amount of conformal radiation delivered was less than in contemporary techniques.²²⁻²⁴ One of these studies also included patients who underwent bladder-preserving therapy primarily with maximal transurethral resection of bladder tumor (TURBT), though some patients also received lower dose (21 Gray) radiation therapy.²² Another cohort study evaluated bladder-sparing therapy with external beam radiation therapy with 30 Gray combined with brachytherapy delivered through a suprapubic cystotomy, with or without partial cystectomy depending on initial response.²⁵ Two cohort studies evaluated bladder-sparing therapy that included both radiation therapy and chemotherapy.^{20, 26} One of these was a population-based study conducted

in the United States, in which bladder-sparing therapy consisted of the combination of TURBT, external beam radiation therapy of variable dosing, and concurrent cisplatin-based chemotherapy.²⁰ The other was a single institution Spanish study that evaluated two bladder-sparing regimens depending on the time period: from 1997-2003, chemotherapy with paclitaxel, methotrexate, 5-fluorouracil, and cisplatin for two cycles, followed by external beam radiation therapy with 45-65 Gray concurrent with 5-fluorouracil and cisplatin, then an additional two cycles of the first chemotherapy regimen; from 2003-2007, chemotherapy with paclitaxel, gemcitabine, and cisplatin for two cycles, followed by intensity-modulated radiation therapy with 55-65 Gray, then an additional two cycles of the first chemotherapy regimen.²⁶ A cohort study based on population-based registry data from the Netherlands compared external beam radiation therapy, brachytherapy, TURBT, or radical cystectomy, but did not provide details about the interventions.²¹ The non-RCT evaluated bladder-sparing therapy with one of three cisplatin-based chemotherapy regimens.²⁷ In two studies, comparison groups were not entirely concurrent (i.e., patients tended to receive one intervention during an earlier time period and a different intervention at a later time period).^{23, 25}

Sample sizes ranged from 145 to 2,455 patients. Duration of followup was reported in six studies and ranged from a median of 18 months²⁶ to at least 5 years.²² One study was conducted in the United States²⁰ and the other eight were conducted in Europe. All studies had methodological limitations (Appendix F). The RCT was rated high risk of bias.¹⁹ Methodological shortcomings included baseline differences between treatment groups and poor reporting of attrition and loss to followup. In addition, its applicability to current practice is uncertain as it used radiation therapy regimens and surgical techniques that appeared outdated. Two nonrandomized studies were rated medium risk of bias^{20, 25} and six were rated high risk of bias. Methodological shortcomings in the nonrandomized studies included failure to report enrollment of a consecutive or random sample and poorly reported methods for ascertaining potential confounders. The high risk of bias nonrandomized studies did not attempt to adjust for potential confounders^{21-23, 26, 27} or did not clearly report the results of adjusted analyses or the factors adjusted for.²⁴ Four cohort studies were conducted in single institutions.²³⁻²⁶ Three other cohort studies evaluated population-based data²⁰⁻²² and the nonrandomized controlled clinical trial evaluated multi-institutional²⁷ data.

Mortality

Seven studies evaluated overall survival with bladder-sparing therapies versus radical cystectomy.¹⁹⁻²⁵ In one RCT (n=183), there was no difference between bladder-sparing therapy with external beam radiation therapy (60 Gray) versus radical cystectomy plus external beam radiation therapy (40 Gray) in median survival duration (18 versus 20 months, p=0.21).¹⁹ A population-based cohort study (n=1,843) found bladder-sparing therapy associated with decreased likelihood of 5-year survival versus radical cystectomy (27.9% vs. 46.5%).²⁰ In multivariate analyses, the difference was statistically significant in a Cox proportional hazards analysis that adjusted for age, sex, comorbid conditions, race/ethnicity, marital status, and socioeconomic, physician, and hospital factors (HR for mortality 0.79, 95% CI 0.67 to 0.93) and in a propensity-adjusted analysis (HR 0.79, 95% CI 0.65 to 0.95). However, the difference was not statistically significant in an instrumental variable analysis (HR 0.94, 95% CI 0.76 to 1.28) that used local area cystectomy rate as the instrumental variable. A retrospective cohort study (n=108) also found radical cystectomy associated with higher likelihood of survival (50% vs. 58% at 10 years) after adjustment for age, tumor stage, nodal status, grade, and tumor multiplicity,

though the difference was not statistically significant (HR 0.62, 95% CI 0.28 to 1.43).²⁵ Four other cohort studies evaluated all-cause mortality but did not attempt to adjust for potential confounders.²¹⁻²⁴ In one study (n=148), both radiation therapy and maximal TURBT were associated with increased risk of 5-year all-cause mortality in patients with T2 and T3 tumors, though the differences were not statistically significant (85% vs. 86% vs. 67%, RR 1.27, 95% CI 0.95 to 1.70 and RR 1.30, 95% CI 0.98 to 1.71 for radiation therapy versus radical cystectomy and maximal TURBT versus radical cystectomy, respectively).²² All patients with T4a bladder cancer in this study died, including 9 patients who underwent radiation therapy, 26 who underwent maximal TURBT, and 6 who underwent radical cystectomy. One study (n=169) found external beam radiation therapy with at least 55 Gray associated with decreased likelihood of 5-year survival (35% vs. 41%) and 8-year survival (18% vs. 36%), though the difference was not statistically significant (p=0.39).²⁴ Another study (n=145) found radiotherapy associated with decreased likelihood of survival at 3 years versus radical cystectomy (39% vs. 69%, p=0.03).²³ One study (n=2,455) found brachytherapy associated with higher unadjusted 5-year survival than radical cystectomy, external beam radiation therapy, or TURBT alone (70% vs. 48%, 29%, and 19%, respectively), but there were substantial differences between groups in age and bladder cancer stage.²¹

Four cohort studies evaluated effects of bladder sparing therapy versus radical cystectomy on risk of bladder cancer-specific mortality, but results were inconsistent.^{20, 22, 24, 25} The population-based U.S. study (n=1,843) found bladder-sparing chemotherapy and radiation associated with lower likelihood of 5-year disease specific survival versus radical cystectomy, though the difference was not statistically significant (52% vs. 65%, adjusted HR 0.78, 95% CI 0.60 to 1.02).²⁰ Another study (n=185) found the combination of external beam radiation therapy followed by brachytherapy associated with lower likelihood of disease-specific survival versus radical cystectomy after adjustment for age, tumor stage, nodal status, and tumor multiplicity (67% vs. 72% at 10 years, HR 0.50, 95% CI 0.20 to 1.25), though the difference was not statistically significant.²⁵ Two other cohort studies did not adjust for potential confounders.^{22, 24} One study (n=148) found bladder-preserving radiation therapy or maximal TURBT each associated with increased risk of 5-year bladder cancer-specific mortality versus radical cystectomy in patients with T2 or T3 tumors (82% vs. 75% vs. 57%), though the difference was only statistically significant for radiation therapy (RR 1.44, 95% CI 1.02 to 2.05).²² The other study (n=169) found no difference between external beam radiation therapy with at least 55 Gray versus radical cystectomy in 5-year disease-specific survival (57% vs. 53%, p=0.38).²⁴

Local and Regional Recurrence and Progression

Two studies evaluated effects of bladder-sparing therapy on local or regional recurrence.^{19, 23} In one RCT (n=183), bladder-sparing external beam radiation therapy (60 Gray) was associated with increased risk of local or regional recurrence versus radical cystectomy plus external beam radiation therapy (40 Gray) over a median followup of 50 months (35.8% vs. 6.8%, RR 5.25, 95% CI 2.31 to 11.9).¹⁹ A cohort study (n=145) found bladder-sparing therapy associated with lower likelihood of achieving local disease control (42% vs. 88% RR 0.48, 95% CI 0.37 to 0.61) and higher likelihood of developing distant metastases (16% vs. 7.7%, RR 2.08, 95% CI 0.52 to 8.37), but the estimate for metastases was imprecise and the study did not perform statistical adjustment for potential confounders.²³

One cohort study found no difference between radical cystectomy versus radiation therapy in risk of local recurrence or distant progression (34% vs. 38%, RR 0.91, 95% CI 0.60 to 1.36).²⁴

Another cohort study found no difference between bladder-sparing chemotherapy and radiation versus radical cystectomy in unadjusted progression free survival (local or distant) (61% vs. 63% at 5 years, $p=0.83$).²⁶ One non-randomized controlled clinical trial found that 72% (54/75) of patients who underwent bladder-sparing cisplatin-based chemotherapy as monotherapy subsequently required salvage radical cystectomy.²⁷ The proportion that underwent cystectomy was not explicitly reported in the other studies.

Quality of Life

No study evaluated effects of bladder-sparing therapy versus radical cystectomy on quality of life.

Key Question 1a. Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?

Key Points

- 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).

Detailed Synthesis

No studies.

Key Question 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?

Key Points

- 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).

Detailed Synthesis

No studies.

Key Question 1c. What is the comparative effectiveness of various combinations of agents and/or radiation therapy used for bladder-preserving chemotherapy?

Key Points

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

Detailed Synthesis

No study compared the effectiveness of different combinations of chemotherapeutic agents and/or radiation treatment. Although three studies included different chemotherapy regimens in their bladder-sparing therapy treatment groups,^{20, 26, 27} they did not analyze the comparative effectiveness of different chemotherapy regimens on clinical outcomes.

Key Question 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?

Key Points

- One RCT found external beam radiation therapy with synchronous chemotherapy 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) and trends towards 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).

Detailed Synthesis

One RCT found external beam radiation therapy with synchronous chemotherapy with fluorouracil and mitomycin C associated with lower likelihood of 2-year locoregional recurrence (33% vs. 46%, HR 0.68, 95% CI 0.48 to 0.95) or invasive locoregional disease (18% vs. 32%, HR 0.57, 95% CI 0.37 to 0.89), and 5-year metastasis (HR 0.72, 95% CI 0.53 to 0.99) versus radiation therapy without chemotherapy in patients with T2 to T4a tumors.²⁸ Effects were similar in subgroups that received different radiotherapy or according to receipt of neoadjuvant chemotherapy (about one-third of patients in both groups). Although chemoradiotherapy also was associated with lower risk of overall (52% vs. 65% at 5 years, HR 0.82, 95% CI 0.63 to 1.09) and bladder cancer mortality (42% vs. 51%, HR 0.77, 95% CI 0.57 to 1.05), differences were not statistically significant. The trial was not blinded and was rated medium risk of bias.

One cohort study found no difference between bladder-preserving radiation therapy versus maximal TURBT in all-cause (85% vs. 86%, RR 0.98, 95% CI 0.82 to 1.18) or bladder cancer-

specific mortality (82% vs. 75%, RR 1.09, 95% CI 0.86 to 1.38) at 5 years in patients with T2 or T3 tumors.²² It did not adjust for potential confounders and was rated high risk of bias.

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?

Key Points

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

Detailed Synthesis

Four retrospective cohort studies evaluated effects of radical cystectomy with regional lymph node dissection versus radical cystectomy without regional lymph node dissection. (Tables 4, 5; Appendix E).²⁹⁻³² Two were U.S. population-based studies based on Surveillance, Epidemiology, and End Results (SEER) program data (n=11,183 and n=1,923),^{29, 31} one (n=268) was a secondary analysis of a multicenter RCT of neoadjuvant chemotherapy before cystectomy,³³ and one (n=169) was a single institution series from Japan.³² All four studies included patients of all stage classifications. In one study duration of followup was at least 2 years but otherwise not specified³¹ and in the other three studies duration of followup was not reported. All four studies had methodological shortcomings, including baseline differences between treatment groups, poor reporting of attrition, and failure to adjust for potential confounders (Appendix F).

One study based on SEER data found regional lymph node dissection with at least four lymph nodes removed was associated with decreased risk of overall mortality over time versus no lymph node dissection (HR 0.53, 95% CI 0.36 to 0.76), after adjustment for age, gender, tumor stage, race/ethnicity, and receipt of radiation or chemotherapy.³¹ Risk of mortality did not differ between patients with fewer than four lymph nodes removed versus no lymph node dissection (HR 0.93, 95% CI 0.69 to 1.27). Another study of SEER data found limited or extended lymph node dissection associated with decreased risk of 10-year bladder cancer specific and overall mortality versus no lymph node dissection (HR 0.75, 95% CI 0.69 to 0.81 and HR 0.78, 95% CI 0.73 to 0.82, respectively).²⁹ A third study found greater unadjusted 5-year survival with standard or limited lymph node dissection than no dissection (60% vs. 46% vs. 33%, respectively, p=0.01) as well as decreased risk of recurrence (5% vs. 22% vs. 50%, p<0.0001).³³ The Japanese study found that cancer-specific survival at 5 years was similar among patients with negative lymph node dissection versus those who did not undergo lymph node dissection (74% vs. 72%, p=0.85), but lower (41%) among patients with positive lymph nodes on dissection.³² However, data were not provided to compare survival between all patients who underwent lymph node dissection versus those who did not.

Key Question 2a. Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?

Key Points

- 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, but for all-cause mortality there was no clear pattern suggesting differential effectiveness according to tumor stage (SOE: low).

Detailed Synthesis

One previously described retrospective cohort study (n=11,183) based on SEER program data evaluated effects of radical cystectomy with no lymph node dissection versus radical cystectomy with limited or extended lymph node dissection (Appendix E).²⁹ It found that lymph node dissection was associated with decreased mortality in patients at all stages of bladder cancer, though the effects on bladder cancer-specific mortality appeared strongest for lower stage tumors. Adjusted hazard ratios (HR) for 10-year bladder cancer-specific mortality ranged from 2.09 (95% CI 1.16 to 3.79) for stage classification Ta/Tis to an HR of 1.11 (95% CI 0.96 to 1.28) for stage classification T4. For all-cause mortality, there was no clear pattern suggesting differential effectiveness of lymph node dissection based on tumor stage (HRs ranged from 1.13 to 1.49).

Key Question 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)?

Key Points

- Eleven cohort studies found more extensive lymph node dissection 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).

Detailed Synthesis

Twelve retrospective cohort studies evaluated effects of the extent of lymph node dissection on clinical outcomes (Tables 4 and 5; Appendix E).²⁹⁻⁴⁰ Six were multicenter studies.^{31, 33, 34, 36, 39,}⁴⁰ One study was a reanalysis of data from patients enrolled in a RCT,³³ five were single institution series,^{30, 32, 35, 37, 38} and one was a U.S. population-based study based on SEER program data.²⁹ The SEER study included data for 11,183 patients and the sample sizes in the other studies ranged from 92 to 1923. Duration of followup was reported in seven studies: one

reported minimum followup of 2 years,³¹ two reported minimum followup of 5 years,^{33, 36} one reported minimum followup of 10 years,³⁰ and the other studies reported mean followup of 38.7 months,³⁷ 59.2 months,³⁵ and median followup of 10.9 years.³⁹ Five studies were conducted in Europe,^{34, 35, 37, 38, 40} two studies evaluated patients in the United States and Europe,³⁶ four studies evaluated U.S. patients,^{29-31, 33} and one study evaluated patients in Japan.³² Six studies were rated medium risk of bias (Appendix F)^{29, 31-33, 35, 40} and six were rated high risk of bias.^{30, 33, 34, 36-39} Common methodological limitations included insufficient information to determine baseline comparability of groups, failure to report attrition, and unclear methods for ascertaining confounders. The high risk of bias studies did not perform statistical adjustment for potential confounders. Two of the high risk of bias studies also evaluated comparisons of a U.S. cohort undergoing one lymph node dissection technique versus a European cohort undergoing a different lymph node dissection technique.^{36, 39} One of these studies compared patients who underwent radical cystectomy with less extensive lymph node dissection in the United States versus patients who underwent more extended lymph node dissection in Europe.³⁶ The other compared outcomes in a U.S. cohort that underwent more extensive lymph node dissection versus a European cohort that underwent more limited lymphadenectomy, based on the median number of lymph nodes removed (38 vs. 22).³⁹ One other study compared patients who underwent less extensive lymph node dissection in an Austrian center versus patients who underwent more extensive lymph node dissection in an Italian center.³⁴ In one study, comparison groups were not entirely concurrent.³⁸

Two studies compared “extended” versus “standard” lymph node dissection methods,^{35, 40} four compared “extended” versus “limited” dissection,^{34-36, 38} and three compared “standard” versus “limited” dissection.^{30, 33, 35} One study compared “extended” versus “super extended” lymph node dissection.³⁹ Standard and limited lymph node dissection was mostly restricted to a pelvic dissection that was bordered proximally by the common iliac bifurcation, laterally by the genitofemoral nerve, medially by the internal iliac artery, posteriorly by the obturator nerve, and the node of Cloquet distally. Extended templates varied and usually involved more proximal lymphadenectomy with dissection of periaortic nodes up to the inferior mesenteric artery³⁸⁻⁴⁰ or described inclusion of more medial tissue such as presacral lymph nodes^{35, 39, 40} or lymph nodes along and medial to the internal iliac artery.^{35, 36} Seven studies, including two studies of “standard” versus “limited” dissection,^{30, 33} performed analyses based on the node yield (number of nodes in pathological specimen) rather than or in addition to the lymph node dissection template used.^{29-33, 35, 37}

Mortality

Seven studies evaluated effects of more versus less extensive lymph node dissection on all-cause mortality.^{29-33, 36, 38, 39} Although studies found standard versus limited lymph node dissection and higher versus lower lymph node yield both associated with decreased risk of all-cause mortality, the effects of more extended versus standard dissection templates were less clear. One study (n=1601) based on SEER data found lymph node dissection involving four or more lymph nodes associated with decreased risk of mortality versus no lymph node dissection (HR 0.53, 95% CI 0.36 to 0.76) after adjustment for age, gender, tumor stage, race/ethnicity, and receipt of radiation or chemotherapy, but no difference between lymph node dissection of fewer than four nodes and no lymph node dissection (HR 0.93, 95% CI 0.69 to 1.27).³¹ However, there was no clear dose-response relationship with increasing number of nodes dissected beyond four. Another study based on US SEER data (n=11,183) found lymph node dissection involving ≥ 10

lymph nodes removed associated with lower 10-year mortality versus lymph node dissection with <10 lymph nodes (30.3% vs. 39.4%, $p<0.001$).²⁹ One study ($n=268$) of patients undergoing standard or limited lymph node dissection found removal of ≥ 10 nodes associated with decreased risk of mortality versus <10 nodes, after adjustment for treatment, age, tumor stage, positive or negative node status, and positive or negative margin status (HR 0.50, 95% CI 0.36 to 0.71).³³ This study also found standard dissection associated with lower risk of mortality than limited dissection in an unadjusted analysis, though the difference did not reach statistical significance (52% vs. 64%, RR 0.84, 95% CI 0.68 to 1.04). Another study ($n=322$) of standard or limited lymph node dissection also found an association between a greater number of lymph nodes examined and lower mortality risk among both node-positive (56% for ≥ 11 vs. 80% for <11 lymph nodes, $p=0.004$) and node-negative (18% for ≥ 8 vs. 59%, $p<0.0005$) patients.³⁰ Findings were similar when patients were stratified according to tumor stage.²⁹ One study ($n=658$) found no difference between extended lymph node dissection performed at a European institution versus limited dissection performed at a U.S. institution in unadjusted 5-year survival in patients with T2 tumors (61% vs. 64%, $p=0.10$), but extended lymph node dissection was associated with higher 5-year survival in patients with T3 tumors (42% vs. 22%, respectively, $p=0.002$).³⁶ Another study ($n=959$) found no difference in unadjusted survival between “super extended” lymph node dissection performed in a U.S. institution versus “extended” lymph node dissection performed in a European institution ($\sim 17\%$ in each group, $p=0.45$).³⁹ A Danish within-institution study ($n=194$) found no difference between extended versus limited lymph node dissection in survival among patients with stage T3b and higher tumors, but extended lymph node dissection was associated with higher (unadjusted) survival in patients with stage T3a or lower cancers (90% vs. 71%, $p<0.02$).³⁸

Five studies also found more extensive lymph node dissection associated with higher likelihood of bladder cancer-specific survival than less extensive lymph node dissection.^{29, 32, 35, 37, 40} In a US study ($n=11,183$), 10-year cancer-specific mortality-free rate was 62.2% with extended versus 54.0% with limited lymph node dissection.²⁹ Hazards ratios after adjustment for age, sex, race/ethnicity, tumor grade, and year of surgery were nonoverlapping (HR 0.65, 95% CI 0.59 to 0.71 and HR 0.83, 95% CI 0.76 to 0.89, respectively). In one Italian study ($n=933$), extended lymph node dissection was associated with higher likelihood of cancer-specific survival than standard lymph node dissection after adjustment for tumor stage and nodal status (HR 1.80, 95% CI 1.37 to 2.37).⁴⁰ In another Italian study ($n=272$), extended lymph node dissection was associated with decreased risk of bladder cancer-specific mortality versus limited or no lymph node dissection after adjustment for tumor stage and number of lymph nodes (HR 0.46, 95% CI 0.36 to 0.89), but there was no difference between standard versus limited or no dissection (HR 0.99, 95% CI 0.55 to 1.35).³⁵ However, confidence intervals for the two estimates overlapped. The same study also found ≥ 14 lymph nodes removed associated with decreased risk of bladder cancer-specific mortality versus 0-14 lymph nodes removed (HR 0.56 95% CI 0.28 to 0.995). In a Japanese study, node yields of <9 lymph nodes was associated with poorer 5-year bladder cancer-specific survival versus yield of ≥ 9 nodes after adjustment for tumor stage (53% vs. 84%, HR 3.48, 95% CI 1.50 to 9.31).³² A German study ($n=447$) found removal of 16 or more nodes associated with greater unadjusted disease-specific survival at 5 years than removal of 15 or fewer nodes (65% vs. 15%, $p<0.013$).³⁷

Recurrence and Progression

Six studies evaluated effects of more extensive versus less extensive lymph node dissection on risk of bladder cancer recurrence or progression.^{30, 33, 36-39} One study (n=268) of patients who underwent standard or limited lymph node dissection found removal of ≥ 10 nodes associated with decreased risk of mortality versus < 10 nodes, after adjustment for treatment, age, tumor stage, positive or negative node status, and positive or negative margin status (HR 0.20, 95% CI 0.07 to 0.56).³³ This study also found standard dissection associated with lower risk of recurrence than limited dissection in an unadjusted analysis (4.8% vs. 22%, RR 0.21, 95% CI 0.09 to 0.48). Another study (n=322) of standard or limited lymph node dissection also found an association between a larger number of lymph nodes examined and lower risk of local recurrence among both node-positive (9% for ≥ 11 vs. 30% for < 11 lymph nodes, $p=0.002$) and node-negative (5% for ≥ 8 vs. 24% for < 8 lymph nodes, $p=0.001$) patients.³⁰ Findings were similar when patients were stratified according to tumor stage. Adjustment was not performed in the other four studies. One study (n=658) found extended lymph node dissection (performed in Europe) associated with lower risk of local or systemic progression than limited lymph node dissection (performed in the United States; 40% vs. 55%, RR 0.74, 95% CI 0.63 to 0.87).³⁶ Similar effects were seen in patients with either T2 or T3 tumors. The difference between extended versus limited lymph node dissection in 5-year recurrence-free survival was not statistically significant for T2 tumors (71% vs. 63%, $p=0.22$), but for T3 tumors extended lymph node dissection was associated with superior recurrence-free survival (49% vs. 19%, $p<0.001$). Another study (n=447) found yields of ≥ 16 lymph nodes associated with decreased risk of local recurrence (17% vs. 27%) and distant metastasis (17% vs. 10%) versus yields of 15 or fewer nodes ($p<0.01$).³⁷ Two other studies found no difference in recurrence-free survival based on the extent of regional lymph node dissection.^{38, 39} One study (n=194) reported 5-year bladder cancer recurrence free survival of 62 percent for extended lymphadenectomy versus 56 percent for standard lymph node dissection ($p=0.33$).³⁸ Risks of distant metastasis and pelvic recurrence were similar. One study (n=959) found no difference between less extensive lymph node dissection (performed in Europe) versus more extensive dissection (performed in the United States) in risk of recurrence (38% vs. 38%, RR 1.00, 95% CI 0.85 to 1.17).³⁹

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?

Key Points

Neoadjuvant Chemotherapy

- Six trials found neoadjuvant chemotherapy (NAC) associated with decreased risk, or a trend towards decreased risk, of mortality versus no NAC. Three trials evaluated standard chemotherapy regimens (cisplatin, methotrexate, and vinblastine [CMV] and methotrexate, vinblastine, doxorubicin, and cisplatin [MVAC]) and three trials utilized 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) associated with

lower risk of disease progression, the largest trial and the only one to show a statistically significant effect found neoadjuvant CMV 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) (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 adjuvant chemotherapy (AC) 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, due to imprecise estimates and inconsistency between studies (SOE: insufficient).

Detailed Synthesis

Six trials (reported in eight publications) evaluated NAC⁴¹⁻⁴⁸ and four trials evaluated AC (Tables 6 and 7; Appendix E)⁴⁹⁻⁵² for muscle-invasive bladder cancer. Four RCTs compared NAC plus radical cystectomy versus radical cystectomy alone,^{41, 44, 47, 48} one compared NAC, radiation therapy and radical cystectomy versus radiation therapy plus radical cystectomy,^{45, 46} and one compared NAC plus radical cystectomy, radiation therapy, or both versus radical cystectomy, radiation therapy, or both.^{42, 43} The chemotherapy regimens evaluated in the NAC trials were MVAC, CMV, cisplatin/methotrexate, and cisplatin/doxorubicin. All four trials of AC compared AC after radical cystectomy versus cystectomy alone.⁴⁹⁻⁵² No study evaluated AC among patients that had received NAC. The chemotherapy regimens evaluated in the AC trials were CMV, cisplatin/gemcitabine, cisplatin/methotrexate, and cisplatin/doxorubicin/cyclophosphamide.

Sample sizes in the NAC trials ranged from 33 to 976 and in the AC trials from 50 to 132. Mean age ranged from 59 to 71 years. The trials enrolled patients with T2-T4a, node-negative bladder cancer, however two NAC trials also included patients with high-grade T1 disease^{45, 46} and one AC trial only included patients with T3-T4a disease.⁴⁹ The four AC trials⁴⁹⁻⁵² included patients with clinically node negative disease found to be node positive following radical cystectomy. In these trials, results were reported separately for node positive and node negative patients. Lymph node dissection was included as part of surgical management in eight of the studies.^{42, 43, 45, 47-52} Average followup ranged from 32 to 104 months.

All RCTs were rated medium risk of bias. Methodological limitations included unclear randomization and allocation concealment methods, lack of blinding, and clinically important baseline differences between groups (Appendix F).

Neoadjuvant Chemotherapy

Mortality

Six trials evaluated effects of NAC versus no NAC on mortality.^{41, 42, 44-48} The largest trial (n=976) found neoadjuvant CMV prior to radical cystectomy, radiation therapy, or both

associated with a decreased risk of mortality versus cystectomy, radiation therapy, or both without NAC after a median followup of 4 years, but the difference did not reach statistical significance (HR 0.85, 95% CI 0.71 to 1.02).⁴² In this trial, use of radical cystectomy and/or radiation therapy was left to the discretion of clinicians and patients, with 43 percent of patients undergoing radiation therapy rather than cystectomy. A subsequent report from this study found NAC associated with a statistically significant decreased risk of mortality (HR 0.74, 95% CI 0.57 to 0.96) in the subgroup of patients who underwent radical cystectomy (n=428) after a median of 8 years of followup.⁴³ It also found a 16 percent reduction in mortality in those patients who received three cycles of CMV before radical cystectomy or radiation therapy, which corresponded to an increase in 3-year survival from 50 to 56 percent, an increase in 10-year survival from 30 to 36 percent, and a median survival advantage of 7 months (from 37 to 44 months). Another trial (n=307) found neoadjuvant MVAC plus radical cystectomy with regional lymph node dissection associated with decreased risk of all-cause mortality (59% vs. 65%, HR 0.75, 95% CI 0.57 to 1.00) and bladder cancer mortality (35% vs. 50%, HR 0.60, 95% CI 0.41 to 0.82) versus cystectomy plus lymph node dissection without NAC after a median of 8.7 years followup.⁴¹ Neoadjuvant MVAC was also associated with longer median duration of survival (77 vs. 46 months, p=0.05). One other trial (n=130) also found neoadjuvant MVAC associated with a non-statistically significant trend towards lower risk of 5-year mortality versus cystectomy without NAC (28% vs. 38%, HR 0.65, 95% CI 0.19 to 2.18); the study was underpowered due to poor accrual and early termination.⁴⁴ Median survival also favored NAC (102 vs. 82 months).

Three other trials that evaluated cisplatin-based regimens not commonly used in current practice also found NAC associated with decreased risk of mortality, or a trend towards decreased risk.^{45, 47, 48} One trial (n=311) found neoadjuvant cisplatin and doxorubicin associated with lower risk of death after adjusting for age, gender, histologic grade, hydronephrosis, and tumor stage (RR 0.69, 95% CI 0.49 to 0.98).⁴⁵ One trial (n=309) found neoadjuvant cisplatin and methotrexate associated with a trend towards higher 5-year survival that was not statistically significant (53% vs. 46% 5-year survival, p=0.24).⁴⁸ Another very small (n=33) trial also found neoadjuvant cisplatin and methotrexate plus cystectomy associated with trends towards higher 5-year survival (64% vs. 46%) and median survival duration (82 vs. 46 months, p=0.76).⁴⁷

Progression

The trial of neoadjuvant CMV found NAC associated with lower risk of metastasis or death versus no NAC after a median of 4 years (45% vs. 53%, HR 0.79, 95% CI 0.66 to 0.93).⁴² A trial of neoadjuvant MVAC found NAC associated with a decreased risk of disease-progression at 5 years (36% vs. 45%, HR 0.64, 95% CI 0.37 to 1.11) and progression-free survival interval (99 vs. 78 months).⁴⁴ A small trial (n=33) found neoadjuvant NAC associated with slightly higher likelihood of 5-year progression-free survival versus no NAC (41% vs. 36%), but the estimate was imprecise and the difference was not statistically significant.⁴⁷

Recurrence

Three RCTs found no effects of NAC on risk of locoregional bladder cancer recurrence.^{42, 43, 45, 48} The largest trial (n=976) found a trend toward improvement in locoregional disease-free survival in those who received CMV prior to radical cystectomy, radiation therapy, or both with a 13 percent decrease in risk of locoregional recurrence or death, but the difference was not statistically significant (HR 0.87, 95% CI 0.75 to 1.01). This same study showed no effect of CMV NAC on locoregional control (HR 0.96, 95% CI 0.80 to 1.15) after 10 years.^{42, 43} When

results were stratified according to receipt of radical cystectomy or radiation therapy, the effect was somewhat stronger in patients who underwent radical cystectomy (HR 0.74, 95% CI 0.58 to 0.95) than radiation therapy (HR 0.91, 95% CI 0.73 to 1.14), but confidence intervals overlapped.⁴³ Another trial (n=311) found no differences between cisplatin plus doxorubicin prior to radical cystectomy versus radical cystectomy alone in risk of recurrence (21% vs. 25%, RR 0.82, 95% CI 0.54 to 1.24) or in time to relapse (median 23 vs. 14 months, p=0.42) after a minimum of 5 years of followup.⁴⁵ The third trial (n=309) found no difference in locoregional or distant recurrence between NAC with cisplatin and methotrexate prior to radical cystectomy after 5 years (10% vs. 9%, RR 1.06, 95% CI 0.53 to 2.13).⁴⁸

Adjuvant Chemotherapy

Mortality

Four trials reported effects of AC on mortality in patients following radical cystectomy.⁴⁹⁻⁵² Though most trials reported results that favored AC, no trial reported a statistically significant effect, and there was some inconsistency. One trial (n=50) found no difference between adjuvant CMV versus no AC in 5-year survival (52% vs. 32%, RR 0.71 95% CI 0.43 to 1.15).⁴⁹ There was also no difference in the subgroup of patients (n=15) found to be node-negative (71% vs. 25%, RR 0.38, 95% CI 0.11 to 1.31). Another trial (n=183) found no difference between adjuvant cisplatin and gemcitabine versus no AC in 5-year survival among all patients (43% vs. 54%, p=0.24) or in the subgroup of node-negative patients (65% vs. 73%, p=0.65).⁵⁰ One trial (n=83) found no difference between adjuvant cisplatin and methotrexate versus no AC in survival among node-negative patients after a median followup of 69 months (49% vs. 38%).⁵² There was also no difference in bladder cancer-specific mortality (46% vs. 52%, RR 0.88, 95% CI 0.56 to 1.38). Another trial (n=91) found no difference between adjuvant cisplatin, doxorubicin, and cyclophosphamide versus no AC in all-cause mortality (34% vs. 50%, p=0.10), bladder cancer-specific mortality (probability 0.29 vs. 0.50) within 3 years in all patients, or among the subgroup of node-negative patients (p=0.14).⁵¹

Progression

One trial (n=83) found no difference between adjuvant cisplatin and methotrexate versus no AC in risk of progression among node-negative patients (49% vs. 44%, RR 0.91, 95% CI 0.61 to 1.37) after a mean followup of 69 months.⁵²

Recurrence

Three trials of AC reported risk of recurrence.⁴⁹⁻⁵¹ Results were inconsistent. One trial (n=50) found adjuvant CMV associated with decreased risk of recurrence after 5 years (52% vs. 76%, RR 0.68, 95% CI 0.44 to 1.06) versus no AC, as well as longer mean time to recurrence (17.5 vs. 11.5 months p=0.01).⁴⁹ A trial (n=183) of adjuvant cisplatin and gemcitabine found no difference in risk of recurrence after a median followup of 35 months (44% vs. 47%, RR 0.95, 95% CI 0.69 to 1.31).⁵⁰ In both trials, results weren't reported separately for patients found to be node-negative following lymph node dissection. The third trial found adjuvant cisplatin, doxorubicin, and cyclophosphamide associated with decreased risk of recurrence at 3 years (probability 0.30 vs. 0.54, p=0.01), with an increase in median time to recurrence of 4.7 years.⁵¹ Effects on recurrence were also observed in the subgroup of patients who were node-negative (p=0.04).

Key Question 3a. What is the comparative effectiveness of various combinations of agents used for neoadjuvant or adjuvant chemotherapy?

Key Points

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

Detailed Synthesis

No RCT directly compared different neoadjuvant or adjuvant chemotherapy regimens. Three retrospective cohort studies compared chemotherapy with MVAC versus cisplatin and gemcitabine.⁵³⁻⁵⁵ One study (n=116) found no difference between neoadjuvant MVAC versus cisplatin and gemcitabine in risk of mortality (HR 0.90, 95% CI 0.52 to 1.56) or bladder cancer recurrence (HR 0.60, 95% CI 0.34 to 1.03) after adjustment for age and tumor stage.⁵³ The study was rated high risk of bias due to large differences in selection of neoadjuvant regimens based on year of treatment (7% of patients received gemcitabine and cisplatin from 1985-1999 vs. 93% from 2000-2011), which may explain differences in the number of lymph nodes evaluated (median 36 for MVAC vs. 53 for gemcitabine plus cisplatin). The other two studies did not attempt to adjust for potential confounders and were also rated high risk of bias. One study (n=66) found no difference in survival between neoadjuvant MVAC versus neoadjuvant cisplatin and gemcitabine, although median overall survival favored MVAC (104.3 vs. 21.8 months, p=0.73).⁵⁴ Another retrospective cohort study (n=114) found no differences between MVAC versus cisplatin and gemcitabine administered either in the neoadjuvant or adjuvant setting in 5-year overall or cancer-specific survival.⁵⁵ Both studies were rated high risk of bias and did not adjust for potential confounders (Appendix F).

Key Question 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?

Key Points

- 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).

Detailed Synthesis

Evidence on the effects of tumor characteristics on effectiveness of chemotherapy was largely limited to tumor stage and nodal status. One trial (n=311) found neoadjuvant cisplatin and doxorubicin associated with higher likelihood of bladder cancer-specific survival versus no NAC in patients with T3-T4a tumors (52% vs. 37%). Although NAC was also associated with higher likelihood of bladder cancer-specific survival in patients with T2 tumors (58% vs. 55%)

and high grade T1 (77% vs. 71%) tumors, the effects were less pronounced.⁴⁵ Another trial reported similar effects of neoadjuvant MVAC on median survival in patients with T2 (105 vs. 75 months) and T3/T4a (65 vs. 24 months) bladder cancer (p=0.45 for interaction between tumor stage and treatment effects).⁴¹ Three other RCTs^{43, 44, 48} that focused on patients with T2-T4a tumors found no interaction between stage of bladder cancer and effectiveness of NAC. In one of these trials, neoadjuvant CMV was associated with greater benefit in high grade tumors than for low grade cancers (p=0.003 for interaction) and there was a trend towards an interaction with tumor size (p=0.06); there was no interaction between nodal status and effects of NAC (p=0.96).⁴³ Another trial found no differences in estimates of effectiveness of NAC in subgroups defined by presence of papillary versus nonpapillary tumors, solitary versus multiple tumors, tumor size, or tumor grade.⁴⁴

Two trials of AC found no clear effects of nodal status on estimates of effectiveness;^{49, 50} one of these trials also found no clear effects of tumor stage on effectiveness.⁵⁰

Key Question 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?

Key Points

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

Detailed Synthesis

Few trials evaluated effect of patient characteristics on the comparative effectiveness of neoadjuvant or adjuvant chemotherapy. Five trials reported no clear interaction between age and estimates of effectiveness of NAC versus no NAC.^{41, 42, 44, 45, 47} One trial of neoadjuvant CMV found no interaction between sex or World Health Organization (WHO) performance status of effects of chemotherapy, but found NAC more effective in patients with better renal function (p=0.024 for interaction).⁴²

Key Question 3d. Does the comparative effectiveness of neoadjuvant or adjuvant chemotherapy differ according to dosing frequency and/or the timing of its administration relative to radical cystectomy?

Key Points

- 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 with methodological shortcomings of adjuvant versus neoadjuvant gemcitabine plus cisplatin to determine effects on bladder cancer recurrence (SOE: insufficient).
- One trial found that neither administration of adjuvant cisplatin plus gemcitabine on day 2 versus day 15 was superior for 5-year survival (SOE: low).

Detailed Synthesis

One trial of patients undergoing radical cystectomy found no differences between five cycles of adjuvant versus two cycles of neoadjuvant plus three cycles of adjuvant MVAC in overall or disease-free survival (60% vs. 56%, RR 0.90, 95% CI 0.61 to 1.33).⁵⁶ The trial was rated medium risk of bias. One retrospective cohort study (rated medium risk of bias) also found no statistically significant difference in overall or disease-specific survival between neoadjuvant versus adjuvant cisplatin/carboplatin based therapies.⁵⁷ Analyses controlling for age, race/ethnicity, sex, smoking history, tumor stage and grade, and chemotherapy type did not change the results. Another retrospective cohort study, rated high risk of bias,⁵⁵ included two therapeutic arms: MVAC and cisplatin plus gemcitabine with regimens given as either NAC or AC. NAC was associated with decreased risk of mortality versus AC, regardless of regimen, though effects were not statistically significant; the HR for overall mortality was 0.61 (95% CI 0.37 to 1.0) and HR for cancer-specific mortality was 0.69 (95% CI 0.37 to 1.29). Another small (n=42) retrospective cohort study also found no difference in recurrence-free survival between adjuvant versus neoadjuvant gemcitabine and cisplatin, but did not adjust for potential confounders.⁵⁸

One RCT (n=132) found no difference between administration of adjuvant cisplatin plus gemcitabine on day 2 versus day 15 in 5-year survival (47% vs. 40%, p=0.88).⁵⁰ One retrospective cohort study found no difference between “standard” cisplatin and gemcitabine (cisplatin 70 mg/m² day 1 and gemcitabine 1000 mg/m² days 1 and 8 for four 21-day cycles) or “split dose” therapy (cisplatin 35 mg/m² and gemcitabine 1000 mg/m² on days 1 and 8 for four 21-day cycles) in overall survival (48% vs. 13%, RR 0.60, 95% CI 0.40 to 0.91), but the estimate was imprecise and the study did not attempt to adjust for potential confounding.⁵⁹

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

Key Points

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 due to 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 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).

Detailed Synthesis

Bladder-Preserving Therapies Versus Radical Cystectomy

Four studies of bladder-sparing therapy versus radical cystectomy reported selected harms.^{19, 22, 23, 27} One RCT (n=183) found no difference between bladder-preserving therapy with external beam radiation therapy with 60 Gray versus radical cystectomy plus external beam radiation therapy with 40 Gray in risk of moderate gastrointestinal adverse events (20% vs. 25%).¹⁹ Three cohort studies also reported selected harms associated with bladder-preserving therapies, but did not perform statistical adjustment for potential confounders. One study (n=78) found no difference between bladder-sparing therapy with radiation therapy versus radical cystectomy in peri-treatment deaths (7.1% vs. 5.6%).²² Another study found that 6.7 percent of patients undergoing bladder-preserving radiation therapy (n=119) experienced grade 3 diarrhea and 6.7 percent experienced grade 3 leukopenia, while 46 percent of patients undergoing radical cystectomy experienced postoperative complications (primarily surgical site infections).²³ The third cohort study found that among patients undergoing bladder-preserving cisplatin-based chemotherapy, 32 percent experienced at least grade 3 leukopenia, 66 percent neutropenia, 13

percent anemia, and 25 percent thrombocytopenia.²⁷ Adverse events in patients undergoing radical cystectomy were not reported.

More Versus Less Extensive Lymph Node Dissection

One study (n=92) found extended lymph node dissection associated with longer operative time than standard lymph node dissection (median 330 vs. 277 minutes), though results were not adjusted for urinary diversion type.³⁴ There were no differences in length of intensive care unit stay or length of hospitalization.

Neoadjuvant Chemotherapy

Harms were inconsistently reported in trials of NAC versus no NAC, though data were available from three trials.^{41, 42, 45} One trial (n=976) reported a mortality rate of 1 percent (5/491) among patients randomized to neoadjuvant CMV prior to radical cystectomy and/or radiation therapy; among 561 patients with planned cystectomy, four (0.7%) did not undergo surgery due to chemotherapy related adverse events.⁴² There was no difference in the number of treatment-related deaths among patients randomized to NAC versus no NAC (3.3% vs. 3.3%).⁴³ Among patients who underwent radical cystectomy, NAC did not increase risk of deaths attributable to cystectomy (2.1% [6/284] vs. 4.3% [12/277] for post-operative wound infections, (7.0% [20/284] vs. 11% [31/277]) for wound dehiscence (2.1% [6/284] vs. 6.5% [18/277]) or development of urinary or fecal fistulae (1.8% [5/284] vs. 6.1% [17/277]).⁴² The rate of serious (WHO grade 3-4) hematologic adverse events among patients who received NAC was 16 percent for leukopenia and 6.5 percent thrombocytopenia. No grade 3 or 4 renal toxic events were reported among patients who received NAC, though 26 percent required dose reductions or dose delays related to impaired renal function.

Another trial (n=307) of neoadjuvant MVAC prior to radical cystectomy reported that among those randomized to NAC, 57 percent (85/150) experienced grade 3 or 4 granulocytopenia, 4.7 percent (7/150) grade 3 thrombocytopenia, and 6.0 percent (9/150) grade 3 anemia.⁴¹ No chemotherapy-associated deaths were reported. The third trial (n=311) found no difference in risk of mortality within 30 days of cystectomy between patients randomized to neoadjuvant cisplatin and doxorubicin versus those randomized to no NAC (1.3% [2/151] vs. 2.5% [4/160]).⁴⁵ There were also no differences in risk of any postoperative complications (48/151 vs. 48/160), though NAC was associated with a higher risk of ileus (13/151 vs. 4/160) and lower risk of wound dehiscence (10/151 vs. 4/160). Hematological and renal adverse events were not reported.

Adjuvant Chemotherapy

Three trials of AC versus no AC reported harms in patients randomized to AC.^{49, 51, 52} One small trial reported one death attributed to neutropenia among 25 patients (4%) randomized to AC after one cycle of CMV.⁴⁹ Two patients (8%) were hospitalized for neutropenia and fever after AC (8%), eight (32%) had additional cycles of chemotherapy due to hematological adverse events, and three (12%) had decreases in renal function requiring dose reduction of chemotherapy; in one patient renal dysfunction (Cr 2.6) was permanent.

One trial (n=114) of adjuvant cisplatin and methotrexate reported renal adverse events in 17 percent (11/66), but the type and severity of events were not further described.⁵² One patient (1.5%) had a hematological adverse event and 11 percent (7/66) required cessation of chemotherapy for reasons that were not reported. A third trial (n=91) reported no deaths or long-

term adverse events in patients randomized to adjuvant cisplatin, doxorubicin, and cyclophosphamide.⁵¹

Adjuvant Versus Neoadjuvant Therapy

One trial found no difference between neoadjuvant versus adjuvant MVAC in risk of death related to toxic effects of chemotherapy (9% [6/70] vs. 9% [6/70]).⁵⁶ The estimate for perioperative death was imprecise (1.6% [1/63] vs. 4.5% [3/66]). Hematologic and renal adverse events were not reported.

Key Question 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?

Key Points

- 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.

Detailed Synthesis

No studies.

Table 2. Characteristics of studies on bladder-preserving treatments

Author, Year	Country, Number of Centers, Study Years, Type of Study	Interventions (Sample Size)	Duration of Followup and Followup Method	Population Characteristics by Treatment Group (Age, Race/Ethnicity, Sex, Stage of Disease, Functional Status)
Bekelman, 2013 ²⁰	US Population-based SEER-Medicare data 1995-2005 Retrospective cohort	A: Bladder-sparing chemoradiation defined by TURBT, EBRT, and concurrent cisplatin-based chemotherapy (n=417) B: Radical cystectomy with or without lymphadenectomy (n=1426)	Not reported	Age (mean): 79.3 ± 6.0 vs. 75.4 ± 6.2 years Male: 72% vs. 63% Stage: Not reported Functional Status: Not reported
Goossens-Laan, 2014 ²¹	Netherlands Population-based cancer registry data 1995-2009 Retrospective cohort	A: Radical cystectomy (n=835) B: EBRT (n=859) C: Interstitial radiotherapy/brachytherapy (n=172) D: Maximal TURBT (n=417)	Not reported	Age: crossover between groups allows total for each group to equal >100%. A: 52% 60, 43% 61-74, 13% 75+ B: 15% 60, 31% 61-74, 48% 75+ C: 10% 60, 9% 61-74, 3% 75+ D: 10% 60, 12% 61-74, 28% 75+ Male: 75% vs. 25% Stage: A: 25% stage 2, 59% stage 3, 30% stage 4 B: 43% stage 2, 24% stage 3, 23% stage 4 C: 10% stage 2, 3% stage 3, 1% stage 4 D: 23% stage 2, 8% stage 3, 16% stage 4 Functional Status: Not reported

Table 2. Characteristics of studies on bladder-preserving treatments (continued)

Author, Year	Country, Number of Centers, Study Years, Type of Study	Interventions (Sample Size)	Duration of Followup and Followup Method	Population Characteristics by Treatment Group (Age, Race/Ethnicity, Sex, Stage of Disease, Functional Status)
Holmang, 1997 ²²	Sweden Population-based Swedish cancer registry data 1987-1988 Retrospective cohort	A: EBRT with 3-field box, 60 Gray or more (n=42) B: Radical TURBT alone (n=70) C: Radical cystectomy, unspecified number received preoperative radiotherapy, 2 of whom received preoperative chemotherapy, no routine lymphadenectomy (n=36)	≥ 5 years, minimum available records, censored for deaths	Age: Not reported Sex: Not reported Stage: 79% vs. 63% vs. 83% T2 or T3, 21% vs. 37% vs. 17% T4a Functional Status: Not reported
James, 2012 ²⁸	United Kingdom 45 centers 2001-2011 Randomized trial	A: EBRT 55 Gy in 20 fractions over 4 weeks or 64 Gy in 32 fractions over 6.5 weeks, fluorouracil 500 mg/m ² during fraction 1 to 5 and 16 to 20 and mitomycin c 12 mg/m ² on day 1; 18 patients underwent modified volume radiotherapy (n=178) B: EBRT alone (n=182)	Median 70 months in group A	Age (median): 72 vs. 71 years Male: 82% vs. 79% Stage: 85% vs. 80% T2, 5.5% vs. 8.4% T3a, 3.8% vs. 3.9% T3b, 3.8% vs. 3.9% T4 WHO performance status 0-1: 97% vs. 97%
Kalogeras, 2008 ²³	Greece Single institution 1995-2006 Retrospective cohort	A: EBRT with box configuration, 64 Gray (n=119) B: Radical cystectomy, no perioperative radiotherapy, no note of lymphadenectomy (n=26)	38 months (range 5-125 months) vs. 37 months (range 8-89 months), mean	Age: 33% vs. 38% < 70 years, 67% vs. 62% > 70 years Sex: Not reported Stage: all patients T2 Functional Status: Not reported
Kotwal, 2008 ²⁴	UK Single institution 1996-2000 Retrospective cohort	A: Radical radiotherapy with 50-55 Gray (n=97) B: Radical cystectomy (n=72), including lymphadenectomy in 52 patients	Not reported	Age (median): 75 years (range 42-99) vs. 68 years (range 37-85 years) vs. Male: 75% vs. 65% Stage: 9% vs. 19% Tis or T1, 38% vs. 31% T2, 49% vs. 43% T3 or T4a, 3% vs. 7% unknown Functional Status: Not reported
Nieuwenhuijzen 2005 ²⁵	Netherlands Single institution 1988-2003 Retrospective cohort	A: EBRT with 30 Gray followed by brachytherapy (n=108), combined with partial cystectomy in 24 patients B: Radical cystectomy with lymphadenectomy (n=77)	Not reported	Age (median): 63 years (range 31-88) vs. 63 years (range 36-84) Male: 82% vs. 81% Stage: 16% vs. 36% T1, 84% vs. 64% T2 Tumor size: 71% vs. 16% < 3 cm, 24% vs. 14% 3-5 cm, 5% vs. 70% unknown size Functional Status: Not reported

Table 2. Characteristics of studies on bladder-preserving treatments (continued)

Author, Year	Country, Number of Centers, Study Years, Type of Study	Interventions (Sample Size)	Duration of Followup and Followup Method	Population Characteristics by Treatment Group (Age, Race/Ethnicity, Sex, Stage of Disease, Functional Status)
Rincon Mayans, 2010 ²⁶	Spain Single institution 1994-2007 Retrospective cohort	A: EBRT with two regimens: from 1997-2003 patients received Taxol®-methotrexate-5-fluorouracil-cisplatin, 45-65 Gray concurrent with 5-fluorouracil-cisplatin, and 2 subsequent cycles of chemotherapy; from 2003-2007, patients received Taxol®-gemcitabine-cisplatin, IMRT with 55-65 Gray (n=43) B: Radical cystectomy, no perioperative radiotherapy, no node of lymphadenectomy (n=145)	51 months vs. 29 months, mean 39 months vs. 18 months, median	Age: Not reported Sex: Not reported Stage: 47% vs. Not reported T1 or T2, 53% vs. Not reported for T3/T4 Functional Status: Not reported
Sell, 1997 ¹⁹	Denmark Multicenter 1983-1986 Randomized controlled trial	A: Radical EBRT with 60 Gray (n=95) B: Preoperative EBRT with 40 Gray followed by radical cystectomy (n=88), including lymphadenectomy in 40/61 patients	50 months, median, followup not further stratified	Age (mean): 61.3 years vs. 61.3 years Male: 80 vs. 82% Stage: 37% vs. 42% T2, 63% vs. 58% T3 or T4a Functional Status: Not reported
Solsona, 2009 ²⁷	Spain Multicenter 1980-1990 Nonrandomized clinical trial	A: Bladder-sparing cisplatin-based chemotherapy (n=75) B: Radical cystectomy with lymphadenectomy (n=71)	84 months among those with a complete response to chemotherapy, no other followup reported	Age (median): 62 years vs. 64 years Male: 91% vs. 87% Stage: Not reported Functional Status: Not reported

EBRT = external beam radiation therapy; IMRT = intensity-modulated radiation therapy; RCT = randomized controlled trial; SEER = Surveillance, Epidemiology, and End Results program; T1 = tumor stage 1; T2 = tumor stage 2; T3 = tumor stage 3; T4 = tumor stage 4; T4a = tumor stage 4a; TURBT = transurethral resection of bladder tumor; UK = United Kingdom; US = United States

Table 3. Summary of results for studies of bladder-preserving treatments

Author, Year	Interventions (Sample Size)	Recurrence	Progression	Mortality
Bekelman, 2013 ²⁰	<p>A: Bladder-sparing chemoradiation defined by TURBT, EBRT, and concurrent cisplatin-based chemotherapy (n=417)</p> <p>B: Radical cystectomy with or without lymphadenectomy (n=1426)</p>	Not reported	Not reported	<p>Overall survival: 28% vs. 47%; HR 0.79 (95% CI 0.67 to 0.93) in Cox proportional hazards model, HR 0.79 (95% CI 0.65 to 0.95) in propensity score-adjusted model, HR 0.94 (95% CI 0.76 to 1.28) in instrumental variable analysis</p> <p>Disease-specific survival: 52% vs. 65% at 5 years; HR 0.78 (95% CI 0.60 to 1.02) in Cox proportional hazards model (similar for propensity score-adjusted model), HR 1.06 (0.85 to 1.82) in instrumental variable analysis</p>

Table 3. Summary of results for studies of bladder-preserving treatments (continued)

Author, Year	Interventions (Sample Size)	Recurrence	Progression	Mortality
Goossens-Laan, 2014 ²¹	A: Radical cystectomy (n=835) B: EBRT (n=859) C: Interstitial radiotherapy/brachytherapy (n=172) D: Maximal TURBT (n=417)	Not reported	Not reported	Unadjusted 5-year survival, A vs. B vs. C vs. D: "Relative": 48% vs. 29% vs. 70% vs. 19%, no significance test
Holmang, 1997 ²²	A: EBRT with 3-field box, 60 Gray or more (n=42) B: Radical TURBT alone (n=70) C: Radical cystectomy, unspecified number received preoperative radiotherapy, 2 of whom received preoperative chemotherapy, no routine lymphadenectomy (n=36)	Not reported	Not reported	T2 or T3 tumors All-cause mortality: 85% (28/33) vs. 86% (38/44) vs. 67% (20/30); RR 1.27 (95% CI 0.95 to 1.70) for A vs. C, RR 1.30 (95% CI 0.98 to 1.71) for B vs. C, and RR 0.98 (95% CI 0.82 to 1.18) for A vs. B Bladder-cancer mortality: 82% (27/33) vs. 75% (33/44) vs. 57% (17/30); RR 1.44 (95% CI 1.02 to 2.05) for A vs. C, RR 1.32 (95% CI 0.93 to 1.89) for B vs. C, RR 1.09 (95% CI 0.86 to 1.38) for A vs. B T4 tumors All-cause mortality: 100% (9/9) vs. 100% (26/26) vs. 100% (6/6)
James, 2012 ²⁸	A: EBRT 55 Gy in 20 fractions over 4 weeks or 64 Gy in 32 fractions over 6.5 weeks, fluorouracil 500 mg/m ² during fraction 1 to 5 and 16 to 20 and mitomycin c 12 mg/m ² on day 1; 18 patients underwent modified volume radiotherapy (n=178) B: EBRT alone (n=182)	2-year locoregional recurrence: 33% vs. 46%, HR 0.68 (95% CI 0.48-0.95) 5-year disease-free survival: difference 8.9% (favors A), HR 0.78 (95% CI 0.60 to 1.03)	2-year invasive locoregional disease: 18% vs. 32%, HR 0.57 (95% CI 0.37 to 0.89) 5-year metastasis rate: difference 11%, HR 0.72 (95% CI 0.53 to 0.99)	Overall mortality: 55% (98/178) vs. 60% (110/182), RR 0.91 (95% CI 0.76 to 1.09) 5-year mortality: 52% vs. 65%, HR 0.82 (95% CI 0.63 to 1.09) favoring A Bladder cancer mortality: 42% (74/178) vs. 51% (92/182), HR 0.77 (95% CI 0.57 to 1.05)

Table 3. Summary of results for studies of bladder-preserving treatments (continued)

Author, Year	Interventions (Sample Size)	Recurrence	Progression	Mortality
Kalogerias, 2008 ²³	A: EBRT with box configuration, 64 Gray (n=119) B: Radical cystectomy, no perioperative radiotherapy, no note of lymphadenectomy (n=26)	Local disease control: 42% (50/119) vs. 88% (23/26), RR 0.48 (95% CI 0.37 to 0.61)	Distant metastasis: 16% (19/119) vs. 7.7% (2/26), RR 2.08 (95% CI 0.52 to 8.37)	3-year overall survival: 39% vs. 69% (p=0.03)
Kotwal, 2008 ²⁴	A: Radical radiotherapy with 50-55 Gray (n=97) B: Radical cystectomy (n=72), including lymphadenectomy in 52 patients	Local or distant recurrence: 34% (33/97) vs. 38% (27/72), RR 0.91 (95% CI 0.60 to 1.36)	Not reported	All-cause mortality: 71% (69/97) vs. 62% (45/72), RR 1.14 (95% CI 0.91 to 1.42) Overall survival: 35% vs. 41% vs. at 5 years, 18% vs. 36% at 8 years (p=0.39) Bladder cancer mortality: 38% (37/97) vs. 44% (32/72), RR 0.86 (0.60 to 1.23) 5-year disease-specific survival: 57% vs. 53% (p=0.38)
Nieuwenhuijzen, 2005 ²⁵	A: EBRT with 30 Gray followed by brachytherapy (n=108), combined with partial cystectomy in 24 patients B: Radical cystectomy with lymphadenectomy (n=77)	Local recurrence: 21% vs. Not reported	Not reported	Overall survival: 62% vs. 67% at 5 years, 50% vs. 58% at 10 years; adjusted HR 0.62 (95% CI 0.28 to 1.43) Disease-specific survival: 73% vs. 72% at 5 years, 67% vs. 72% at 10 years; adjusted HR 0.5 (95% CI 0.20 to 1.25)
Rincon Mayans, 2010 ²⁶	A: EBRT with two regimens: from 1997-2003 patients received Taxol®-methotrexate-5-fluorouracil-cisplatin, 45-65 Gray concurrent with 5-fluorouracil-cisplatin, and 2 subsequent cycles of chemotherapy; from 2003-2007, patients received Taxol®-gemcitabine-cisplatin, IMRT with 55-65 Gray (n=43) B: Radical cystectomy, no perioperative radiotherapy, no note of lymphadenectomy (n=145)	Not reported	Progression-free survival: 69% vs. 72% at 3 years, 61% vs. 63% at 5 years (p=0.83)	Not reported

Table 3. Summary of results for studies of bladder-preserving treatments (continued)

Author, Year	Interventions (Sample Size)	Recurrence	Progression	Mortality
Sell, 1997 ¹⁹	A: Radical EBRT with 60 Gray (n=95) B: Preoperative EBRT with 40 Gray followed by radical cystectomy (n=88), including lymphadenectomy in 40/61 patients	Local recurrence: 35.8% (34/95) vs. 6.8% (6/88), RR 5.25 (95% CI 2.31 to 11.9)	Distant metastasis: 31.5% (30/95) vs. 34.0% (30/88), RR 1.08, 95% CI 0.71 to 1.63	Overall survival (median): 18 vs. 20 months (p=0.21)
Solsona, 2009 ³⁷	A: Bladder-sparing cisplatin-based chemotherapy (n=75) B: Radical cystectomy with lymphadenectomy (n=71)	Need for cystectomy: 72% (54/75) vs. N/A	Not reported	5-year disease-specific survival: 65% vs. Not reported

CI = confidence interval; EBRT = external beam radiation therapy; HR = hazard ratio; IMRT = intensity modulated radiation therapy; N/A = not applicable; RR=relative risk; TURBT = transurethral resection of bladder tumor

Table 4. Characteristics of studies on lymph node dissection with radical cystectomy

Author, Year	Country, Number of Centers, Study Years, Type of Study	Interventions (Sample Size)	Duration of Followup and Followup Method	Population Characteristics by Treatment Group (Age, Race/Ethnicity, Sex, Stage of Disease, Functional Status)
Abdollah, 2012 ²⁹	USA 1988-2006 Retrospective cohort	<p>A: Cystectomy with extended lymph node dissection (≥ 10 lymph nodes removed and examined) (A +B n= 8394)</p> <p>B: Cystectomy with limited lymph node dissection (<10 lymph nodes removed and examined)</p> <p>C: Cystectomy without pelvic lymph node dissection (n=2789)</p>	Not reported	<p>A+B vs. C</p> <p>Age (mean): 67.1 vs. 68.8, $p < 0.001$</p> <p>Male: 75% vs. 73%, $p < 0.01$</p> <p>Caucasian: 90% vs. 90%</p> <p>Stage: Ta/Tis: 2% vs. 6%</p> <p>T1: 10% vs. 15%</p> <p>T2: 38% vs. 43%</p> <p>T3: 30% vs. 18%</p> <p>T4: 20% vs. 18%; $p < 0.001$</p> <p>Grade: G1/G2: 7% vs. 12%</p> <p>G3: 53% vs. 56%</p> <p>G4: 40% vs. 32%; $p < 0.001$</p> <p>Functional status: Not reported</p>

Table 4. Characteristics of studies on lymph node dissection with radical cystectomy (continued)

Author, Year	Country, Number of Centers, Study Years, Type of Study	Interventions (Sample Size)	Duration of Followup and Followup Method	Population Characteristics by Treatment Group (Age, Race/Ethnicity, Sex, Stage of Disease, Functional Status)
Brossner, 2004 ³⁴	Austria and Italy Two centers 1998-2002 Retrospective cohort	<p>A (Italian cohort): Cystoprostatectomy in men or pelvicctomy in women, with "extended" lymphadenectomy, including the perivesical, hypogastric, obturator, external iliac, common iliac and aortal lymph nodes, into the region of the inferior mesenteric artery (n=46).</p> <p>B (Austrian cohort): Cystoprostatectomy in men or pelvicctomy in women, with "minimal" lymphadenectomy, including perivesical lymph nodes and lymphatic tissue of the obturator fossa, confined laterally by the external iliac vein and medial by the obturator nerve (n=46).</p>	30 days Unclear method of followup	Age (mean): 66.3 vs. 68.2 years Race/Ethnicity: Not reported Male: Not reported Stage: pT1: 4 vs. 6; pT2-3a: 24 vs. 18; pT3b-4: 18 vs. 22; Node positive: 18 vs. 10 Functional Status: Not reported
Brunocilla, 2013 ³⁵	Italy 1995-2011 Retrospective cohort	<p>A: Limited template: Cystectomy including external and obturator lymph nodes; or no lymphadenectomy (n=116)</p> <p>B: Standard template: Cystectomy including external, obturator, internal iliac, and 2 cm common iliac lymph nodes up to the cross with the ureters (n=94)</p> <p>C: Extended template: Cystectomy including external, obturator, internal iliac, presacral, and complete common iliac lymph nodes up to the aortic bifurcation (n=39)</p> <p>D: Super-extended template: Cystectomy including external, obturator, internal iliac, presacral, complete common iliac lymph nodes up to the aortic bifurcation, preaortic and precaval lymph nodes up to inferior mesenteric artery (n=23)</p> <p>Selection of template was based on preference and skills of the surgeons</p>	Mean: 59.2±44.3 months	<p>Reported for 0-14 lymph nodes removed (n=128) vs. ≥14 lymph nodes removed (n=154):</p> <p>Age (mean): 69.6±8.4 vs. 667.3±8.1; p=0.010 Male: 82.8% vs. 83.1% Race/Ethnicity: Not reported Stage: T0: 18% vs. 12% T1: 16% vs. 13% T2: 19% vs. 27% T3: 29% vs. 32% T4: 18% vs. 16% Tumor Grade: G1-G2: 25% vs. 22% G3: 75% vs. 78% Functional status: Not reported</p>

Table 4. Characteristics of studies on lymph node dissection with radical cystectomy (continued)

Author, Year	Country, Number of Centers, Study Years, Type of Study	Interventions (Sample Size)	Duration of Followup and Followup Method	Population Characteristics by Treatment Group (Age, Race/Ethnicity, Sex, Stage of Disease, Functional Status)
Dhar, 2008 ³⁶	USA and Switzerland Two centers 1987-2000 Retrospective cohort	A (Switzerland cohort): Cystectomy with extended lymphadenectomy, with cephalad dissection extended to the crossing of the ureters with the common iliac arteries and removal of all tissue along the lateral and medial portion of internal iliac vessels. (n=322). B (USA cohort): Cystectomy with limited lymphadenectomy, with boundaries of the pelvic sidewall between the genitofemoral and obturator nerves, and bifurcation of the iliac vessels to the circumflex iliac vein. (n=336).	5 years A: Every 6 months for 2 years and annually thereafter. B: 3 and 6 months after surgery, 6-month intervals until 5 years and annually thereafter.	Age (median): 66.9 vs. 61.6 years, p<0.001 Race/Ethnicity: Not reported Male: 78% vs. 79% Stage: Not reported Functional status: Not reported
Herr, 2002 ³⁰	USA Single center 1980-1990 Retrospective cohort	A: Radical cystectomy with standard lymphadenectomy, including the distal common iliac, external iliac, hypogastric, obturator, presacral and perivesical lymph nodes (n=not reported) B: Cystectomy with limited lymphadenectomy, with obturator and perivesical lymph nodes removed en bloc with the bladder. (n=not reported)	Minimum 10 years	Age: Not reported Male: Not reported Race/Ethnicity: Not reported Stage: 188 T2, 134 T2-T3 Functional status: Not reported
Herr, 2004 ³³	USA Multiple centers 1987-1998 Reanalysis of RCT	A: Cystectomy with standard lymphadenectomy (n=146), median 15 lymph nodes B: Cystectomy with limited lymphadenectomy (n=98), median 7 lymph nodes C: Cystectomy with no lymphadenectomy (n=24)	Until death	Overall characteristics, not reported by treatment group: Age: 148/268 <65 years, 120/268 ≥ 65 years Male 81% (216/268) Race/Ethnicity: Not reported Stage: 69% (184/268) T0-T2 31% (84/268) T3-T4 Functional status: 100% SWOG 0 or 1

Table 4. Characteristics of studies on lymph node dissection with radical cystectomy (continued)

Author, Year	Country, Number of Centers, Study Years, Type of Study	Interventions (Sample Size)	Duration of Followup and Followup Method	Population Characteristics by Treatment Group (Age, Race/Ethnicity, Sex, Stage of Disease, Functional Status)
Konety, 2003 ³¹	USA Population based study (SEER data) 1988-1996 Retrospective cohort	Patients with bladder cancer who underwent cystectomy, number of lymph nodes examined: 0 (n=645), 1-3 (n=203), 4-6 (n=239), 7-9 (n=164), 10-14 (n=163), 15-19 (n=106), ≥20 (n=81), missing data (n=322)	Minimum 2 years; Median in surviving post-cystectomy patients: 63.5 months	Age: <35: 70 (3.6%); 35-44: 86 (4.5%); 45-54: 237 (12.3%); 55-64: 476 (24.8%); 65-74: 681 (35.4%); 75-84: 349 (18.2%); ≥85: 24 (1.3%) Race/Ethnicity: White: 1698/1923 (93.6%); Black: 117/1923 (6.5%) Male: 1265/1923 (65.8%) Stage: In situ or 1: 150 (12.9%); Stage 2: 249 (21.4%); Stage 3: 300 (25.8%); Stage 4: 465 (39.9%); missing: 759 Functional status: Not reported
Leissner, 2000 ³⁷	Germany Single center 1986-1997 Retrospective cohort	Patients with bladder cancer who underwent cystectomy, number of lymph nodes examined: 1-5, 6-10, 11-15, 16-20, and >20 (N=447)	Minimum 2 years; Mean: 38.7 months	Age: 62.8 years Male: male: female ratio 4.5:1 Race/Ethnicity: Not reported Smoking status: Not reported Stage of disease (for all patients with radical cystectomy): pTis: 15 (3.4%); pT1: 100 (22.4%); pT2a: 88 (19.7%); pT2b: 51(11.4%); pT3: 146 (32.7%); pT4: 47 (10.5%) Tumor grade: Not reported Functional status: Not reported
Poulsen, 1998 ³⁸	Denmark Single center 1990-1997 Retrospective cohort	A: Radical cystectomy with extended lymphadenectomy, bounded proximally by bifurcation of the aorta, laterally by the genitofemoral nerve, distally by the circumflex iliac vein and Cloquet's lymph node and posteriorly by the internal iliac vessel, including the presacral nodes and obturator fossa (n=126) B: Cystectomy with limited lymphadenectomy, bounded proximally by bifurcation of the common iliac vessels, while the lateral, distal and posterior boundaries were the same as for the extended dissection, including dissection of the obturator fossa. (n=68)	4-month intervals for the first year, then annually.	Age, mean: 61.8 vs. 63.2 years Race/Ethnicity: Not reported Male: 102/126 vs. 55/68 Stage: T0-Ta: 7.1% vs. 5.9%; Tis: 13.5% vs. 5.9%; T1: 12.7% vs. 25%; T2: 10.3% vs. 13.2%; T3a: 13.5% vs. 16.2%; T3b: 35.7% vs. 29.4%; T4a: 4.0% vs. 1.5%; T4b: 1.6% vs. 1.5%; prostate: 0.8% vs. 1.5%; adenocarcinoma: 0.8% vs. 0% Functional status: Not reported

Table 4. Characteristics of studies on lymph node dissection with radical cystectomy (continued)

Author, Year	Country, Number of Centers, Study Years, Type of Study	Interventions (Sample Size)	Duration of Followup and Followup Method	Population Characteristics by Treatment Group (Age, Race/Ethnicity, Sex, Stage of Disease, Functional Status)
Shirotake, 2010 ³²	Japan Single center 1987-2008 Retrospective cohort	A: Cystectomy with lymphadenectomy (n=107) B: Cystectomy without lymphadenectomy (n=62, includes those without lymphadenectomy or unknown number of nodes removed) Neoadjuvant chemotherapy, n=16, mostly T3-4 Adjuvant chemotherapy, n=26, T3-4 or Node positive	3-month intervals for 2 years and every 6 months thereafter	Age, mean: 67.65 vs. 69.4 years Race/Ethnicity: Not reported Male: overall 127/169 Stage: ≤T2: 52/107 vs. 34/62; T3-4: 55/107 vs. 28/62 Functional status: Not reported
Simone, 2013 ⁴⁰	Italy Two centers 2002-2010 Retrospective cohort	A: Cystectomy with extended lymphadenectomy, dissected nodes up to and, in some cases, above the aortic bifurcation including the presacral nodes (n=349) B: Cystectomy with standard lymphadenectomy, dissected nodes with an upper boundary at the iliac bifurcation (not including presacral and common nodes) (n=584)	Not reported	Age, mean: 65.4 years vs. 66.9 years Race/Ethnicity: Not reported Male: 309/349 vs. 502/584 Stage: T0, a, is, 1: 94/349 vs. 140/584; T2: 98/349 vs. 131/584; T3: 108/349 vs. 235/584; T4: 49/349 vs. 78/584 Functional status: Not reported

Table 4. Characteristics of studies on lymph node dissection with radical cystectomy (continued)

Author, Year	Country, Number of Centers, Study Years, Type of Study	Interventions (Sample Size)	Duration of Followup and Followup Method	Population Characteristics by Treatment Group (Age, Race/Ethnicity, Sex, Stage of Disease, Functional Status)
Zehnder, 2011 ³⁹	USA and Switzerland Two centers 1985-2005 Retrospective cohort	<p>A (USA cohort): Cystectomy with lymphadenectomy, pure intrapelvic template plus removal of lymphatic tissue along the common iliac vessels, the distal vena cava/aorta to the IMA takeoff and complete dissection of the presacral space from the bifurcation of the aorta into the sacral fossa. (n=554)</p> <p>B (Switzerland cohort): Cystectomy with lymphadenectomy, pure intrapelvic template ended proximally at the mid-upper third of the common iliac vessels, included the presacral region medial to the internal iliac vessels but left tissue containing the hypogastric nerves located medial to the retracted ureters and inferior to the aortic bifurcation (n=405)</p> <p>Both groups used pure intrapelvic template for lymphadenectomy, with boundaries of the genitofemoral nerve and the pelvic side wall laterally, the circumflex iliac vein and Cloquet's node distally, the obturator fossa with full exposure of the intrapelvic course of the obturator nerve and the internal iliac vessels posteriorly, and the tissue medial to these vessels.</p>	<p>A: 4-month intervals in year 1, 6-month intervals in year 2, annually thereafter; Median followup: 10.9 years</p> <p>B: 3, 6, 12 months postoperatively, annually thereafter; Median followup: 9.9 years</p>	<p>Age, median: 67 vs. 67 years Race/Ethnicity: Not reported Male: 421/554 vs. 314/405 Stage: T2: 253/554 vs. 169/554; T3: 301/554 vs. 236/405 Functional status: Not reported</p>

pT1 = tumor stage 1 determined by pathology; pT2 = tumor stage 2 determined by pathology; pT3a = tumor stage 3a determined by pathology; pT3b = tumor stage 3b determined by pathology; pT4 = tumor stage 4 determined by pathology; SEER = Surveillance, Epidemiology and End Results Program; T0 = tumor stage 0; T1 = tumor stage 1; T2 = tumor stage 2; T3 = tumor stage 3; T3a = tumor stage 3a; T3b = tumor stage 3b; T4 = tumor stage 4; T4a = tumor stage 4a; Ta = tumor stage a; Tis = tumor stage is; US = United States

Table 5. Summary of results for studies of lymph node dissection

Author, Year	Interventions	Recurrence	Progression	Mortality
Abdollah, 2012 ²⁹	<p>A: Cystectomy with extended lymph node dissection (≥10 lymph nodes removed and examined) (A +B n= 8394)</p> <p>B: Cystectomy with limited lymph node dissection (<10 lymph nodes removed and examined)</p> <p>C: Cystectomy without pelvic lymph node dissection (n=2789)</p>	Not Reported	Not Reported	<p>A+B vs. C Adjusted HR (95%CI): 10-year cancer-specific mortality- free: 1.33 (1.24-1.44) Ta/Tis: 2.09 (1.16-3.79) T1: 1.60 (1.18-2.17) T2: 1.68 (1.47-1.91) T3: 1.15 (1.01-1.33) T4: 1.11 (0.9-1.28) 10-year overall mortality-free: 1.29 (1.22-1.37) Ta/Tis: 1.49 (1.02-2.17) T1: 1.29 (1.06-1.57) T2: 1.44 (1.31-1.58) T3: 1.13 (1.01-1.28) T4: 1.24 (1.11-1.39)</p> <p>A vs. B 10-year cancer-specific mortality-free rates: 62.2% vs. 54.0% (log rank p<0.001) Ta/Tis: 70.8% vs. 85.7%, p=0.1 T1:85.8% vs. 78.%,p=0.01 T2:76.1% vs67.7%,p<0.001 T3: 48.7% vs 39.7%,p<0.001 T4: 38.6% vs 32.5%,p=0.02 10-year overall mortality –free rates: 39.4% vs. 30.3% (log rank p<0.001) Ta/Tis:39.1% vs 63.3%,p=0.05 T1:66.7% vs 51.2%,p<0.001 T2:50.0% vs 40.4%,p<0.001 T3:28.2% vs 19.7%,p<0.001 T4:21.5% vs 14.8%,p<0.001</p>

Table 5. Summary of results for studies of lymph node dissection (continued)

Author, Year	Interventions	Recurrence	Progression	Mortality
Brossner, 2004 ³⁴	<p>A (Italian cohort): Cystoprostatectomy in men or pelvicectomy in women, with "extended" lymphadenectomy, including the perivesical, hypogastric, obturator, external iliac, common iliac and aortal lymph nodes, into the region of the inferior mesenteric artery (n=46).</p> <p>B (Austrian cohort): Cystoprostatectomy in men or pelvicectomy in women, with "minimal" lymphadenectomy, including perivesical lymph nodes and lymphatic tissue of the obturator fossa, confined laterally by the external iliac vein and medial by the obturator nerve (n=46).</p>	Not reported	Not reported	<p>Perioperative mortality: 2.2% (1/46) (pulmonary embolus) vs. 4.3% (2/46) (pneumonia) vs. 2.2% (1/46) (pulmonary embolus), RR 0.50 (95% CI 0.047 to 5.32)</p>

Table 5. Summary of results for studies of lymph node dissection (continued)

Author, Year	Interventions	Recurrence	Progression	Mortality
Brunocilla, 2013 ³⁵	<p>A: Limited template: Cystectomy including external and obturator lymph nodes; or no lymphadenectomy (n=116)</p> <p>B: Standard template: Cystectomy including external, obturator, internal iliac, and 2 cm common iliac lymph nodes up to the cross with the ureters (n=94)</p> <p>C: Extended template: Cystectomy including external, obturator, internal iliac, presacral, and complete common iliac lymph nodes up to the aortic bifurcation (n=39)</p> <p>D: Super-extended template: Cystectomy including external, obturator, internal iliac, presacral, complete common iliac lymph nodes up to the aortic bifurcation, preaortic and precaval lymph nodes up to inferior mesenteric artery (n=23)</p> <p>Selection of template was based on preference and skills of the surgeons</p>	Not reported	Not reported	<p>Cancer-specific survival, hazard ratio (95%CI)</p> <p>Univariable: B vs. A: 0.828 (0.547-1.255) C vs. A: 0.350 (0.221-0.740) ≥14 lymph nodes removed vs. 0-14 lymph nodes removed: 0.576 (0.382-0.847)</p> <p>Multivariable: B vs. A: 0.986 (0.547-1.354) C vs. A: 0.455 (0.365-0.894) ≥14 lymph nodes removed vs. 0-14 lymph nodes removed: 0.556 (0.282-0.995)</p>

Table 5. Summary of results for studies of lymph node dissection (continued)

Author, Year	Interventions	Recurrence	Progression	Mortality
Dhar, 2008 ³⁶	<p>A (Switzerland cohort): Cystectomy with extended lymphadenectomy, with cephalad dissection extended to the crossing of the ureters with the common iliac arteries and removal of all tissue along the lateral and medial portion of internal iliac vessels. (n=322).</p> <p>B (USA cohort): Cystectomy with limited lymphadenectomy, with boundaries of the pelvic sidewall between the genitofemoral and obturator nerves, and bifurcation of the iliac vessels to the circumflex iliac vein. (n=336).</p>	<p>A vs. B 5 year recurrence-free survival (median followup: 40 vs. 25, p<0.001) pT2: 63% vs. 71%, p=0.10 pT3: 49% vs. 19%, p<0.0001</p>	<p>A vs. B Progression (local or systemic): 40% (130/322) vs. 55% (184/336), RR 0.74 (95% CI 0.63 to 0.87) Local progression (p for log-rank test): pT2: 4% vs. 24%, p<0.0001 pT3: 10% vs. 60%, p<0.0001 Systemic progression (includes those with both local and systemic progression): pT2: 27% vs. 14%, p=0.0048 pT3: 45% vs. 20%, p=0.0012</p>	<p>A vs. B 5 year overall survival (median followup: 51 vs. 36 months, p<0.001) pT2: 61% vs. 64%, p=0.10 pT3: 42% vs. 22%, p=0.0002</p>
Herr, 2002 ³⁰	<p>A: Radical cystectomy with standard lymphadenectomy, including the distal common iliac, external iliac, hypogastric, obturator, presacral and perivesical lymph nodes (n=not reported)</p> <p>B: Cystectomy with limited lymphadenectomy, with obturator and perivesical lymph nodes removed en bloc with the bladder. (n=not reported)</p>	<p>Local recurrence (uncertain followup): N0 patients: 5% (7/131) when 8 or more nodes, 24% (31/127) when 1-8 nodes, p=0.001; N+ patients, 9% (3/34) when 11 or more nodes, 30% (10/30) when 1-11 nodes, p=0.002</p> <p>5-year recurrence-free survival: Stage ≤T3a: 85% vs. 64%, p<0.02; Stage ≥T3b: 27% vs. 39%, p=0.87</p>	<p>Not reported</p>	<p>0-year survival Node negative patients (n=258): 82% when 8 or more nodes, 63% when 4-7 nodes, 23% when 0-3 nodes, p=0.004. 59% (75/127) ≥ 8 vs. 18% (23/131) <8 lymph nodes</p> <p>Node positive patients (n=64): 45% when > 14 nodes, 39% when 9-14 nodes, 16% when 1-8 nodes, p=0.02. 56% (19/34) ≥ 11 vs. 80% (24/30) for < 11 lymph nodes, p=0.004</p>

Table 5. Summary of results for studies of lymph node dissection (continued)

Author, Year	Interventions	Recurrence	Progression	Mortality
Herr, 2004 ³³	<p>A: Cystectomy with standard lymphadenectomy (n=146), median 15 LN</p> <p>B: Cystectomy with limited lymphadenectomy (n=98), median 7 LN</p> <p>C: Cystectomy with no lymphadenectomy (n=24)</p>	<p>A vs. B vs. C</p> <p>Local Recurrence (no median followup reported):</p> <p>7/146 (5%) vs. 22/98 (22%) vs. 12/24 (50%), p<0.0001</p> <p>RR 0.21, 95% CI 0.09 to 0.48</p> <p>≥10 nodes removed vs. <10 nodes removed: 6% vs. 25%, p<0.0001, multivariate Cox proportional hazards model <10 nodes (HR 0.20, 95% CI 0.07 to 0.56)</p>	Not reported	<p>A vs. B vs. C</p> <p>5-year overall survival: 60% vs. 46% vs. 33%, p=0.01</p> <p>≥10 nodes removed vs. <10 nodes removed: 5-year overall survival: 61% vs. 44%, p=0.0007, multivariate Cox proportional hazards model <10 nodes HR 0.50, 95% CI 0.36 to 0.71</p> <p>A vs. B</p> <p>Risk of mortality: 52% (59/146) vs. 64% (63/98), RR 0.94, 95% CI 0.68 to 1.04</p>
Konety, 2003 ³¹	Patients with bladder cancer who underwent cystectomy, number of lymph nodes examined: 0 (n=645), 1-3 (n=203), 4-6 (n=239), 7-9 (n=164), 10-14 (n=163), 15-19 (n=106), ≥20 (n=81)	Not reported	Not reported	<p>Risk of death by number of lymph nodes examined; Adjusted hazard ratio (95% CI):</p> <p>0: 1 (reference)</p> <p>1-3: 0.93 (0.69 to 1.27)</p> <p>4-6: 0.52 (0.36 to 0.76)</p> <p>7-9: 0.57 (0.39 to 0.81)</p> <p>10-14: 0.38 (0.25 to 0.57)</p> <p>15-19: 0.57 (0.39 to 0.85)</p> <p>≥20: 0.48 (0.30 to 0.76)</p> <p>≥4: 0.53 (0.36 to 0.76)</p>
Leissner, 2000 ³⁷	Patients with bladder cancer who underwent cystectomy, number of lymph nodes examined: 1-5, 6-10, 11-15, 16-20, and >20 (N=447)	<p>≥16 nodes removed vs. ≤15 nodes removed :</p> <p>Local recurrence: 17% vs. 27%, p<0.01</p>	<p>≥16 nodes removed vs. ≤15 nodes removed :</p> <p>Distant metastasis: 10.5% vs. 17%, p<0.01</p>	<p>≥16 nodes removed vs. ≤15 nodes removed :</p> <p>5-year bladder cancer- specific survival: 65% vs. 51%, p<0.013</p>

Table 5. Summary of results for studies of lymph node dissection (continued)

Author, Year	Interventions	Recurrence	Progression	Mortality
Poulsen, 1998 ³⁸	<p>A: Radical cystectomy with extended lymphadenectomy, bounded proximally by bifurcation of the aorta, laterally by the genitofemoral nerve, distally by the circumflex iliac vein and Cloquet's lymph node and posteriorly by the internal iliac vessel, including the presacral nodes and obturator fossa (n=126).</p> <p>B: Cystectomy with limited lymphadenectomy, bounded proximally by bifurcation of the common iliac vessels, while the lateral, distal and posterior boundaries were the same as for the extended dissection, including dissection of the obturator fossa. (n=68).</p>	<p>5-year recurrence-free survival: 62% vs. 56%, p=0.33</p> <p>5-year recurrence-free survival: Stage ≤T3a: 85% vs. 64%, p<0.02; Stage ≥T3b: 27% vs. 39%, p=0.87</p>	<p>5-year risk of distant metastasis: 29% vs. 30%, p not reported</p> <p>5-year risk of pelvic metastasis: 10% vs. 10%, p not reported</p>	<p>5-year survival: Stage ≤T3a,N0: 90% vs. 71%, p<0.02; Stage ≥T3b,N0: 38% vs. 67%, p=0.46</p>
Shirotake, 2010 ³²	<p>A: Cystectomy with lymphadenectomy (n=107).</p> <p>B: Cystectomy without lymphadenectomy (n=62, includes those without lymphadenectomy or unknown number of nodes removed).</p> <p>Neoadjuvant chemotherapy, n=16, mostly T3-4</p> <p>Adjuvant chemotherapy, n=26, T3-4 or Node positive</p>	Not reported	Not reported	<p>Node positive (N+) vs. Node negative (N-) vs. Nodes not removed or unknown (Nx)</p> <p>5-year Cancer-specific survival: 40.8% vs. 72.3% vs. 73.5%; N+ vs. N-, p=0.0471, Nx vs. N-, p=0.846</p> <p>≥9 nodes removed vs. <9 nodes removed, 5-year Cancer-specific survival, node-positive and node negative patients: 84.3% vs. 52.7%, adjusted HR 3.48 (95% CI 1.50 to 9.31)</p> <p>Node-negative patients: adjusted HR 6.94 (95% CI 1.88 to 38.21)</p>
Simone, 2013 ⁴⁰	<p>A: Cystectomy with extended lymphadenectomy, dissected nodes up to and, in some cases, above the aortic bifurcation including the presacral nodes (n=349).</p> <p>B: Cystectomy with standard lymphadenectomy, dissected nodes with an upper boundary at the iliac bifurcation (not including presacral and common nodes) (n=584).</p>	Not reported	Not reported	<p>Bladder-cancer specific survival: Adjusted HR 1.80 (95% CI 1.37 to 2.37)</p>

Table 5. Summary of results for studies of lymph node dissection (continued)

Author, Year	Interventions	Recurrence	Progression	Mortality
Zehnder, 2011 ³⁹	<p>A (California cohort): Cystectomy with lymphadenectomy, pure intrapelvic template plus removal of lymphatic tissue along the common iliac vessels, the distal vena cava/aorta to the IMA takeoff and complete dissection of the presacral space from the bifurcation of the aorta into the sacral fossa (n=554).</p> <p>B (Switzerland cohort): Cystectomy with lymphadenectomy, pure intrapelvic template ended proximally at the mid-upper third of the common iliac vessels, included the presacral region medial to the internal iliac vessels but left tissue containing the hypogastric nerves located medial to the retracted ureters and inferior to the aortic bifurcation (n=405).</p> <p>Both groups used pure intrapelvic template for lymphadenectomy, with boundaries of the genitofemoral nerve and the pelvic side wall laterally, the circumflex iliac vein and Cloquet's node distally, the obturator fossa with full exposure of the intrapelvic course of the obturator nerve and the internal iliac vessels posteriorly, and the tissue medial to these vessels.</p>	<p>Recurrence: 38% (210/554) vs. 38% (154/405), RR 1.0 (95% CI 0.85 to 1.17)</p> <p>Recurrence-free survival: ~58% in each group (p=0.75)</p>	Not reported	Overall survival: ~17% in each group (p=0.45)

CI = confidence interval; HR = hazard ratio; IMA = inferior mesenteric artery; N+ = Node positive; N = Nodes; N- = Node negative; N0 = Node stage 0; N2 = Node stage 2; Nx = nodes not removed or unknown; pT2 = Tumor stage 2 determined by pathology; pT3 = Tumor stage 3 determined by pathology; pT3a = Tumor stage 3a determined by pathology; RR= relative risk; T2 = Tumor stage 2; T3 = Tumor stage 3; T3a = Tumor stage 3a; T3b = Tumor stage 3b; T4 = Tumor stage 4

Table 6. Characteristics of studies on adjuvant and neoadjuvant chemotherapy

Type of Chemotherapy	Author, Year	Country, Number of Centers, Study Years, Type of Study	Interventions (Sample Size)	Duration of Followup and Cystoscopic Followup Method	Population Characteristics by Treatment Group (Age, Race/Ethnicity, Sex, Stage of Disease, Functional Status)
Neoadjuvant	Dash, 2008 ⁵⁹	United States Single Center 2000-2006 Retrospective cohort	A: NAC: Gemcitabine + Cisplatin, predominately given as: "Single dose" cisplatin administration consisted of 4 cycles, with 21 day intervals of cisplatin 70 mg/m ² and gemcitabine 1000 mg/m ² on day 1, and gemcitabine 1000 mg/m ² on day 8. "Split-dose" cisplatin administration consisted of 4 cycles, with 21 day intervals of cisplatin 35 mg/m ² and gemcitabine 1000 mg/m ² on days 1 and 8. (n=42) B: NAC: Methotrexate, vinblastine, doxorubicin and cisplatin given as 4 cycles at 28-day intervals. Doses were not reported. (n=54)	Overall duration of followup: Not reported Median followup for survivors: Gemcitabine/Cisplatin: 24.2 months; MVAC: 48.1 months Followup method not reported	A vs. B Age (median): 64 vs. 63 Male: 76% (32/42) vs. 8% (43/54) Race/Ethnicity: Not reported Stage of disease: T2: 45% (19/42) vs. 59% (32/54) T3: 45% (19/42) vs. 28% (15/54) T4: 10% (4/42) vs. 13% (7/54) Functional status: Not reported
	Fairey, 2013 ⁵³	United States Single Center 1985-2011 Retrospective cohort	A. NAC, 4 cycles of GC at 21-day intervals over 12 weeks + cystectomy with super-extended pelvic LN dissection (n= 58) B. NAC, 4 cycles of M-VAC at 28-day intervals over 16 weeks + cystectomy with super-extended pelvic LN dissection (n= 58)	Median followup 2.1 years for GC group and 7.4 years for M-VAC group. Method: Every 4 months in year 1, every 6 months in year 2 and annually thereafter.	Age (median): 67 vs. 63 Male: 76% vs. 79% Race/Ethnicity: Not reported Stage of disease: T2: 48% vs. 48% T3: 31% vs. 24% T4: 20% vs. 28% Functional status: Not reported
	Grossman, 2003 ⁴¹	USA 126 centers 1987-1998 Randomized controlled trial	A: NAC, three 28-day cycles with methotrexate 30 mg/m ² on days 1, 15 and 22; vinblastine 3 mg/m ² on days 2, 15 and 22; doxorubicin 30 mg/m ² and cisplatin 70 mg/m ² on day 2 (MVAC) + cystectomy with LN dissection (n=153) B: Cystectomy with LN dissection (n=154)	Median: 8.7 years vs. 8.4 years	Age (mean): 63 vs. 63 Male: 83% vs. 81% Race/Ethnicity: Not reported Smoker: Not reported Stage: T2: 40% vs. 40% T3/T4a: 60% vs. 60% Functional status: Not reported

Table 6. Characteristics of studies on adjuvant and neoadjuvant chemotherapy (continued)

Type of Chemotherapy	Author, Year	Country, Number of Centers, Study Years, Type of Study	Interventions (Sample Size)	Duration of Followup and Cystoscopic Followup Method	Population Characteristics by Treatment Group (Age, Race/Ethnicity, Sex, Stage of Disease, Functional Status)
Neoadjuvant	International Collaboration of Trialists, 1999 ⁴²	20 countries 106 centers 1989-1995 Randomized controlled trial	<p>A: NAC every 21 days for 3 cycles with methotrexate 30 mg/m², vinblastine 4 mg/m² on day 1 and day 8; cisplatin 100 mg/m² on day 2 (CMV) + cystectomy +/- LN dissection or RT or RT and cystectomy (n=491)</p> <p>B: cystectomy with LN dissection or radiotherapy or RT and cystectomy. (n=485)</p> <p>Cystectomy as salvage therapy for recurrence in RT group. Local radical treatment chosen before randomization for each patient</p>	<p>Median: 4 years. Method: Option for group A: cystoscopy, bimanual palpation, TURBT after 3 cycles of chemotherapy before radiotherapy or cystectomy to assess for response.</p>	<p>Age (median): 64 vs. 64 Male: 433/491 vs. 430/485 Race/Ethnicity: Not reported Stage: T2: 34% vs. 34% T3: 58% vs. 58% T4: 85 vs. 8% Tumor grade: G1: 1%vs. 0.2% G2: 11%vs. 13% G3: 885 vs. 87% Unknown grade: 0% vs. 0.2% Functional status: WHO 0: 69% vs. 69% WHO 1: 26% vs. 26% WHO 2: 4% vs. 4% WHO 3: 0.2% vs. 0.2% Nodal status: N0: 67% vs. 63% NX: 33% vs. 37% Radical treatment: Radiotherapy: 42% vs. 43% Cystectomy: 50% vs. 49% Radiotherapy + cystectomy: 8% vs. 8%</p>

Table 6. Characteristics of studies on adjuvant and neoadjuvant chemotherapy (continued)

Type of Chemotherapy	Author, Year	Country, Number of Centers, Study Years, Type of Study	Interventions (Sample Size)	Duration of Followup and Cystoscopic Followup Method	Population Characteristics by Treatment Group (Age, Race/Ethnicity, Sex, Stage of Disease, Functional Status)
Neoadjuvant	International Collaboration of Trialists, 2011 ⁴³	20 countries 106 centers 1989-1995 Randomized controlled trial	A: NAC every 21 days for 3 cycles methotrexate 30 mg/m ² and vinblastine 4 mg/m ² on day 1 and 8, cisplatin 100 mg/m ² day 2 (CMV) + RT, cystectomy or RT and cystectomy (n=491) B: RT cystectomy or RT+cystectomy (n=485) The choice of definitive treatment was based on patient and physician choice, not randomly assigned.	Median: 8 years	Per group numbers not reported Age (mean): 64 Male: 863 (88%) Race/Ethnicity: Not reported Stage: T2: 334 (34%) T3: 567 (58%) T4a: 75 (8%) Functional Status: WHO 0-3 (most 0-1) Local definitive treatment: RT: 43% (415/976, 193 vs. 210) Cystectomy: 50% (485/976, 216 vs. 212) RT + cystectomy: 8% (76/976)
	Kitamura, 2014 ⁴⁴	Japan 28 centers 2003-2009 Randomized controlled trial	A: NAC, 2 cycles 28 days apart with methotrexate 30 mg/m ² on days 1, 15, and 22, vinblastine 3 mg/m ² on days 2, 15, and 22, doxorubicin 30 mg/m ² on day 2, and cisplatin 70 mg/m ² on day 2 + radical cystectomy (n=64) B: Cystectomy with LN dissection including the external iliac, internal iliac, and obturator nodes (n=66)	Median: 55 months	Age (median): 63 vs. 63 Male: 89% vs. 91% Race/Ethnicity: Not reported Stage: T2: 55% vs. 53% T3: 42% vs. 42% T4a: 3.1% vs. 4.5%
	Malmstrom, 1996 ⁴⁵ Rintala, 1993 ⁴⁶	Finland, Norway, Sweden 36 centers 1985-1989 Randomized controlled trial	A: NAC, 2 cycles separated by 3 weeks with cisplatin 70 mg/m ² and doxorubicin 30 mg/m ² + RT + cystectomy with LN dissection (n=151) B: RT and cystectomy with LN dissection (n=160)	Rintala, 1993: Mean: 18 months Malmstrom, 1996: Minimum of 5 years	Age (mean): 64 vs. 64 Male: 82% vs. 76% Race/Ethnicity: Not reported Stage: T1G3: 18% vs. 19% T2: 34% vs. 40% T3: 46% vs. 34% T4a: 2% vs. 6% Functional status: WHO 0: 74% vs. 76% WHO 1-2: 26% vs. 24%

Table 6. Characteristics of studies on adjuvant and neoadjuvant chemotherapy (continued)				
Author, Year	Country, Number of Centers, Study Years, Type of Study	Interventions (Sample Size)	Duration of Followup and Cystoscopic Followup Method	Population Characteristics by Treatment Group (Age, Race/Ethnicity, Sex, Stage of Disease, Functional Status)
Pal, 2012 ⁵⁴	United States Single Center 1995-2012 Retrospective cohort	A: NAC with methotrexate, vinblastine, doxorubicin, cisplatin (n=22) B: NAC with gemcitabine, carboplatin (n=24) C: NAC with "other" chemotherapeutic regimens (n=15) Target doses were assumed to be a total of 3 months of NAC	Median followup: 28.7 months Method of followup: Not reported	A vs. B vs. C Age (median): 60.1 vs. 68.6 vs. 77.3 Male: 90.9% vs. 79.2% vs. 86.7% Race/Ethnicity: Not reported Tumor stage (clinical stage): ≤ T2: 81.8% vs 91.7% vs. 73.3% T3: 4.5% vs. 8.3% vs. 20.0% T4: 9.1% vs. 0 vs. 6.7% Tumor Grade: II (intermediate): 1/22 vs. 0/24 vs. 1/15 III (high): 95.4% vs. 100% vs. 93.3% Functional Status: Charlson Comorbidity Index: 4.0 vs. 5.0 vs. 6.0; p<0.05
Sengelov, 2002 ⁴⁷	Denmark 1989-1993 Randomized controlled trial, based on two associated trials DAVECA 8901 and 8902	A: NAC, 3 cycles at 3 week intervals with cisplatin 100 mg/m ² , methotrexate 250 mg/m ² + cystectomy with LN dissection or XRT 3 weeks after chemotherapy (n=79; 17 underwent cystectomy) B: Cystectomy with LN dissection or XRT (n=74; 16 underwent cystectomy)	Minimum 42 months	Below comparisons are cystectomy (n=33) vs. XRT (n=120), no comparisons done within cystectomy only group in this paper Age: 66 vs. 63 Male: 79% (26/33) vs. 82% (98/120) Race/Ethnicity: Not reported Stage of disease: T1: 6% vs. 0 T2: 21% vs. 13% T3A: 39% vs. 28% T3B: 18% vs. 28% T4A: 12% vs. 16% T4B: 0 vs. 15% Functional/Performance status: 0: 55% vs. 37% 1: 42% vs. 58% 2: 3% vs. 5%

Table 6. Characteristics of studies on adjuvant and neoadjuvant chemotherapy (continued)

Author, Year	Country, Number of Centers, Study Years, Type of Study	Interventions (Sample Size)	Duration of Followup and Cystoscopic Followup Method	Population Characteristics by Treatment Group (Age, Race/Ethnicity, Sex, Stage of Disease, Functional Status)
Sherif, 2002 ⁴⁸	Sweden, Finland, Norway Multicenter, number not reported 1991-1997 Randomized controlled trial	A: NAC, 3 cycles at 3 week intervals with cisplatin 100 mg/m ² , methotrexate 250 mg/m ² + cystectomy with LN dissection (n=155) B: Cystectomy with LN dissection (n=154)	Median: 5.3 years. Method: Every 4 months for 2 years, then every 6 months for 2 years, then yearly for 1 year (physical exam, creatinine, chest X-ray, Intravenous pyelography at 4, 16 and 36 months).	Age (mean): 64.6 vs. 65.1 Male: 75% vs. 86% Race/Ethnicity: Not reported Stage: T2: 41% vs. 42% T3: 52% vs. 49% T4a: 7% vs. 8% Tx: 1% vs. 0% Functional status: Not reported

Table 6. Characteristics of studies on adjuvant and neoadjuvant chemotherapy (continued)

Type of Chemotherapy	Author, Year	Country, Number of Centers, Study Years, Type of Study	Interventions (Sample Size)	Duration of Followup and Cystoscopic Followup Method	Population Characteristics by Treatment Group (Age, Race/Ethnicity, Sex, Stage of Disease, Functional Status)
Adjuvant	Bono, 1997 ⁵²	Italy Nine centers 1984-1987 Randomized controlled trial	A: Radical cystectomy with LN dissection + adjuvant chemotherapy with cisplatin 70 mg/m ² day 1, and methotrexate 40 mg/m ² days 8 and 15 every 21 days for 4 cycles starting 21-28 days after surgery (n=35 for pN0 and n= 31 for pN+) B: Radical cystectomy with LN dissection (n=48) pN0 patients were randomized into the groups A or B; pN+ patients were assigned to group A	Mean: 69.12 months Method: Every 3 months for 2 years with blood work, chest X-ray, abdominal ultrasound, clinical exam. CT scan of abdomen and bone scan every 6 months for 2 years.	Age (mean): 62 vs. 62, 60 in pN+ group Male: 104/114, number in each group Not reported Race/Ethnicity: not reported Stage: pT2N0: 20% vs. 27% , pT2N+: 10% pT3aN0: 43% vs. 39%, pT3aN+: 32% pT3b-4aN0: 37% vs. 35%, pT3b-4aN+: 58% Nodal status: pN+ 22% Functional status: not reported
	Cognetti, 2012 ⁵⁰	Italy 45 centers 2001-2007 Randomized controlled trial	A: Cystectomy +/- LN dissection + adjuvant chemotherapy (AC) every 28 days for 4 cycles with gemcitabine 1000 mg/m ² days 1,8, and 15 plus cisplatin 70 mg/m ² on day 2 or day 15 (total n=97; cisplatin day 2 (A1), n=43, cisplatin day 15 (A2), n=46) B: Cystectomy +/- LN dissection + treatment on relapse (n=86)	Median: 35 months Method: Every 3 months for 2 years, then every 6 months for 3 years, yearly thereafter. CT scan every 6 months for 3 years then yearly thereafter.	Age (mean): 64 vs. 63 Male: 93% vs. 87% Race/Ethnicity: Not reported Stage: pT1: 3% vs. 1% pT2: 30%vs. 22% pT3: 47% vs. 57% pT4: 120% vs. 20% LN status: pN0: 48% vs. 57% pN1: 21% vs. 22% pN2: 31% vs. 21% Functional status: ECOG PS 0: 81% vs. 71% ECOG PS 1-2: 17% vs. 24% ECOG PS missing: 2% vs. 5%

Table 6. Characteristics of studies on adjuvant and neoadjuvant chemotherapy (continued)

Author, Year	Country, Number of Centers, Study Years, Type of Study	Interventions (Sample Size)	Duration of Followup and Cystoscopic Followup Method	Population Characteristics by Treatment Group (Age, Race/Ethnicity, Sex, Stage of Disease, Functional Status)
Freiha, 1996 ⁴⁹	USA Single center 1986-1993 Randomized controlled trial	A: Radical cystectomy with LN dissection + adjuvant chemotherapy, 4 cycles every 21 day with methotrexate 30 mg/m ² , and vinblastine 4 mg/m ² day 1 and 8, 100 mg/m ² cisplatin on day 2 (CMV) (n= 25) B: Radical cystectomy with LN dissection (n=25)	Mean, median: 57 and 62 months Method: Every 3 months for year 1, every 4 months for year 2 and every 6 months thereafter. Physical exam, blood studies, chest X-ray. Urine cytology every 6 months. CT at months 3,6,9,15,24	Age (mean): 59 vs. 64 Male: 92% vs. 88% Race/Ethnicity: Not reported Stage: T3bN0: 16% vs. 28% T4N0: 12% vs. 4% pN+: 1 node: 16% vs. 40% pN+, 2 nodes: 20% vs. 12% pN+, 3 nodes: 16% vs. 8% pN+, 4+ nodes: 20% vs. 8% Functional status: Not reported
Skinner, 1991 ⁵¹	USA Single center 1980-1988 Randomized controlled trial	A: Cystectomy with LN dissection + AC, 4 cycles at 28-day intervals starting 6 weeks after surgery with cisplatin 100 mg/m ² , doxorubicin 60 mg/m ² and cyclophosphamide 600 mg/m ² (n=44) B: Cystectomy with LN dissection (n=47)	Median: 32 months, with all but 6 patients followed beyond 1 year. Method: Every 4 month for 1 year, then every 6 months for 3 years, then yearly thereafter(Chest X-ray, urogram, laboratory tests, physical exam. CT, MRI or bone scans based on symptoms/ abnormal lab values).	Age (median): 61 vs. 62 Male: 77% vs. 74% Race/Ethnicity: Not reported Stage: T1 or 2: 7% vs. 11% T3a: 23% vs. 15% T3b: 45% vs. 51% T4: 25% vs. 23% Tumor grade: G2 5% vs. 9% G3 50% vs. 50% G4 45% vs. 41% missing: 0% vs. 2% Lymph node status: 0 nodes 61% vs. 66% 1 +LN 16% vs. 21% ≥2 +LN 23% vs. 13% (6/47) Functional status: Not reported

Table 6. Characteristics of studies on adjuvant and neoadjuvant chemotherapy (continued)

Type of Chemotherapy	Author, Year	Country, Number of Centers, Study Years, Type of Study	Interventions (Sample Size)	Duration of Followup and Cystoscopic Followup Method	Population Characteristics by Treatment Group (Age, Race/Ethnicity, Sex, Stage of Disease, Functional Status)
Neoadjuvant Vs. Adjuvant	Matsubara, 2013 ⁵⁸	Japan Single center 2005-2010 Retrospective cohort	A: NAC, 4 cycles at 4 week intervals with gemcitabine 1000 mg/m ² and cisplatin 70 mg/m ² + cystectomy with LN dissection (n=25) B. Cystectomy with LN dissection + AC, 4 cycles at 4 week intervals with gemcitabine 1000 mg/m ² and cisplatin 70 mg/m ² (n=17)	Median: 28.6 months	Age (mean): 65 vs. 65 Male: 60% vs. 94% Race/Ethnicity: Not reported Stage of disease: ≤ cT2: 36% vs. 24% > cT2: 64% vs. 77% Functional status: Not reported
	Milikan, 2001 ⁵⁶	United States Single Center 1986-1998 Randomized controlled trial	A: Cystectomy + 5 cycles adjuvant chemotherapy with methotrexate 30 mg/m ² , vinblastine 3 mg/m ² , doxorubicin 30 mg/m ² , cisplatin 70 mg/m ² (M-VAC) beginning 4 weeks postoperatively (n=70) B: 2 cycles NAC with methotrexate 30 mg/m ² , vinblastine 3 mg/m ² , doxorubicin 30 mg/m ² , cisplatin 70 mg/m ² + cystectomy, followed by 3 additional cycles of chemotherapy beginning 6 weeks postoperatively (n=70)	Median followup: 6.8 years Followup method: Not reported	Age (median): 67 vs. 66 years Male: 64% vs. 79% Race/Ethnicity: Not reported Stage of disease: < T3b: 33% vs. 30% T3b: 56% vs. 60% T4a: 9% vs. 10% Upper tract: 3% vs. 0% Functional status: Not reported
	Wosnitzer, 2012 ⁵⁷	United States Single Center 1988-2009 Retrospective cohort	A: Neoadjuvant chemotherapy, cisplatin or carboplatin based (n=73) B: Adjuvant chemotherapy, cisplatin or carboplatin based (n=73)	Median followup: 12.8 vs. 14 months	Age (mean): 64 vs. 66 years Male: 71% vs. 73% Race/Ethnicity: Caucasian: 82% vs. 77%; African American: 4% vs. 3%; Latin: 11% vs. 1%; Other: 8% vs. 14% Stage of disease >T2: 25% vs. 55%; Node status >N0: 7% vs. 40% Functional status: Not reported
	Yeshchina, 2012 ⁵⁵	United States Single Center 1988-2010 Retrospective cohort	A: Methotrexate, vinblastine, doxorubicin, cisplatin (n=77; 45 neoadjuvant, 32 adjuvant) B: Gemcitabine, cisplatin (n=37; 16 neoadjuvant, 21 adjuvant)	Median followup: 30 vs. 25 months Followup method Not reported	Age (mean): 62.86 vs. 66.03 years Male: 66% vs. 70% Race/Ethnicity: White: 84% vs. 78% Stage: T2: 82% vs. 76%; >T2: 18% vs. 24% Functional status: Not reported

CMV = cisplatin, methotrexate, vinblastine; CT = computerized tomography; ECOG PS= eastern cooperative oncology group performance status; G1 = Grade 1; G2 = Grade 2; G3 = Grade 3; G4 = Grade 4; LN = lymph node; MRI, magnetic resonance imaging; MVAC = Methotrexate, Vinblastine, Doxorubicin, Cisplatin; N+ = without regional lymph node involvement; N+ = without regional

lymph node involvement; N0 = without regional lymph node involvement; NAC = neoadjuvant chemotherapy; Nx = nodes not removed or unknown; pN+ = pathologically node-positive; pN0 = Node stage 0 determined by pathology; pT2 = Tumor stage 2 determined by pathology; pT3 = Tumor stage 3 determined by pathology; pT3a = Tumor stage 3a determined by pathology; pT3b = Tumor stage 3a determined by pathology; pT4a = Tumor stage 4a determined by pathology; RT = radiotherapy; T1 = Tumor stage 1; T2 = Tumor stage 2; T3 = Tumor stage 3; T3a = Tumor stage 3a; T3b = Tumor stage 3b; T4 = Tumor stage 4; TURBT = transurethral resection of bladder ; Tx = Tumor stage unknown; WHO = World Health Organization; XRT=radiation therapy

Table 7. Summary of results for adjuvant and neoadjuvant chemotherapy studies

Type of Chemotherapy	Author, Year	Interventions (Number Analyzed for Recurrence)	Recurrence	Progression	Mortality
Neoadjuvant	Dash, 2008 ⁵⁹	<p>A: NAC: Gemcitabine + Cisplatin, predominately given as: "Single dose" cisplatin administration consisted of 4 cycles, with 21 day intervals of cisplatin 70 mg/m2 and gemcitabine 1000 mg/m2 on day 1, and gemcitabine 1000 mg/m2 on day 8. "Split-dose" cisplatin administration consisted of 4 cycles, with 21 day intervals of cisplatin 35 mg/m2 and gemcitabine 1000 mg/m2 on days 1 and 8. (n=42)</p> <p>B: NAC: Methotrexate, vinblastine, doxorubicin and cisplatin given as 4 cycles at 28-day intervals. Doses were not reported. (n=54)</p>	Not reported	Not reported	Not reported

Table 7. Summary of results for adjuvant and neoadjuvant chemotherapy studies (continued)

Type of Chemotherapy	Author, Year	Interventions (Number Analyzed for Recurrence)	Recurrence	Progression	Mortality
	Fairey, 2013 ⁵³	<p>A. NAC, 4 cycles of GC at 21-day intervals over 12 weeks + cystectomy with super-extended pelvic LN dissection (n= 58)</p> <p>B. NAC, 4 cycles of M-VAC at 28-day intervals over 16 weeks + cystectomy with super-extended pelvic LN dissection (n= 58)</p>	<p>A vs. B</p> <p>Cumulative incidence of recurrence, adjusted HR 0.60 (95%CI 0.34-1.03)</p> <p>Cumulative incidence of recurrence in pTanyN1-3M0 patients with median time to recurrence: 4 months vs. 7.4 months, p=0.019</p> <p>Multivariable analysis showed no independent association between type of NAC and recurrence.</p> <p>Multivariable analysis showed no independent association between age and recurrence.</p>	Not reported	<p>A vs. B</p> <p>Overall mortality: adjusted HR 0.90 (95% CI 0.52-1.56)</p> <p>Multivariable analysis showed no independent association between type of NAC and overall mortality (HR 1.11, 95% CI 0.64-1.91, p=0.721).</p> <p>Multivariable analysis showed no independent association between age and overall mortality.</p>

Table 7. Summary of results for adjuvant and neoadjuvant chemotherapy studies (continued)

Author, Year	Interventions (Number Analyzed for Recurrence)	Recurrence	Progression	Mortality
Grossman, 2003 ⁴¹	<p>A: Neoadjuvant chemotherapy, three 28-day cycles with methotrexate 30 mg/m² on days 1, 15 and 22; vinblastine 3 mg/m² on days 2, 15 and 22; doxorubicin 30 mg/m² and cisplatin 70 mg/m² on day 2 (MVAC) + radical cystectomy with LN dissection (n=153)</p> <p>B: Radical cystectomy with LN dissection (n=154)</p>			<p><i>A vs. B</i></p> <p>All-cause mortality: 59% (90/153) vs. 65%, HR 0.75 (95% CI 0.57 to 1.00)</p> <p>Bladder cancer-specific mortality: 35% vs. 50%, HR 0.60 (95% CI 0.41 to 0.82)</p> <p>Median survival (months), unstratified: 77 vs. 46, p=0.05 log rank test</p> <p>Survival at 5 years: 57% vs. 43%, p=0.06</p> <p>Median survival (months) stratified for age: age <65: 104 vs. 67, age ≥ 65: 61 vs. 30 p=0.05, log rank test</p> <p>Median survival (months) stratified for tumor stage: T2: 105 vs. 75; T3/T4a: 65 vs. 24, p=0.05, log rank test</p> <p><i>B vs. A</i></p> <p>Cystectomy only group had a 33% increased risk of death compared to the MVAC/cystectomy group (stratified analysis). Survival: HR 1.33 (95% CI 1.00 to 1.76) Disease-specific survival HR 1.66 (1.22-2.45), p=0.002</p>

Table 7. Summary of results for adjuvant and neoadjuvant chemotherapy studies (continued)

Author, Year	Interventions (Number Analyzed for Recurrence)	Recurrence	Progression	Mortality
International Collaboration of Trialists, 1999 ⁴²	<p>A: NAC every 21 days for 3 cycles with methotrexate 30 mg/m², vinblastine 4 mg/m² on day 1 and day 8; cisplatin 100 mg/m² on day 2 (CMV) + cystectomy +/- LN dissection or RT or RT and cystectomy (n=491)</p> <p>B: Cystectomy with LN dissection or radiotherapy or RT and cystectomy. (n=485)</p> <p>Cystectomy as salvage therapy for recurrence in RT group. Local radical treatment chosen before randomization for each patient.</p>	<p>Locoregional disease free survival: 47% vs. 42%, HR 0.87, 95% CI 0.73 to 1.01</p> <p>Median locoregional disease free survival (months): 23.5 vs. 20</p> <p>No effect on locoregional control, HR 0.96, 95% CI 0.80 to 1.15)</p> <p>Disease free survival: 46% vs. 39%, HR 0.82, 95% CI 0.70 to 0.97</p> <p>Median disease free survival (months): 20 vs. 16.5</p>	<p>Metastasis free survival: 45% vs. 53%, HR 0.79 95% CI 0.66 to 0.93,</p> <p>Median metastasis free survival (months): 32 vs. 25</p>	<p>Deaths: 229/491 vs. 256/485, RR 0.88, 95% CI 0.78 to 1.00</p> <p>Survival: HR 0.85, 95% CI 0.71 to 1.02</p>
International Collaboration of Trialists, 2011 ⁴³	<p>A: NAC every 21 days for 3 cycles methotrexate 30 mg/m² and vinblastine 4 mg/ m² on day 1 and 8, cisplatin 100 mg/m² day 2 (CMV) + RT, cystectomy or RT and cystectomy (n=491)</p> <p>B: RT, cystectomy or RT+cystectomy (n=485)</p>	<p>Cystectomy patients only:</p> <p>Locoregional recurrence: 40% (84/212) vs. 39% (84/216) RR 1.02, 95% CI 0.80 to 1.29</p> <p>Locoregional disease-free survival 55% (119/216) vs. 65% (137/212), HR 0.74, 95% CI 0.58 to 0.95)</p>		<p>Cystectomy patients only:</p> <p>Overall survival in patients: HR 0.74, 95% CI 0.57 to 0.96)</p> <p>Overall 3 year survival: 55.5% vs. 50% (95% CI for difference -0.5-11.0)</p> <p>Overall 10-year survival 36% vs. 30%</p> <p>Median survival (months): 44 vs. 37.5</p>

Table 7. Summary of results for adjuvant and neoadjuvant chemotherapy studies (continued)

Author, Year	Interventions (Number Analyzed for Recurrence)	Recurrence	Progression	Mortality
Kitamura, 2014 ⁴⁴	<p>A: NAC, 2 cycles 28 days apart with methotrexate 30 mg/m² on days 1, 15, and 22, vinblastine 3 mg/m² on days 2, 15, and 22, doxorubicin 30 mg/m² on day 2, and cisplatin 70 mg/m² on day 2 + radical cystectomy (n=64)</p> <p>B: Cystectomy with LN dissection including the external iliac, internal iliac, and obturator nodes (n=66)</p>		<p>A vs. B Disease progression at 5 years: 36% (23/64) vs. 45% (29/64), HR 0.64 (95% CI 0.37-1.11) Progression-free survival at 5 years: 68% vs. 56% Progression-free survival interval (median, months): 99 vs. 78</p>	<p>A vs. B Mortality: HR 0.65 (95% CI 0.19-2.18) Overall survival at 5 years: 72% vs. 62% Survival interval (median, months): 102 vs. 82 No differences in estimates based on age, tumor stage, papillary vs. nonpapillary, solitary vs. multiple, tumor size, tumor grade</p>

Table 7. Summary of results for adjuvant and neoadjuvant chemotherapy studies (continued)

Author, Year	Interventions (Number Analyzed for Recurrence)	Recurrence	Progression	Mortality
Malmstrom, 1996 ⁴⁵	<p>A: NAC, 2 cycles separated by 3 weeks with cisplatin 70 mg/m² and doxorubicin 30 mg/m² + RT + cystectomy with LN dissection (n=151)</p> <p>B: RT + cystectomy with LN dissection (n=160)</p>	<p>Overall: 21% vs. 25%, RR 0.82, 95% CI 0.54 to 1.24 Median interval to relapse (months): 23 vs. 14, p=0.42</p>		<p>5- year overall survival: 59% vs. 51%, p=0.10, log rank test</p> <p>5- year cancer specific survival: 64% vs. 54%, p=0.07, log rank test</p> <p>Risk of death, adjusted for age, gender, histologic grade, hydronephrosis, and tumor stage: RR 0.69, 95% CI 0.49-0.98</p> <p>5-year survival by age: < 60 years (N=75): 61% vs. 49%, p=0.21 ≥ 60 years (N=236): 58% vs. 51%, p=0.21</p> <p>5- year cancer- specific survival by tumor grade: T1: 77% vs. 71%, not statistically significant T2 58% vs. 55%, not statistically significant T3-T4a: 52% (n=72) vs. 37% (n=65), p=0.03, log rank test</p>

Table 7. Summary of results for adjuvant and neoadjuvant chemotherapy studies (continued)

Author, Year	Interventions (Number Analyzed for Recurrence)	Recurrence	Progression	Mortality
Rintala, 1993 ⁴⁶	Same study as Malmstrom, 1996 ⁴⁵			<p>Risk of death: RR 0.6, 95% CI 0.4-0.9</p> <p>Survival, all patients (n=311), study states statistically significant difference in favor of A, p=0.034, log rank test, data not presented</p> <p>Survival, cystectomized patients (n=266), study states no statistically significant difference, p= 0.093, log rank test, data not presented</p> <p>Survival, T2-T4a (n=253), study states statistically significant difference in favor of A, p= 0.018, data not presented</p> <p>Survival, cystectomized patients T2-T4a (n=210), study states statistically significant difference in favor of A, p=0.057, data not presented</p> <p>Survival, patients with T2-T4a, according to downstaging, p0-1 vs. p2 (n=213), study states in favor of p0-1, p=0.0005, data not presented</p>
Pal, 2012 ⁵⁴	<p>A: NAC with methotrexate, vinblastine, doxorubicin, cisplatin (n=22)</p> <p>B: NAC with gemcitabine, carboplatin (n=24)</p> <p>C: NAC with "other" chemotherapeutic regimens (n=15)</p> <p>Target doses were assumed to be a total of 3 months of NAC</p>	Not reported	Not reported	<p>Survival (months):</p> <p>A/B vs. C: 35.3 vs. 16.3; P=0.055</p> <p>A vs. B: 104.3 vs. 21.8; P=0.73</p>

Table 7. Summary of results for adjuvant and neoadjuvant chemotherapy studies (continued)

Author, Year	Interventions (Number Analyzed for Recurrence)	Recurrence	Progression	Mortality
Sengelov, 2002 ⁴⁷	<p>A: NAC, 3 cycles at 3 week intervals with cisplatin 100 mg/m², methotrexate 250 mg/m² + cystectomy with LN dissection or XRT 3 weeks after chemotherapy (n=79; 17 underwent cystectomy)</p> <p>B: Cystectomy with LN dissection or XRT (n=74; 16 underwent cystectomy)</p>	Not reported	<p>For cystectomy patients only (n=33, 17 vs. 16)</p> <p>Progression-free survival rate at 5 years: 41% vs. 36%</p>	<p>For cystectomy patients only (n=33, 17 vs. 16)</p> <p>Median survival: 82.5 months vs. 45.8 months, p = 0.76</p> <p>5-year survival rates: 64% vs. 46%</p>
Sherif, 2002 ⁴⁸	<p>A: NAC, 3 cycles at 3 week intervals with cisplatin 100 mg/m², methotrexate 250 mg/m² + cystectomy with LN dissection (n=155)</p> <p>B: Cystectomy with LN dissection (n=154)</p>	<p>Recurrence, locoregional and distant metastasis: 6% (9/155) vs. 8% (12/154), RR 0.75, 95% CI 0.32 to 1.72</p> <p>Locoregional only: 10% (15/155) vs. 9% (14/154), RR 1.06, 95% CI 0.53 to 2.13</p> <p>Distant metastasis only: 13% (20/155) vs. 16% (24/154), RR 0.83, 95% CI 0.48 to 1.44</p>		<p>Overall 5-year survival: 53% vs. 46% (p=0.2375, log rank test)</p> <p>Overall survival, HR 0.8, 95% CI 0.6 to 1.1</p> <p>5 year survival, T2 group, p=0.5356, log rank test</p> <p>Overall survival, T2 group, HR 0.8, 95% CI 0.5 to 1.5</p> <p>5 year survival, T3-T4a group, p=0.2740, log rank test</p> <p>Overall survival, T3-T4a group, HR 0.8, 95% CI 0.6 to 1.2</p>

Table 7. Summary of results for adjuvant and neoadjuvant chemotherapy studies (continued)

	Author, Year	Interventions (Number Analyzed for Recurrence)	Recurrence	Progression	Mortality
Adjuvant	Bono, 1997 ⁵²	A: Radical cystectomy with LN dissection + adjuvant chemotherapy every 21 days for 4 cycles starting 21-28 days after surgery with cisplatin 70 mg/m ² day 1, and methotrexate 40 mg/m ² days 8 and 15 (n=35 for pN0 and n= 31 for pN+, total n=66) B: Radical cystectomy with LN dissection (n=48)		Node negative patients: Progression: 49% vs. 44%, RR 0.91, 95% CI 0.61 to 1.37	Node negative patients: Survival: 49% (17/35) vs. 38% (8/48) Bladder cancer- specific mortality: 46% (16/35) vs. 52% (25/48), RR 0.88, 95% CI 0.56 to 1.38 All- cause mortality: 51% (18/35) vs. 63% (30/48) pN+ from group A Survival: 32% (10/31) Died of disease: 58% (18/31) Death, any cause: 68% (21/31)
	Cognetti, 2012 ⁵⁰	A: Cystectomy +/- LN dissection + adjuvant chemotherapy (AC) every 28 days for 4 cycles with gemcitabine 1000 mg/m ² days 1,8, and 15 plus cisplatin 70 mg/m ² on day 2 or day 15 (GC) (n=97) A1: cisplatin on day 2 (n=43) A2: cisplatin on day 15 (n=46) B: Cystectomy +/- LN dissection + treatment on relapse (n=86)	Overall recurrence: 44% (43/97) vs. 47% (40/86), RR 0.95, 95% CI 0.69 to 1.31 5 year disease-free survival: Overall: 42% vs. 37%, p=0.70, HR 1.08, 95% CI 0.73-1.59 Node-negative patients: 58% vs. 60%, p=0.97 Node-positive patients: 19% vs. 19%, p=0.80		5-year survival: Overall: 43% vs. 54%, p=0.24 Overall, A1 vs. A2: 47% vs. 40%, p=0.88 Lymph node negative disease: 65% vs. 73%, p=0.65 Lymph node positive disease: 26% vs. 28%, p=0.71 Mortality: HR = 1.29, 95% CI 0.84 to 1.99 Independent of treatment arm, mortality hazard was significantly associated with nodal status and T stage: pN1 vs. pN0: HR 2.42, 95% CI 1.38 to 4.26 pN2 vs. pN0: HR 4.33, 95% CI 2.6 to 7.2 pT3 vs. pT1-2: HR 2.01, 95% CI 1.14 to 3.56 pT4 vs. pT1-2: HR 2.57, 95% CI 1.34 to 4.92

Table 7. Summary of results for adjuvant and neoadjuvant chemotherapy studies (continued)

Author, Year	Interventions (Number Analyzed for Recurrence)	Recurrence	Progression	Mortality
Freiha, 1996 ⁴⁹	<p>A: Radical cystectomy with LN dissection + adjuvant chemotherapy, 4 cycles every 21 day with methotrexate 30 mg/m², and vinblastine 4 mg/m² day 1 and 8, 100 mg/m² cisplatin on day 2 (CMV) (n=25)</p> <p>B: Radical cystectomy with LN dissection (n=25)</p>	<p>Recurrence: 52% (13/25) vs. 76% (19/25) RR 0.68, 95% CI 0.44 to 1.06</p> <p>Mean / median interval to recurrence: 17.5 /16.2 months (range: 4-37 months) vs. 11.5 / 10.1 months (range: 2-34 months), p=0.01, log rank test</p> <p>6/19 recurrences in group B, 6 received CMV therapy</p>		<p>Survival: 52% (13/25) vs. 32% (8/25), RR 0.71, 95% CI 0.43 to 1.15</p> <p>Survival according to nodal status</p> <p>N0: 71 % (5/7) vs. 25% (2/8), RR 0.68, 95% CI 0.11 to 1.31</p> <p>N+: 44% (8/18) vs. 35% (6/17) ≤ N3: 46% (6/13) vs. 40% (6/15) > N3: 40% (2/5) vs. 0% (0/2)</p>

Table 7. Summary of results for adjuvant and neoadjuvant chemotherapy studies (continued)

Author, Year	Interventions (Number Analyzed for Recurrence)	Recurrence	Progression	Mortality	
Skinner, 1991 ⁵¹	<p>A: Cystectomy with LN dissection + AC, 4 cycles at 28-day intervals starting 6 weeks after surgery with cisplatin 100 mg/m², doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² (n=44)</p> <p>B: Cystectomy with LN dissection (n=47)</p>	<p>Probability of recurrence at 3 years: 0.30 (SE=0.08) vs. 0.54 (SE=0.08), p=0.011, unstratified Wilcoxon test Median time to recurrence 4.7 years. Benefit of chemotherapy was significant for time to recurrence, (p=0.0010, stratified Wilcoxon) after stratifying for the 3 nodal groups.</p>		<p>All- cause mortality: 34% vs. 50%, p=0.10 Probability of bladder cancer-specific mortality within 3 years: 0.29 (SE=0.08) vs. 0.50 (SE=0.08)</p> <p>Node negative patients, no overall survival benefit from chemotherapy, p=0.14 Benefit of chemotherapy was significant for survival, (p=0.0062, stratified Wilcoxon) after stratifying for the 3 nodal groups (N0, N1, N2+)</p>	
Neoadjuvant vs. Adjuvant	Matsubara, 2012 ⁵⁸	<p>A: NAC, 4 cycles at 4 week intervals with gemcitabine 1000 mg/m² and cisplatin 70 mg/m² + cystectomy with LN dissection (n=25)</p> <p>B. Cystectomy with LN dissection + AC, 4 cycles at 4 week intervals with gemcitabine 1000 mg/m² and cisplatin 70 mg/m² (n=17)</p>	<p>A vs. B Recurrence (metastatic): 9/25 (36%) vs. 3/17 (18%) Recurrence-free survival (at median followup): 66.7% vs. 76%, p=0.124, log-rank Overall HR 0.65 (95% CI 0.36-1.17) trending in favor of NAC</p>	Not reported	Not reported
	Milikan, 2001 ⁵⁶	<p>A: Cystectomy + 5 cycles adjuvant chemotherapy with methotrexate 30 mg/m², vinblastine 3 mg/m², doxorubicin 30 mg/m², cisplatin 70 mg/m² (M-VAC) beginning 4 weeks postoperatively (n=70)</p> <p>B: 2 cycles NAC with methotrexate 30 mg/m², vinblastine 3 mg/m², doxorubicin 30 mg/m², cisplatin 70 mg/m² + cystectomy, followed by 3 additional cycles of chemotherapy beginning 6 weeks postoperatively (n=70)</p>	<p>A vs. B Disease- free survival: 42/70 (60%) vs. 39/70 (56%), NSD, RR 0.90 95% CI 0.61-1.33</p>	<p>A vs. B Time to progression: NSD, numbers Not reported</p>	<p>A vs. B Overall survival: NSD, numbers Not reported</p>

Table 7. Summary of results for adjuvant and neoadjuvant chemotherapy studies (continued)

Author, Year	Interventions (Number Analyzed for Recurrence)	Recurrence	Progression	Mortality
Wosnitzer, 2012 ⁵⁷	<p>A: Neoadjuvant chemotherapy, cisplatin or carboplatin based (n=73)</p> <p>B: Adjuvant chemotherapy, cisplatin or carboplatin based (n=73)</p>	Not reported	Not reported	<p>A vs. B</p> <p>Disease specific survival: Univariate HR=1.28 (95%CI: 0.76-2.16), p=0.36; multivariate HR=1.24 (95%CI: 0.70-2.18), p=0.46</p> <p>Overall survival: Univariate HR=1.12 (95% CI: 0.73-1.73), p=0.60; multivariate HR=1.08 (95% CI: 0.67-1.73), p=0.76</p> <p>Cisplatin based treatment: median survival: 11 vs. 12.5 months Disease specific survival: NSD, data Not reported Overall survival: NSD, data Not reported</p> <p>MVAC treatment: median survival: 16 vs. 22 months Disease specific survival: NSD, p=0.555 Overall survival: NSD, p=0.573</p> <p>Gemcitabine/cisplatin treatment: median survival: 11 vs. 10.5 months Disease specific survival: HR=10.06 (95%CI: 1.01-112.2), p=0.049 Overall survival: NSD, p=0.607</p> <p>Carboplatin based treatments: median survival: 8.9 vs. 10 months Disease specific survival: NSD, p=0.764 Overall survival: NSD, p=0.388</p>

Table 7. Summary of results for adjuvant and neoadjuvant chemotherapy studies (continued)

Author, Year	Interventions (Number Analyzed for Recurrence)	Recurrence	Progression	Mortality
Yeshchina, 2012 ⁵⁵	<p>A: Methotrexate, vinblastine, doxorubicin, cisplatin (n=77; 45 neoadjuvant, 32 adjuvant)</p> <p>B: Gemcitabine, cisplatin (n=37; 16 neoadjuvant, 21 adjuvant)</p>	Not reported	Not reported	<p>Neoadjuvant vs. Adjuvant: Overall survival: HR=0.61 (95% CI: 0.37-1.00), p=0.51 Cancer specific survival: HR=0.69 (95%CI: 0.37-1.29), p=0.247</p> <p>A vs. B: 5-year overall survival: 47% vs. 35%, p=0.346 5-year disease specific survival: 61% vs. 50%, p=0.482</p>

AC = adjuvant chemotherapy; CI = confidence interval; CMV = cisplatin, methotrexate, vinblastine; NSD = no significant difference; GC = gemcitabine plus cisplatin; HR = hazard ratio; LN = lymph node; M-C = Mantel-Cox; MVAC, methotrexate, vinblastine, doxorubicin, cisplatin; N+ = without regional lymph node involvement; N0 = without regional lymph node involvement; N1 = Node stage 1; N2+ = Node stage 2 positive; N3 = Node stage 3; NAC = neoadjuvant chemotherapy; pN0 = Node stage 0 determined by pathology; pN1 = Node stage 1 determined by pathology; pN2 = Node stage 2 determined by pathology; pT1 = Tumor stage 1 determined by pathology; pT2 = Tumor stage 2 determined by pathology; pT3 = Tumor stage 3 determined by pathology; pT4 = Tumor stage 4 determined by pathology; RCT = randomized controlled trial; RR = relative risk; RT = radiotherapy; SE = standard error; T1 = Tumor stage 1; T2 = Tumor stage 2; T3 = Tumor stage 3; T4a = Tumor stage 4a; XRT = radiation therapy

Discussion

Key Findings and Strength of Evidence

The key findings of this review are summarized in the summary of evidence table (Table 8) and the factors used to determine the overall strength of evidence grades are summarized in Appendix G.

We found limited evidence with which to evaluate the effectiveness of bladder-preserving therapies for muscle-invasive bladder cancer versus radical cystectomy. The only randomized controlled trial (RCT) of bladder-preserving therapy versus radical cystectomy had important methodological limitations, used lower doses of radiation therapy than in current practice, did not use radiation therapy in combination with chemotherapy, and may have used outdated surgical techniques, as patients were treated in the early 1980's.¹⁹ 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, though bladder-preserving treatment was associated with increased risk of local or regional recurrence (35.8% vs. 6.8%) (strength of evidence [SOE]: low). Cohort studies 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 transurethral resection of bladder tumor (TURBT).²² It reported high 5-year mortality rates that were similar for radiation therapy and maximal TURBT, and did not attempt to adjust for potential confounders. One RCT found external beam radiation therapy with synchronous chemotherapy associated with trends towards 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, suggesting that if bladder-preserving treatment is used, combination therapies may be more effective than single modality therapy.²⁸

Some evidence from cohort studies suggested that more extensive lymph node dissection with cystectomy might be more effective than less extensive lymph node dissection at improving survival and decreasing risk of recurrence (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^{36, 39}), there was variability in the lymph node dissection techniques evaluated, and there was some inconsistency in results. In addition, although a standard lymph node dissection template was associated with decreased mortality compared with a limited lymph node dissection template, additional benefits of extended or super extended versus standard lymph node dissection templates was unclear. More extensive lymph node dissection was associated with longer operative times in one study (SOE: low),³⁴ but other harms were poorly reported.

Evidence was somewhat stronger on the effects of neoadjuvant and adjuvant chemotherapy in patients with muscle-invasive bladder cancer. Six RCTs consistently found neoadjuvant chemotherapy (NAC) associated with decreased risk, or a trend towards decreased risk, of mortality versus no NAC (SOE: moderate). Three trials evaluated currently recommended chemotherapy regimens (cisplatin, methotrexate, and vinblastine [CMV] and methotrexate, vinblastine, doxorubicin, and cisplatin [MVAC])^{41, 42, 44} and three trials evaluated other cisplatin-based combination regimens (cisplatin with methotrexate or doxorubicin).⁴⁶⁻⁴⁸ There was limited

evidence of similar estimates of effectiveness of NAC in subgroups based on tumor or patient characteristics. Compared with evidence on NAC, evidence on benefits of adjuvant chemotherapy (AC) was not as strong. Although four trials found AC 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 neoadjuvant or adjuvant chemotherapy with MVAC versus cisplatin and gemcitabine, but had serious methodological limitations including failure to adjust for confounders or nonconcurrent comparisons, precluding reliable conclusions (SOE: insufficient).⁵³⁻⁵⁵ One trial and two cohort studies found neither neoadjuvant nor adjuvant MVAC superior for overall or bladder cancer-specific survival (SOE: low).⁵⁵⁻⁵⁷ 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). Renal adverse events were not well-reported in the studies included in this review, despite known nephrotoxic effects of cisplatin.⁶⁰ No study compared benefits or harms of cisplatin versus carboplatin-based chemotherapy regimens.

Table 8. 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.

Table 8. Summary of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
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.
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.

Table 8. Summary of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
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.
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.

Table 8. Summary of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	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.
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.
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.

Table 8. Summary of evidence (continued)

Key Question	Outcome	Strength-of-Evidence Grade	Conclusion
	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; NLR = negative likelihood ratio; OR=odds ratio; PLR=positive likelihood ratio; SOE = strength of evidence

Findings in Relationship to What Is Already Known

Our findings regarding bladder-preserving therapy are consistent with a recent review conducted to inform an International Consultation on Urological Diseases/European Association of Urology guideline on radical cystectomy and bladder-preserving therapy⁶¹ that concluded that open radical cystectomy remains the standard of treatment for muscle invasive bladder cancer. However, it 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 and bladder preservation using multiple modalities.

Our findings are also consistent with systematic reviews that found lymph node dissection associated with better outcomes than no lymph node dissection, and more extensive lymph node dissection associated with better outcomes than less extensive dissection. Like our review, prior

reviews found serious methodological shortcomings in the evidence,^{62, 63} precluding strong conclusions.

Our findings are also consistent with prior systematic reviews that found platinum-based neoadjuvant chemotherapy associated with improved survival versus no neoadjuvant chemotherapy,⁶⁴⁻⁶⁶ despite some differences between the methods used to conduct the reviews. For example, prior reviews included studies of patient who received cisplatin monotherapy, which is not used in clinical practice, as well as non-cisplatin 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.⁶⁵ Other differences in the methods used by prior reviews include access to and analysis of individual patient data, unpublished data, and trials published only as abstracts.⁶⁵ Our findings are also consistent with systematic reviews that found less definitive evidence that adjuvant chemotherapy is more effective than no adjuvant chemotherapy.^{66, 67} Although one review based on individual patient data found adjuvant chemotherapy associated with reduced risk of mortality (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.⁶⁷

Applicability

Some issues could impact the applicability of our findings. The only RCT of bladder-sparing therapy was conducted in the early 1980's and used doses of radiation therapy that are lower than employed in current practice.¹⁹ Surgical techniques may have also been outdated. Among the available cohort studies, few evaluated currently recommended tri-modality regimens (radiation therapy, cisplatin-based chemotherapy, and TURBT).⁶⁸

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.^{36, 39}

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 are of potential relevance 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- 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. 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. Radical cystectomy is recommended as first line therapy for muscle invasive bladder cancer in European guidelines.¹¹ Research indicates that radical cystectomy is not performed in a substantial proportion of patients with

muscle-invasive bladder cancer, indicating discordance between practice guidelines and clinical practice.¹⁵

We also 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.³¹

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 of AC was more limited than for NAC.

Limitations of the Review Process

Our review has some limitations. We were unable to perform meta-analysis, due to 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 due to 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.^{69, 70}

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 our review.^{65, 67}

We also did not have access to individual patient data, but findings of systematic reviews with access to such data reported findings similar to our review.^{65, 67}

Our review did not address all potentially important questions related to management of muscle-invasive bladder cancer, such as the comparative effectiveness and harms of different surgical techniques (e.g., robotic versus open approach), effects of timing of radical cystectomy on clinical outcomes, comparative effectiveness and harms of different followup strategies, or effectiveness of treatment strategies in patients who are upstaged or have high-risk disease (e.g., node-positive or positive surgical margins) after surgery, though evidence for each of these areas appears to be sparse.

Limitations of the Evidence Base

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.^{36, 39}

Although RCTs were available on the effects of neoadjuvant and adjuvant chemotherapy, 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. For example, estimates of harms were primarily based on older trials that did not use the antiemetics and growth factors that are often utilized in current practice.

Other limitations of the evidence base included 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 well-defined patient groups would help to clarify situations in which bladder-sparing therapy is an acceptable alternative. Addressing previous limitations of observational studies, such as failure to adequately measure and adjust for potential confounders or to analyze clearly defined inception cohorts of patients with clinically nonmetastatic disease (i.e., not exclude patients who undergo radical cystectomy and undergo pathological upstaging), would help to make them more informative. 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 life⁷¹ and harms, which have been poorly studied to date.

Randomized controlled trials that evaluate more versus less extensive regional lymph node dissection using standardized definitions and techniques are needed (e.g., based on the lymph node dissection template rather than the node yield, which can be highly variable using similar methods)⁷² and 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. Trials are also needed to evaluate the effectiveness and harms of newer, dose-dense chemotherapy regimens (to date only evaluated in noncomparative studies^{73, 74}) versus traditional dose chemotherapy regimens; one ongoing trial is designed to determine which patients are more likely to benefit from dose-dense regimens.⁷⁵ A number of ongoing trials are evaluating noncisplatin-based chemotherapy regimens⁶⁶ and trials of extended versus standard lymph node dissection are also in progress or have recently been completed.^{76, 77}

Conclusions

Neoadjuvant chemotherapy 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 define patient subgroups in which such therapies are a potential option.

References

1. Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. *CA: a Cancer Journal for Clinicians*. 2014;64(1):9-29. PMID: No PMID.
2. U.S. Cancer Statistics Working Group. United States Cancer Statistics: 1999–2009 Incidence and Mortality Web-based Report. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. Atlanta: 2013. www.cdc.gov/uscs. PMID: No PMID.
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 on October 16th, 2013. [not found in PubMed]
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. American Cancer Society. Bladder Cancer; Early Detection, Diagnosis, and Staging Topics.
6. Konety BR, Joyce GF, F. W. Bladder and upper tract urothelial cancer. Vol 07-5512. Washington, DC: US Government Printing Office; 2007. PMID: 17437776
7. Cancer Research UK. Bladder cancer stage and grade. London: Cancer Research UK; 2013.
8. American Cancer Society. How is bladder cancer staged? In: Society AC, editor; 2014. PMID: No PMID.
9. Babjuk M, Burger M, Zigeuner R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. *Eur Urol*. 2013 Oct;64(4):639-53. PMID: 23827737.
10. 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.
11. Stenzl A, Witjes JA, Compérat E. Guidelines on Bladder Cancer Muscle-invasive and Metastatic. EAU. 2012. PMID: No PMID.
12. 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.
13. 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.
14. 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.
15. 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.
16. Herr HW. Transurethral resection of muscle-invasive bladder cancer: 10-year outcome. *J Clin Oncol*. 2001 Jan 1;19(1):89-93. PMID: 11134199.
17. Agency for Healthcare Research and Quality. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. 2014. PMID: No PMID.
18. U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Procedure Manual [Web Page]. 2008. www.uspreventiveservicestaskforce.org/uspstf08/methods/procmanual.htm. Accessed on April 4th, 2014.
19. 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.

20. Bekelman JE, Handorf EA, Guzzo T, et al. Radical cystectomy versus bladder-preserving therapy for muscle-invasive urothelial carcinoma: examining confounding and misclassification bias in cancer observational comparative effectiveness research. *Value Health*. 2013 Jun;16(4):610-8. PMID: 23796296.
21. Goossens-Laan CA, Leliveld AM, Verhoeven RHA, et al. Effects of age and comorbidity on treatment and survival of patients with muscle-invasive bladder cancer. *Int J Cancer*. 2014 Aug 15;135(4):905-12. PMID: 24420527.
22. 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.
23. Kalogeras D, Lampri E, Goussia A, et al. Radical therapy for muscle-infiltrating bladder cancer (cystectomy or radiotherapy): does age affect the final therapeutic benefit for the patient? *Journal of B.U.ON*. 2008 Jul-Sep;13(3):353-8. PMID: 18979549.
24. Kotwal S, Choudhury A, Johnston C, et al. Similar treatment outcomes for radical cystectomy and radical radiotherapy in invasive bladder cancer treated at a United Kingdom specialist treatment center. *Int J Rad Oncol Biol, Phys*. 2008 Feb 1;70(2):456-63. PMID: 17904301.
25. Nieuwenhuijzen JA, Pos F, Moonen LMF, et al. Survival after bladder-preservation with brachytherapy versus radical cystectomy; a single institution experience. *Eur Urol*. 2005 Aug;48(2):239-45. PMID: 16005375.
26. Rincon Mayans A, Rosell Costa D, Zudaire Bergera JJ, et al. Response and progression-free survival in T2 to T4 bladder tumors treated with trimodality therapy with bladder preservation. *Actas Urol Esp*. 2010 Oct;34(9):775-80. PMID: 20843454.
27. Solsona E, Climent MA, Iborra I, et al. Bladder preservation in selected patients with muscle-invasive bladder cancer by complete transurethral resection of the bladder plus systemic chemotherapy: long-term follow-up of a phase 2 nonrandomized comparative trial with radical cystectomy. *Eur Urol*. 2009 Apr;55(4):911-9. PMID: 18722046.
28. James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med*. 2012 Apr 19;366(16):1477-88. PMID: 22512481.
29. Abdollah F, Sun M, Schmitges J, et al. Stage-specific impact of pelvic lymph node dissection on survival in patients with non-metastatic bladder cancer treated with radical cystectomy. *BJU International*. 2012 Apr;109(8):1147-54. PMID: 21883849.
30. Herr HW, Bochner BH, Dalbagni G, et al. Impact of the number of lymph nodes retrieved on outcome in patients with muscle invasive bladder cancer. *J Urol*. 2002 Mar;167(3):1295-8. PMID: 11832716.
31. 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.
32. Shirotake S, Kikuchi E, Matsumoto K, et al. Role of pelvic lymph node dissection in lymph node-negative patients with invasive bladder cancer. *Jpn J Clin Oncol*. 2010 Mar;40(3):247-51. PMID: 19887521.
33. Herr HW, Faulkner JR, Grossman HB, et al. Surgical factors influence bladder cancer outcomes: a cooperative group report. *J Clin Oncol*. 2004 Jul 15;22(14):2781-9. PMID: 15199091.
34. Brossner C, Pycha A, Toth A, et al. Does extended lymphadenectomy increase the morbidity of radical cystectomy? *BJU International*. 2004 Jan;93(1):64-6. PMID: 14678370.

35. Brunocilla E, Perneti R, Schiavina R, et al. The number of nodes removed as well as the template of the dissection is independently correlated to cancer-specific survival after radical cystectomy for muscle-invasive bladder cancer. *Int Urol Nephrol*. 2013 Jun;45(3):711-9. PMID: 23666588.
36. 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.
37. Leissner J, Hohenfellner R, Thuroff JW, et al. Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder; significance for staging and prognosis. *BJU International*. 2000 May;85(7):817-23. PMID: 10792159.
38. Poulsen AL, Horn T, Steven K. Radical cystectomy: extending the limits of pelvic lymph node dissection improves survival for patients with bladder cancer confined to the bladder wall. *J Urol*. 1998 Dec;160(6 Pt 1):2015-9; discussion 20. PMID: 9817313.
39. 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.
40. Simone G, Papalia R, Ferriero M, et al. Stage-specific impact of extended versus standard pelvic lymph node dissection in radical cystectomy. *Int J Urol*. 2013 Apr;20(4):390-7. PMID: 22970939.
41. 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.
42. 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.
43. International Collaboration of Trialists, Medical Research Council Advanced Bladder Cancer Working P, European Organisation for R, et al. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. *J Clin Oncol*. 2011 Jun 1;29(16):2171-7. PMID: 21502557.
44. 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.
45. Malmstrom PU, Rintala E, Wahlqvist R, et al. Five-year followup of a prospective trial of radical cystectomy and neoadjuvant chemotherapy: Nordic Cystectomy Trial I. The Nordic Cooperative Bladder Cancer Study Group. *J Urol*. 1996 Jun;155(6):1903-6. PMID: 8618283.
46. 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.
47. Sengelov L, von der Maase H, Lundbeck F, et al. Neoadjuvant chemotherapy with cisplatin and methotrexate in patients with muscle-invasive bladder tumours. *Acta Oncologica*. 2002;41(5):447-56. PMID: 12442921.
48. 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.
49. Freiha F, Reese J, Torti FM. A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. *J Urol*. 1996 Feb;155(2):495-9; discussion 9-500. PMID: 8558644.

50. Cognetti F, Ruggeri EM, Felici A, et al. Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial. *Ann Oncol.* 2012 Mar;23(3):695-700. PMID: 21859900.
51. Skinner DG, Daniels JR, Russell CA, et al. The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. *J Urol.* 1991 Mar;145(3):459-64; discussion 64-7. PMID: 1997689.
52. Bono AV, Benvenuti C, Gibba A, et al. Adjuvant chemotherapy in locally advanced bladder cancer. Final analysis of a controlled multicentre study. *Acta Urologica Italica.* 1997;11(1):5-8. PMID: No PMID.
53. 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.
54. 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.
55. 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.
56. 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.
57. 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.
58. Matsubara N, Mukai H, Naito Y, et al. Comparison between neoadjuvant and adjuvant gemcitabine plus cisplatin chemotherapy for muscle-invasive bladder cancer. *Asia Pac J Clin Oncol.* 2013 Dec;9(4):310-7. PMID: 23127231.
59. Dash A, Pettus JAt, Herr HW, et al. A role for neoadjuvant gemcitabine plus cisplatin in muscle-invasive urothelial carcinoma of the bladder: a retrospective experience. *Cancer.* 2008 Nov 1;113(9):2471-7. PMID: 18823036.
60. Pabla N, Z D. Cisplatin nephrotoxicity: Mechanisms and renoprotective strategies. *Kidney Int.* 2008;73:994-1007. PMID: No PMID.
61. 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.
62. 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 Jul 26 PMID: 25074764.
63. Mandel P, Tilki D, Eslick GD. Extent of lymph node dissection and recurrence-free survival after radical cystectomy: A meta-analysis. *Urol Oncol.* 2014 Jul 11 PMID: 25027683.
64. 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.
65. Advanced Bladder Cancer Overview Collaboration. Neo-adjuvant chemotherapy for invasive bladder cancer. *Cochrane Database of Syst Rev.* 2004: CD006018 PMID: 15846746.

66. 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.
67. Vale CL. Adjuvant chemotherapy for invasive bladder cancer (individual patient data). *Cochrane Database of Systematic Reviews*. 2006(2):CD006018. PMID: 16625650.
68. 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.
69. 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.
70. 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.
71. 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.
72. Kim SP, Karnes RJ. Standard or Extended Lymphadenectomy in Radical Cystectomy: What Metric of Surgical Quality for Lymph Node Dissections Matters in Improving Patient Outcomes? *Eur Urol*. 2011;60(5):953-4. PMID: No PMID.
73. Plimack ER, Hoffman-Censits JH, Viterbo R, et al. Accelerated methotrexate, vinblastine, doxorubicin, and cisplatin is safe, effective, and efficient neoadjuvant treatment for muscle-invasive bladder cancer: results of a multicenter phase II study with molecular correlates of response and toxicity. *J Clin Oncol*. 2014 Jun 20;32(18):1895-901. PMID: 24821881.
74. Choueiri TK, Jacobus S, Bellmunt J, et al. Neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with pegfilgrastim support in muscle-invasive urothelial cancer: pathologic, radiologic, and biomarker correlates. *J Clin Oncol*. 2014 Jun 20;32(18):1889-94. PMID: 24821883.
75. Southwest Oncology Group T. S1314, Co-expression Extrapolation (COXEN) Program to Predict Chemotherapy Response in Patients with Bladder Cancer. 2014. PMID: No PMID.
76. Southwest Oncology Group T. 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 Cystectomy for Muscle Invasive Urothelial Cancer. <https://clinicaltrials.gov/show/NCT01224665> on April 22nd, 2015
77. Tilki D, Brausi M, Colombo R, et al. Lymphadenectomy for bladder cancer at the time of radical cystectomy. *Eur Urol*. 2013 Aug;64(2):266-76. PMID: 23648149.

Abbreviations

Abbreviation	Term
AC	Adjuvant chemotherapy
AHRQ	Agency for Healthcare Research and Quality
CER	Comparative Effectiveness Review
CMV	Cisplatin, methotrexate, and vinblastine
EPC	Evidence-based Practice Center
MVAC	Methotrexate, vinblastine, doxorubicin, and cisplatin
NAC	Neoadjuvant chemotherapy
PICOTS	Populations, interventions, comparators, outcomes, timing, and study designs
RCT	Randomized controlled trial
SOE	Strength of evidence
SRC	Scientific Resource Center
TEP	Technical Expert Panel
TURBT	Transurethral resection of bladder tumor
WHO	World Health Organization

Appendix A. Primary Search Strategies (Ovid MEDLINE)

1. exp Urinary Bladder Neoplasms/
2. (((non or "not") adj (invas\$ or invad\$ or infiltrat\$)) or noninvas\$ or noninvad\$ or noninfiltrat\$) adj5 muscle\$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3. (cis or Tis or ta or t1\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4. 2 or 3
5. ((sign or signs or symptom\$ or possib\$ or suspect\$ or potential\$) adj5 (bladder\$ adj3 (cancer\$ or tumor\$ or tumour\$ or neoplas\$ or carcino\$ or malig\$ or adenocarcin\$))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
6. 4 or 5
7. 1 and 6
8. exp Biological Markers/
9. 7 and 8
10. ((urin\$ adj3 biomark\$) or bladder tumor associated antigen\$ or nuclear matrix protein or nmp22 or fluorescence in situ hybrid\$ or (fish adj assay\$) or fibroblast growth factor receptor 3 or fgfr3 or cxbladder or immunocyt or cytokeratin fragment\$ or cyfra 21-1 or (cytokerat\$ adj3 (tpa or tps)) or survivin or telomeras\$ or vascular endothelial growth factor\$ or vegf or metalloproteinase\$ or mmp-2 or mmp-9 or twist homolog\$ or twist1 or nidogen-2 or nid2).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
11. 7 and 10
12. ((assess\$ or analyz\$ or judg\$ or consider\$ or quantif\$ or predict\$ or identif\$ or adapt\$) adj7 risk\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
13. exp Surgical Procedures, Operative/
14. exp Drug Therapy/
15. exp Antineoplastic Agents/
16. exp Radiotherapy/
17. (th or su or rt or dh or dt).fs.
18. 13 or 14 or 15 or 16 or 17
19. 12 and 18
20. 7 and 19
21. (mitomycin\$ or apaziquone or paclitaxel or gemcitabine or thiotepa or valrubicin or doxorubicin or bacillus calmette guerin or bcg or interferon\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word,

- protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
22. 7 and 21
 23. (electromotiv\$ or emda).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
 24. 1 and 23
 25. (blue adj5 cystoscop\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
 26. 1 and 25
 27. exp Radiotherapy/
 28. rt.fs.
 29. 27 or 28
 30. 7 and 29
 31. 9 or 11 or 20 or 22 or 24 or 26 or 30
 32. exp Urinary Bladder Neoplasms/
 33. ((invas\$ or invad\$ or infiltrat\$) adj5 muscul\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
 34. (t2\$ or t3\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
 35. 33 or 34
 36. 32 and 35
 37. cystectom\$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
 38. ((excis\$ or remov\$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 bladder\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
 39. 37 or 38
 40. (bladder\$ adj5 (spare or sparing or spares or spared or preserv\$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
 41. (avoid\$ adj7 cystectom\$).mp.
 42. 40 or 41
 43. exp Lymph Node Excision/
 44. ((excis\$ or remov\$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 (lymph\$ or node or nodes)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
 45. 43 or 44

46. (adjuvant\$ or neoadjuvant\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
47. (abraxane or carboplatin\$ or cisplatin\$ or docetaxel or doxorubicin or epirubicin or 5-fluorouracil or gemcitabine or methotrexate or mitomycin or paclitaxel or valrubicin or vinblastin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
48. 46 or 47
49. 39 or 42 or 45 or 48
50. 36 and 49
51. 31 or 50
52. limit 51 to yr="1990 -Current"
53. limit 52 to english language
54. limit 52 to abstracts
55. 53 or 54

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

1. ((Urinar\$ or urothel\$) adj5 (bladder\$ adj3 (neoplas\$ or cancer\$ or tumor\$ or tumour\$ or carcino\$ or adenocarcin\$ or malig\$))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
2. (((non or "not") adj (invas\$ or invad\$ or infiltrat\$)) or noninvas\$ or noninvad\$ or noninfiltrat\$) adj5 muscle\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3. (cis or Tis or ta or t1\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4. 2 or 3
5. ((sign or signs or symptom\$ or possib\$ or suspect\$ or potential\$) adj5 (bladder\$ adj3 (cancer\$ or tumor\$ or tumour\$ or neoplas\$ or carcino\$ or malig\$ or adenocarcin\$))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
6. 4 or 5
7. 1 and 6
8. ((urin\$ adj3 biomark\$) or bladder tumor associated antigen\$ or nuclear matrix protein or nmp22 or fluorescence in situ hybrid\$ or (fish adj assay\$) or fibroblast growth factor receptor 3 or fgfr3 or exbladder or immunocyt or cytokeratin fragment\$ or cyfra 21-1 or (cytokerat\$ adj3 (tpa or tps)) or survivin or telomeras\$ or vascular endothelial growth factor\$ or vegf or metalloproteinase\$ or mmp-2 or mmp-9 or twist homolog\$ or twist1 or nidogen-2 or nid2).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
9. 7 and 8
10. ((assess\$ or analyz\$ or judg\$ or consider\$ or quantif\$ or predict\$ or identif\$ or adapt\$) adj7 risk\$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
11. (surger\$ or surgic\$ or surgeon\$ or cystectom\$ or excis\$ or (remov\$ adj3 bladder\$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

12. ((drug\$ adj3 (therap\$ or treat\$ or regimen\$ or protocol\$)) or pharmacother\$ or chemother\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
13. Antineoplastic\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
14. (Radiother\$ or ((radio\$ or irradiat\$ or radiat\$ or x-ray or gamma) adj3 (treat\$ or therap\$ or protocol\$))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
15. 11 or 12 or 13 or 14
16. 10 and 15
17. 7 and 16
18. (mitomycin\$ or apaziquone or paclitaxel or gemcitabine or thiotepa or valrubicin or doxorubicin or bacillus calmette guerin or bcg or interferon\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
19. 7 and 18
20. (electromotiv\$ or emda).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
21. 1 and 20
22. (blue adj5 cystoscop\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
23. 1 and 22
24. 9 or 17 or 19 or 21 or 23
25. ((Urinar\$ or urothel\$) adj5 (bladder\$ adj3 (neoplas\$ or cancer\$ or tumor\$ or tumour\$ or carcino\$ or adenocarcin\$ or malig\$))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
26. ((invas\$ or invad\$ or infiltrat\$) adj5 muscl\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
27. (t2\$ or t3\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
28. 26 or 27
29. 25 and 28
30. cystectom\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
31. ((excis\$ or remov\$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 bladder\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
32. 30 or 31
33. (bladder\$ adj5 (spare or sparing or spares or spared or preserv\$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
34. (avoid\$ adj7 cystectom\$.mp.
35. 33 or 34
36. ((excis\$ or remov\$ or biops\$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 (lymph\$ or node or nodes)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
37. (adjuvant\$ or neoadjuvant\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

38. (abraxane or carboplatin\$ or cisplatin\$ or docetaxel or doxorubicin or epirubicin or 5-fluorouracil or gemcitabine or methotrexate or mitomycin or paclitaxel or valrubicin or vinblastin).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
39. 37 or 38
40. 32 or 35 or 36 or 39
41. 29 and 40
42. 24 or 41
43. limit 42 to yr="1990 -Current"

Database: EBM Reviews – Cochrane Database of Systematic Reviews

1. ((Urinar\$ or urothel\$) adj5 (bladder\$ adj3 (neoplas\$ or cancer\$ or tumor\$ or tumour\$ or carcino\$ or adenocarcin\$ or malig\$))).mp. [mp=title, abstract, full text, keywords, caption text]

Database: EBM Reviews – Database of Abstracts of Reviews of Effects

1. ((Urinar\$ or urothel\$) adj5 (bladder\$ adj3 (neoplas\$ or cancer\$ or tumor\$ or tumour\$ or carcino\$ or adenocarcin\$ or malig\$))).mp. [mp=title, full text, keywords]
2. (((non or "not") adj (invas\$ or invad\$ or infiltrat\$)) or noninvas\$ or noninvad\$ or noninfiltrat\$) adj5 muscle\$).mp. [mp=title, full text, keywords]
3. (cis or Tis or ta or t1\$).mp. [mp=title, full text, keywords]
4. 2 or 3
5. ((sign or signs or symptom\$ or possib\$ or suspect\$ or potential\$) adj5 (bladder\$ adj3 (cancer\$ or tumor\$ or tumour\$ or neoplas\$ or carcino\$ or malig\$ or adenocarcin\$))).mp. [mp=title, full text, keywords]
6. 4 or 5
7. 1 and 6
8. ((urin\$ adj3 biomark\$) or bladder tumor associated antigen\$ or nuclear matrix protein or nmp22 or fluorescence in situ hybrid\$ or (fish adj assay\$) or fibroblast growth factor receptor 3 or fgfr3 or cxbladder or immunocyt or cytokeratin fragment\$ or cyfra 21-1 or (cytokerat\$ adj3 (tpa or tps)) or survivin or telomeras\$ or vascular endothelial growth factor\$ or vegf or metalloprotein\$ or mmp-2 or mmp-9 or twist homolog\$ or twist1 or nidogen-2 or nid2).mp. [mp=title, full text, keywords]
9. 7 and 8
10. ((assess\$ or analyz\$ or judg\$ or consider\$ or quantif\$ or predict\$ or identif\$ or adapt\$) adj7 risk\$).mp. [mp=title, full text, keywords]
11. (surger\$ or surgic\$ or surgeon\$ or cystectom\$ or excis\$ or (remov\$ adj3 bladder\$)).mp. [mp=title, full text, keywords]
12. ((drug\$ adj3 (therap\$ or treat\$ or regimen\$ or protocol\$)) or pharmacother\$ or chemother\$).mp. [mp=title, full text, keywords]
13. Antineoplastic\$.mp. [mp=title, full text, keywords]
14. (Radiother\$ or ((radio\$ or irradiat\$ or radiat\$ or x-ray or gamma) adj3 (treat\$ or therap\$ or protocol\$))).mp. [mp=title, full text, keywords]

15. 11 or 12 or 13 or 14
16. 10 and 15
17. 7 and 16
18. (mitomycin\$ or apaziquone or paclitaxel or gemcitabine or thiotepa or valrubicin or doxorubicin or bacillus calmette guerin or bcg or interferon\$).mp. [mp=title, full text, keywords]
19. 7 and 18
20. (electromotiv\$ or emda).mp. [mp=title, full text, keywords]
21. 1 and 20
22. (blue adj5 cystoscop\$).mp. [mp=title, full text, keywords]
23. 1 and 22
24. 9 or 17 or 19 or 21 or 23
25. ((Urinar\$ or urothel\$) adj5 (bladder\$ adj3 (neoplas\$ or cancer\$ or tumor\$ or tumour\$ or carcino\$ or adenocarcin\$ or malig\$))).mp. [mp=title, full text, keywords]
26. ((invas\$ or invad\$ or infiltrat\$) adj5 muscul\$).mp. [mp=title, full text, keywords]
27. (t2\$ or t3\$).mp. [mp=title, full text, keywords]
28. 26 or 27
29. 25 and 28
30. cystectom\$.mp. [mp=title, full text, keywords]
31. ((excis\$ or remov\$ or ((cut or cutting or cuts) adj3 (out or away)))) adj5 bladder\$).mp. [mp=title, full text, keywords]
32. 30 or 31
33. (bladder\$ adj5 (spare or sparing or spares or spared or preserv\$)).mp. [mp=title, full text, keywords]
34. (avoid\$ adj7 cystectom\$).mp.
35. 33 or 34
36. ((excis\$ or remov\$ or biops\$ or ((cut or cutting or cuts) adj3 (out or away)))) adj5 (lymph\$ or node or nodes)).mp. [mp=title, full text, keywords]
37. (adjuvant\$ or neoadjuvant\$).mp. [mp=title, full text, keywords]
38. (abraxane or carboplatin\$ or cisplatin\$ or docetaxel or doxorubicin or epirubicin or 5-fluorouracil or gemcitabine or methotrexate or mitomycin or paclitaxel or valrubicin or vinblastin).mp. [mp=title, full text, keywords]
39. 37 or 38
40. 32 or 35 or 36 or 39
41. 29 and 40
42. 24 or 41

Database: EBM Reviews – Health Technology Assessment

1. ((Urinar\$ or urothel\$) adj5 (bladder\$ adj3 (neoplas\$ or cancer\$ or tumor\$ or tumour\$ or carcino\$ or adenocarcin\$ or malig\$))).mp. [mp=title, text, subject heading word]

Database: EBM Reviews – NHS Economic Evaluation Database

1. ((Urinar\$ or urothel\$) adj5 (bladder\$ adj3 (neoplas\$ or cancer\$ or tumor\$ or tumour\$ or carcino\$ or adenocarcin\$ or malig\$))).mp. [mp=title, text, subject heading word]

2. (((non or "not") adj (invas\$ or invad\$ or infiltrat\$)) or noninvas\$ or noninvad\$ or noninfiltrat\$) adj5 muscle\$.mp. [mp=title, text, subject heading word]
3. (cis or Tis or ta or t1\$).mp. [mp=title, text, subject heading word]
4. 2 or 3
5. ((sign or signs or symptom\$ or possib\$ or suspect\$ or potential\$) adj5 (bladder\$ adj3 (cancer\$ or tumor\$ or tumour\$ or neoplas\$ or carcino\$ or malig\$ or adenocarcin\$))).mp. [mp=title, text, subject heading word]
6. 4 or 5
7. 1 and 6
8. ((urin\$ adj3 biomark\$) or bladder tumor associated antigen\$ or nuclear matrix protein or nmp22 or fluorescence in situ hybrid\$ or (fish adj assay\$) or fibroblast growth factor receptor 3 or fgfr3 or cxbladder or immunocyt or cytokeratin fragment\$ or cyfra 21-1 or (cytokerat\$ adj3 (tpa or tps)) or survivin or telomeras\$ or vascular endothelial growth factor\$ or vegf or metalloproteinase\$ or mmp-2 or mmp-9 or twist homolog\$ or twist1 or nidogen-2 or nid2).mp. [mp=title, text, subject heading word]
9. 7 and 8
10. ((assess\$ or analyz\$ or judg\$ or consider\$ or quantif\$ or predict\$ or identif\$ or adapt\$) adj7 risk\$).mp. [mp=title, text, subject heading word]
11. (surger\$ or surgic\$ or surgeon\$ or cystectom\$ or excis\$ or (remov\$ adj3 bladder\$)).mp. [mp=title, text, subject heading word]
12. ((drug\$ adj3 (therap\$ or treat\$ or regimen\$ or protocol\$)) or pharmacother\$ or chemother\$).mp. [mp=title, text, subject heading word]
13. Antineoplastic\$.mp. [mp=title, text, subject heading word]
14. (Radiother\$ or ((radio\$ or irradiat\$ or radiat\$ or x-ray or gamma) adj3 (treat\$ or therap\$ or protocol\$))).mp. [mp=title, text, subject heading word]
15. 11 or 12 or 13 or 14
16. 10 and 15
17. 7 and 16
18. (mitomycin\$ or apaziquone or paclitaxel or gemcitabine or thiotepa or valrubicin or doxorubicin or bacillus calmette guerin or bcg or interferon\$).mp. [mp=title, text, subject heading word]
19. 7 and 18
20. (electromotiv\$ or emda).mp. [mp=title, text, subject heading word]
21. 1 and 20 (0)
22. (blue adj5 cystoscop\$).mp. [mp=title, text, subject heading word]
23. 1 and 22
24. 9 or 17 or 19 or 21 or 23
25. ((Urinar\$ or urothel\$) adj5 (bladder\$ adj3 (neoplas\$ or cancer\$ or tumor\$ or tumour\$ or carcino\$ or adenocarcin\$ or malig\$))).mp. [mp=title, text, subject heading word]
26. ((invas\$ or invad\$ or infiltrat\$) adj5 muscul\$).mp. [mp=title, text, subject heading word]
27. (t2\$ or t3\$).mp. [mp=title, text, subject heading word]
28. 26 or 27
29. 25 and 28
30. cystectom\$.mp. [mp=title, text, subject heading word]
31. ((excis\$ or remov\$ or ((cut or cutting or cuts) adj3 (out or away)))) adj5 bladder\$.mp. [mp=title, text, subject heading word]

32. 30 or 31
33. (bladder\$ adj5 (spare or sparing or spares or spared or preserv\$)).mp. [mp=title, text, subject heading word]
34. (avoid\$ adj7 cystectom\$).mp.
35. 33 or 34
36. ((excis\$ or remov\$ or biops\$ or ((cut or cutting or cuts) adj3 (out or away))) adj5 (lymph\$ or node or nodes)).mp. [mp=title, text, subject heading word]
37. (adjuvant\$ or neoadjuvant\$).mp. [mp=title, text, subject heading word]
38. (abraxane or carboplatin\$ or cisplatin\$ or docetaxel or doxorubicin or epirubicin or 5-fluorouracil or gemcitabine or methotrexate or mitomycin or paclitaxel or valrubicin or vinblastin).mp. [mp=title, text, subject heading word]
39. 37 or 38
40. 32 or 35 or 36 or 39
41. 29 and 40
42. 24 or 41

Appendix B. PICOTS

Table B1. PICOTS

PICOTS	Include
Populations	<ul style="list-style-type: none"> Patients with node-negative, non-metastatic muscle-invasive bladder cancer (stages T2, T3, T4a)
Interventions	<ul style="list-style-type: none"> Bladder-preserving chemotherapy and/or radiation therapy [KQ 1, KQ 4] Partial cystectomy [KQ 1; KQ 4] Maximal TURBT [KQ 1; KQ 4] Regional lymph node excision in conjunction with cystectomy or partial cystectomy [KQ 2] Cystectomy plus Neoadjuvant and/or adjuvant chemotherapy [KQ 3; KQ 4] Include: Chemotherapy Regimens: carboplatin and gemcitabine; cisplatin and gemcitabine; “CMV” (cisplatin, methotrexate, and vinblastine) and “MVAC” (methotrexate, vinblastine, doxorubicin, and cisplatin); trials of other cisplatin-based combination regimens. Exclude: Trials that evaluate chemotherapy with a single agent.
Comparators	<ul style="list-style-type: none"> Cystectomy alone [KQ 1; KQ 3; KQ 4] Cystectomy in combination with chemotherapy [KQ 1; KQ 4] Bladder-preserving chemotherapy, radiation therapy (external beam or interstitial radiation therapy), partial cystectomy, and/or maximal transurethral resection of bladder tumor [KQ 2]
Outcomes	<ul style="list-style-type: none"> Mortality, disease-specific and all-cause (primary outcome) [KQ 1; KQ 2; KQ 3] Recurrence of bladder cancer [KQ 1; KQ 2; KQ 3] Progression or metastasis of bladder cancer [KQ 1; KQ 2; KQ 3] Quality of life [KQ 1; KQ 2; KQ 3] Functional status [KQ 1; KQ 2; KQ 3] Complications or adverse effects related to treatment [KQ 4]
Timing	<ul style="list-style-type: none"> Any duration of followup
Setting	<ul style="list-style-type: none"> Any settings
Study Design	<ul style="list-style-type: none"> RCTs, cohort studies must be comparative Systematic reviews must evaluate quality of individual studies

CMV, cisplatin, methotrexate, and vinblastine; KQ=key question; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; PICOTS=populations, interventions, comparators, outcomes, timing, setting; RCTs, randomized controlled trials; T2, tumor stage 2; T3, tumor stage 3; T4a, tumor stage 4a; TURBT, transurethral resection of bladder tumor.

Appendix C. Included Studies

Abdollah F, Sun M, Schmitges J, et al. Stage-specific impact of pelvic lymph node dissection on survival in patients with non-metastatic bladder cancer treated with radical cystectomy. *BJU Int.* 2012;109(8):1147-54. PMID: 21883849.

Bekelman JE, Handorf EA, Guzzo T, et al. Radical cystectomy versus bladder-preserving therapy for muscle-invasive urothelial carcinoma: examining confounding and misclassification bias in cancer observational comparative effectiveness research. *Value Health.* 2013;16(4):610-8. PMID: 23796296.

Bono AV, Benvenuti C, Gibba A, et al. Adjuvant chemotherapy in locally advanced bladder cancer. Final analysis of a controlled multicentre study. *Acta Urologica Italica.* 1997;11(1):5-8. PMID: No PMID.

Brossner C, Pycha A, Toth A, et al. Does extended lymphadenectomy increase the morbidity of radical cystectomy? *BJU Int.* 2004;93(1):64-6. PMID: 14678370.

Brunocilla E, Perneti R, Schiavina R, et al. The number of nodes removed as well as the template of the dissection is independently correlated to cancer-specific survival after radical cystectomy for muscle-invasive bladder cancer. *Int Urol Nephrol.* 2013;45(3):711-9. PMID: 23666588.

Cognetti F, Ruggeri EM, Felici A, et al. Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial. *Ann Oncol.* 2012;23(3):695-700. PMID: 21859900.

Dash A, Pettus JAt, Herr HW, et al. A role for neoadjuvant gemcitabine plus cisplatin in muscle-invasive urothelial carcinoma of the bladder: a retrospective experience. *Cancer.* 2008;113(9):2471-7. PMID: 18823036.

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

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;31(8):1737-43. PMID: 23141776.

Freiha F, Reese J, Torti FM. A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. *J Urol.* 1996;155(2):495-9; discussion 9-500. PMID: 8558644.

Goossens-Laan CA, Leliveld AM, Verhoeven RHA, et al. Effects of age and comorbidity on treatment and survival of patients with muscle-invasive bladder cancer. *Int J Cancer.* 2014;135(4):905-12. PMID: 24420527.

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;349(9):859-66. PMID: 12944571.

Herr HW, Bochner BH, Dalbagni G, et al. Impact of the number of lymph nodes retrieved on outcome in patients with muscle invasive bladder cancer. *J Urol.* 2002;167(3):1295-8. PMID: 11832716.

Herr HW, Faulkner JR, Grossman HB, et al. Surgical factors influence bladder cancer outcomes: a cooperative group report. *J Clin Oncol.* 2004;22(14):2781-9. PMID: 15199091

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;158(2):389-92. PMID: 9224309.

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;354(9178):533-40. PMID: 10470696.

International Collaboration of Trialists, Medical Research Council Advanced Bladder Cancer Working P, European Organisation for R, et al. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. *J Clin Oncol.* 2011;29(16):2171-7. PMID: 21502557.

James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med.* 2012;366(16):1477-88. PMID: 22512481

Kalogeras D, Lampri E, Goussia A, et al. Radical therapy for muscle-infiltrating bladder cancer (cystectomy or radiotherapy): does age affect the final therapeutic benefit for the patient? *Journal of BUON.* 2008;13(3):353-8. PMID: 18979549.

- 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;25(6):1192-8. PMID: 24669010.
- 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;169(3):946-50. PMID: 12576819.
- Kotwal S, Choudhury A, Johnston C, et al. Similar treatment outcomes for radical cystectomy and radical radiotherapy in invasive bladder cancer treated at a United Kingdom specialist treatment center. *Int J Radiat Oncol Biol Phys*. 2008;70(2):456-63. PMID: 17904301.
- Leissner J, Hohenfellner R, Thuroff JW, et al. Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder; significance for staging and prognosis. *BJU Int*. 2000;85(7):817-23. PMID: 10792159.
- Malmstrom PU, Rintala E, Wahlqvist R, et al. Five-year followup of a prospective trial of radical cystectomy and neoadjuvant chemotherapy: Nordic Cystectomy Trial I. The Nordic Cooperative Bladder Cancer Study Group. *J Urol*. 1996;155(6):1903-6. PMID: 8618283.
- Matsubara N, Mukai H, Naito Y, et al. Comparison between neoadjuvant and adjuvant gemcitabine plus cisplatin chemotherapy for muscle-invasive bladder cancer. *Asia Pac J Clin Oncol*. 2013;9(4):310-7. PMID: 23127231.
- 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;19(20):4005-13. PMID: 11600601.
- Nieuwenhuijzen JA, Pos F, Moonen LMF, et al. Survival after bladder-preservation with brachytherapy versus radical cystectomy; a single institution experience. *Eur Urol*. 2005;48(2):239-45. PMID: 16005375.
- 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;10(4):246-50. PMID: 22981208.
- Poulsen AL, Horn T, Steven K. Radical cystectomy: extending the limits of pelvic lymph node dissection improves survival for patients with bladder cancer confined to the bladder wall. *J Urol*. 1998;160(6 Pt 1):2015-9; discussion 20. PMID: 9817313.
- Rincon Mayans A, Rosell Costa D, Zudaire Bergera JJ, et al. Response and progression-free survival in T2 to T4 bladder tumors treated with trimodality therapy with bladder preservation. *Actas Urol Esp*. 2010;34(9):775-80. PMID: 20843454.
- 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.
- 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.
- 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.
- 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.
- Shirotake S, Kikuchi E, Matsumoto K, et al. Role of pelvic lymph node dissection in lymph node-negative patients with invasive bladder cancer. *Jpn J Clin Oncol*. 2010;40(3):247-51. PMID: 19887521.
- Simone G, Papalia R, Ferriero M, et al. Stage-specific impact of extended versus standard pelvic lymph node dissection in radical cystectomy. *Int J Urol*. 2013;20(4):390-7. PMID: 22970939.
- Skinner DG, Daniels JR, Russell CA, et al. The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. *J Urol*. 1991;145(3):459-64; discussion 64-7. PMID: 1997689.
- Solsona E, Climent MA, Iborra I, et al. Bladder preservation in selected patients with muscle-invasive bladder cancer by complete transurethral resection of the bladder plus systemic chemotherapy: long-term follow-up of a phase 2 nonrandomized comparative trial with radical cystectomy. *Eur Urol*. 2009;55(4):911-9. PMID: 18722046.
- 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;118(2):358-64. PMID: 21717438.
- 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;79(2):384-90. PMID: 22196406.

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;186(4):1261-8. PMID: 21849183.

Appendix D. Excluded Studies

Abol-Enein H. Neo-adjuvant chemotherapy in the treatment of invasive transitional bladder cancer. A controlled, prospective randomized study. *Br J Urol*. 1997;79(Suppl. 4):43. PMID: No PMID. Excluded: not a study.

Abol-Enein H, El-Baz M, Abd El-Hameed MA, et al. Lymph node involvement in patients with bladder cancer treated with radical cystectomy: a patho-anatomical study--a single center experience. *J Urol*. 2004;172(5 Pt 1):1818-21. PMID: 15540728. Excluded: wrong comparator.

Abratt RP, Barnes DR, Pontin AR, et al. Radical radiation and oral and intra-vesical misonidazole for bladder cancer. *Int J Radiat Oncol Biol Phys*. 1987;13(7):1053-5. PMID: CN-00048657 UPDATE. Excluded: too old.

Abratt RP, Craighead P, Reddi VB, et al. A prospective randomised trial of radiation with or without oral and intravesical misonidazole for bladder cancer. *Br J Cancer*. 1991;64(5):968-70. PMID: 1931628. Excluded: wrong intervention.

Advanced Bladder Cancer Meta-analysis C. Adjuvant chemotherapy for invasive bladder cancer (individual patient data). *Cochrane Database Syst Rev*. 2006(2):CD006018. PMID: 16625650. Excluded: systematic review or meta-analysis used as source document only to identify individual studies.

Advanced Bladder Cancer Meta-analysis Collaboration. Neo-adjuvant chemotherapy for invasive bladder cancer. *Cochrane Database Syst Rev*. 2004(2). PMID: 15846746. Excluded: systematic review or meta-analysis used as source document only to identify individual studies.

Advanced Bladder Cancer Meta-analysis Collaboration. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. *Eur Urol*. 2005;48(2):189-99; discussion 99-201. PMID: 15939530. Excluded: systematic review or meta-analysis used as source document only to identify individual studies.

Advanced Bladder Cancer Meta-analysis Collaboration. WITHDRAWN: Neoadjuvant cisplatin for advanced bladder cancer. *Cochrane Database Syst Rev*. 2011(6):CD001426. PMID: 21678333. Excluded: systematic review or meta-analysis used as source document only to identify individual studies.

Advanced Bladder Cancer Overview C. Neoadjuvant chemotherapy for invasive bladder cancer. *Cochrane Database Syst Rev*. 2005(2):CD005246. PMID: 15846746. Excluded: systematic review or meta-analysis used as source document only to identify individual studies.

Akin Y, Celik O, Ates M, et al. Evaluation of open and laparoscopic radical cystoprostatectomy combined with orthotopic neobladder: a single-surgeon experience. *Urol Int*. 2013;90(3):348-53. PMID: 23406677. Excluded: wrong intervention.

Albers P, Park S-I, Niegisch G, et al. Randomized phase III trial of 2nd line gemcitabine and paclitaxel chemotherapy in patients with advanced bladder cancer: short-term versus prolonged treatment [German Association of Urological Oncology (AUO) trial AB 20/99]. *Ann Oncol*. 2011;22(2):288-94. PMID: 20682548. Excluded: wrong intervention.

Ali-el-Dein B, el-Baz M, Aly AN, et al. Intravesical epirubicin versus doxorubicin for superficial bladder tumors (stages pTa and pT1): a randomized prospective study. *J Urol*. 1997;158(1):68-73; discussion -4. PMID: 9186325. Excluded: wrong intervention.

Alva AS, Tallman CT, He C, et al. Efficient delivery of radical cystectomy after neoadjuvant chemotherapy for muscle-invasive bladder cancer: a multidisciplinary approach. *Cancer*. 2012;118(1):44-53. PMID: 21598245. Excluded: wrong comparator.

Anderstrom C, Johansson S, Nilsson S, et al. A prospective randomized study of preoperative irradiation with cystectomy or cystectomy alone for invasive bladder carcinoma. *Eur Urol*. 1983;9(3):142-7. PMID: 6861819. Excluded: wrong intervention.

Angulo Cuesta J, Flores Corral N. [Systemic chemotherapy with cisplatin, methotrexate, and vinblastine, and bladder preservation in T2/T3a bladder cancer]. *Actas Urol Esp*. 1997;21(1):28-33. PMID: 9182442. Excluded: not English language, but possibly relevant.

Aota Y, Yoshida K. [Intra-arterial chemotherapy for locally advanced bladder cancer]. *Hinyokika Kiyo*. 1999;45(2):149-53. PMID: 10212791. Excluded: not English language, but possibly relevant.

Azuma H, Inamoto T, Ibuki N, et al. Utility of the novel bladder preservation therapy, BOAI-CDDP-radiation (OMC-regimen), for elderly patients with invasive bladder cancer. *Int J Oncol*. 2011;38(1):13-24. PMID: 21109921. Excluded: wrong intervention.

Azuma H, Inamoto T, Takahara K, et al. A great option for elderly patients with locally invasive bladder cancer, BOAI-CDDP-radiation (OMC regimen). *Int J Oncol*. 2013;43(4):1087-94. PMID: 23934264. Excluded: wrong intervention.

- Bajorin DF. Plenary debate of randomized phase III trial of neoadjuvant MVAC plus cystectomy versus cystectomy alone in patients with locally advanced bladder cancer. *J Clin Oncol*. 2001;19(18 Suppl):17S-20S. PMID: 11560966. Excluded: not a study.
- Bassi P. Dose Response of Bacillus Calmette-Guerin (BCG) in superficial bladder cancer: a phase III randomized trial low-dose vs standard-dose BCG regimen. *J Urol*. 1992;146:32-5. PMID: No PMID. Excluded: not a study.
- Bassi P. Neoadjuvant MVAC chemotherapy of invasive bladder cancer: results of a multicenter phase III trial. *J Urol*. 1999;161(Suppl. 4):264. PMID: No PMID. Excluded: not a study.
- Bellmunt Molins J, Ribas A, Albanell J, et al. [Preliminary results of a phase II randomized controlled trial comparing M-VAC and M-CAVI in patients with bladder cancer (T2-4 N0-1 M0)]. *Arch Esp Urol*. 1996;49(5):465-72. PMID: 8766083. Excluded: not English language, but possibly relevant.
- Berian Polo JM, Zudaire Bergera JJ, Robles Garcia JE, et al. [Infiltrating bladder carcinoma: influence of complementary treatment on local control and survival]. *Actas Urol Esp*. 1994;18 Suppl:520-6. PMID: 8073942. Excluded: not English language, but possibly relevant.
- Birkenhake S, Martus P, Kuhn R, et al. Radiotherapy alone or radiochemotherapy with platin derivatives following transurethral resection of the bladder. Organ preservation and survival after treatment of bladder cancer. *Strahlenther Onkol*. 1998;174(3):121-7. PMID: 9524620. Excluded: wrong comparator.
- Blank LECM, Koedooder K, van Os R, et al. Results of bladder-conserving treatment, consisting of brachytherapy combined with limited surgery and external beam radiotherapy, for patients with solitary T1-T3 bladder tumors less than 5 cm in diameter. *Int J Radiat Oncol Biol Phys*. 2007;69(2):454-8. PMID: 17560734. Excluded: wrong population.
- Böhm M, Vom Dorp F, Schostak M, et al. Urine cytology - Update 2013: A systematic review of recent literature. *Urinzytologie - Update 2013: Eine systematische Übersicht der neueren Literatur*. 2013;52(9):1207-24. PMID: 24026058. Excluded: not English language, but possibly relevant.
- Bongiovanni L, Pirozzi F, Guidi F, et al. Bradeion (SEPT4) as a urinary marker of transitional cell bladder cancer: a real-time polymerase chain reaction study of gene expression. *J Urol*. 2012;187(6):2223-7. PMID: 22503047. Excluded: wrong intervention.
- Brod JL, Kuhn R, Schafhauser W, et al. Radiochemotherapy in locally invasive non-metastatic carcinoma of the bladder. *Adv Exp Med Biol*. 2003;539(Pt A):143-53. PMID: 15088903. Excluded: wrong study design for Key Question.
- Caffo O, Fellin G, Graffer U, et al. Gemcitabine and radiotherapy plus cisplatin after transurethral resection as conservative treatment for infiltrating bladder cancer: Long-term cumulative results of 2 prospective single-institution studies. *Cancer*. 2011;117(6):1190-6. PMID: 20960501. Excluded: wrong comparator.
- Cam K, Yildirim A, Ozveri H, et al. The efficacy of neoadjuvant chemotherapy in invasive bladder cancer. *Int Urol Nephrol*. 2002;33(1):49-52. PMID: 12090338. Excluded: wrong study design for Key Question.
- Chahal R, Sundaram SK, Iddenden R, et al. A study of the morbidity, mortality and long-term survival following radical cystectomy and radical radiotherapy in the treatment of invasive bladder cancer in Yorkshire. *Eur Urol*. 2003;43(3):246-57. PMID: 12600427. Excluded: wrong population.
- Choi W, Porten S, Kim S, et al. Identification of distinct basal and luminal subtypes of muscle-invasive bladder cancer with different sensitivities to frontline chemotherapy. *Cancer Cell*. 2014;25(2):152-65. PMID: 24525232. Excluded: wrong study design for Key Question.
- Choueiri TK, Jacobus S, Bellmunt J, et al. Neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with pegfilgrastim support in muscle-invasive urothelial cancer: pathologic, radiologic, and biomarker correlates. *J Clin Oncol*. 2014;32(18):1889-94. PMID: 24821883. Excluded: wrong comparator.
- Chung PWM, Bristow RG, Milosevic MF, et al. Long-term outcome of radiation-based conservation therapy for invasive bladder cancer. *Urol*. 2007;25(4):303-9. PMID: 17628296. Excluded: wrong comparator.
- Clark PE, Stein JP, Groshen SG, et al. The management of urethral transitional cell carcinoma after radical cystectomy for invasive bladder cancer. *J Urol*. 2004;172(4 Pt 1):1342-7. PMID: 15371837. Excluded: wrong study design for Key Question.
- Cole CJ, Pollack A, Zagars GK, et al. Local control of muscle-invasive bladder cancer: preoperative radiotherapy and cystectomy versus cystectomy alone. *Int J Radiat Oncol Biol Phys*. 1995;32(2):331-40. PMID: 7751174. Excluded: wrong intervention.

- Coppin CM, Gospodarowicz MK, James K, et al. Improved local control of invasive bladder cancer by concurrent cisplatin and preoperative or definitive radiation. The National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol.* 1996;14(11):2901-7. PMID: 8918486. Excluded: wrong population.
- Crowell J, Fall B. Screening for bladder cancer. *Am Fam Physician.* 2012;85(4):401-2. PMID: 22335321. Excluded: not a study.
- Culp SH, Dickstein RJ, Grossman HB, et al. Refining patient selection for neoadjuvant chemotherapy before radical cystectomy. *J Urol.* 2014;191(1):40-7. PMID: 23911605. Excluded: wrong comparator.
- Damrauer JS, Hoadley KA, Chism DD, et al. Intrinsic subtypes of high-grade bladder cancer reflect the hallmarks of breast cancer biology. *Proc Natl Acad Sci U S A.* 2014;111(8):3110-5. PMID: 24520177. Excluded: wrong comparator.
- Danesi DT, Arcangeli G, Cruciani E, et al. Conservative treatment of invasive bladder carcinoma by transurethral resection, protracted intravenous infusion chemotherapy, and hyperfractionated radiotherapy: long term results. *Cancer.* 2004;101(11):2540-8. PMID: 15481058. Excluded: wrong intervention.
- Davis R, Jones JS, Barocas DA, et al. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. *J Urol.* 2012;188(6 SUPPL.):2473-81. PMID: 23098784. Excluded: not a study.
- De Castro F, Sanchez PL, Aguera LG, et al. [Infiltrating carcinoma of the bladder: preliminary results of multidisciplinary protocols with radiotherapy and neoadjuvant chemotherapy]. *Actas Urol Esp.* 1992;16(2):127-32. PMID: 1590087. Excluded: not English language, but possibly relevant.
- De Neve W, Lybeert ML, Goor C, et al. T1 and T2 carcinoma of the urinary bladder: long term results with external, preoperative, or interstitial radiotherapy. *Int J Radiat Oncol Biol Phys.* 1992;23(2):299-304. PMID: 1587750. Excluded: wrong intervention.
- De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. *J Clin Oncol.* 2012;30(2):191-9. PMID: 22162575. Excluded: wrong population.
- Donat SM, Siegrist T, Cronin A, et al. Radical cystectomy in octogenarians--does morbidity outweigh the potential survival benefits? *J Urol.* 2010;183(6):2171-7. PMID: 20399461. Excluded: wrong intervention.
- Droller MJ. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. *J Urol.* 2000;163(5):1602-3. PMID: 10798921. Excluded: not a study.
- Droller MJ. Chemoradiotherapy for muscle invading bladder carcinoma. Final report of a single institutional organ-sparing program. *J Urol.* 2002;167(5):2297-8. PMID: 11956495. Excluded: not a study.
- Dunst J, Sauer R, Schrott KM, et al. Organ-sparing treatment of advanced bladder cancer: a 10-year experience. *Int J Radiat Oncol Biol Phys.* 1994;30(2):261-6. PMID: 7928455. Excluded: wrong comparator.
- Durkan GC, Nutt JE, Marsh C, et al. Alteration in urinary matrix metalloproteinase-9 to tissue inhibitor of metalloproteinase-1 ratio predicts recurrence in nonmuscle-invasive bladder cancer. *Clin Cancer Res.* 2003;9(7):2576-82. PMID: 12855633. Excluded: wrong intervention.
- Durkan GC, Nutt JE, Rajjayabun PH, et al. Prognostic significance of matrix metalloproteinase-1 and tissue inhibitor of metalloproteinase-1 in voided urine samples from patients with transitional cell carcinoma of the bladder. *Clin Cancer Res.* 2001;7(11):3450-6. PMID: 11705862. Excluded: wrong intervention.
- Efstathiou JA, Bae K, Shipley WU, et al. Late pelvic toxicity after bladder-sparing therapy in patients with invasive bladder cancer: RTOG 89-03, 95-06, 97-06, 99-06. *J Clin Oncol.* 2009;27(25):4055-61. PMID: 19636019. Excluded: wrong comparator.
- Eijan AM, Sandes E, Puricelli L, et al. Cathepsin B levels in urine from bladder cancer patients. *Oncol Rep.* 2000;7(6):1395-9. PMID: 11032951. Excluded: wrong intervention.
- Eijsten A, Knonagel H, Hotz E, et al. Reduced bladder capacity in patients receiving intravesical chemoprophylaxis with mitomycin C. *Br J Urol.* 1990;66(4):386-8. PMID: 2121309. Excluded: wrong comparator.
- El-Monim HA, El-Baradie MM, Younis A, et al. A prospective randomized trial for postoperative vs. preoperative adjuvant radiotherapy for muscle-invasive bladder cancer. *Urol.* 2013;31(3):359-65. PMID: 21353794. Excluded: wrong comparator.
- El-Shazli S, Anwar H, Ramzy S, et al. Extended lymphadenectomy to the lower paraaortic nodes during radical cystectomy. *J Egypt Natl Canc Inst.* 2004;16(1):22-8. PMID: 15716994. Excluded: wrong outcome.

Ennis RD, Petrylak DP, Singh P, et al. The effect of cystectomy, and perioperative methotrexate, vinblastine, doxorubicin and cisplatin chemotherapy on the risk and pattern of relapse in patients with muscle invasive bladder cancer. *J Urol*. 2000;163(5):1413-8. PMID: 10751847. Excluded: wrong population.

Faba OR, Palou J, Urdaneta G, et al. Invasive bladder cancer in the eighties: transurethral resection or cystectomy? *Int Braz J Urol*. 2011;37(1):49-55;discussion - 6. PMID: 21385480. Excluded: wrong comparator.

Fahmy NM, Mahmud S, Aprikian AG. Delay in the surgical treatment of bladder cancer and survival: systematic review of the literature. *Eur Urol*. 2006;50(6):1176-82. PMID: 16846680. Excluded: wrong outcome.

Fechner G, Siener R, Reimann M, et al. Randomised phase II trial of gemcitabine and paclitaxel second-line chemotherapy in patients with transitional cell carcinoma (AUO Trial AB 20/99). *Int J Clin Pract*. 2006;60(1):27-31. PMID: 16409425. Excluded: wrong intervention.

Fedeli U, Fedewa SA, Ward EM. Treatment of muscle invasive bladder cancer: evidence from the National Cancer Database, 2003 to 2007. *J Urol*. 2011;185(1):72-8. PMID: 21074192. Excluded: wrong outcome.

Fiorito C, Gontero P. [Adverse events after intravesical therapy: are we always ready to recognize and prevent them?]. *Urologia*. 2013;80 Suppl 21:27-32. PMID: 23559132. Excluded: not English language, but possibly relevant.

Fleischmann A, Thalmann GN, Markwalder R, et al. Extracapsular extension of pelvic lymph node metastases from urothelial carcinoma of the bladder is an independent prognostic factor. *J Clin Oncol*. 2005;23(10):2358-65. PMID: 15800327. Excluded: wrong study design for Key Question.

Fossa SD, Aass N, Ous S, et al. Survival after curative treatment of muscle-invasive bladder cancer. *Acta Oncol*. 1996;35 Suppl 8:59-65. PMID: 9073049. Excluded: wrong comparator.

Froehner M, Brausi MA, Herr HW, et al. Complications following radical cystectomy for bladder cancer in the elderly. *Eur Urol*. 2009;56(3):443-54. PMID: 19481861. Excluded: not a study.

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;63(1):45-57. PMID: 22917985. Excluded: not a study.

Garcia-Baquero R, Puerta P, Beltran M, et al. Methylation of a novel panel of tumor suppressor genes in urine moves forward noninvasive diagnosis and prognosis of bladder cancer: a 2-center prospective study. *J Urol*. 2013;190(2):723-30. PMID: 23485510. Excluded: wrong intervention.

Gondo T, Yoshioka K, Nakagami Y, et al. Robotic versus open radical cystectomy: prospective comparison of perioperative and pathologic outcomes in Japan. *Jpn J Clin Oncol*. 2012;42(7):625-31. PMID: 22581913. Excluded: wrong comparator.

Gore JL, Litwin MS, Lai J, et al. Use of radical cystectomy for patients with invasive bladder cancer. *J Natl Cancer Inst*. 2010;102(11):802-11. PMID: 20400716. Excluded: wrong comparator.

Gray PJ, Fedewa SA, Shipley WU, et al. Use of potentially curative therapies for muscle-invasive bladder cancer in the United States: results from the National Cancer Data Base. *Eur Urol*. 2013;63(5):823-9. PMID: 23200811. Excluded: wrong outcome.

Gruschwitz T, Grimm MO. Studieearly recognition in urology. *Früherkennung in der urologie*. 2012;18(3):243-7. PMID: No PMID. Excluded: not English language, but possibly relevant.

Hall R. Neo-adjuvant CMV chemotherapy and cystectomy of radiotherapy in muscle invasive bladder cancer. First analysis of MRC/EORTC intercontinental trial. *Proc Ann Meet Am Soc Clin Oncol*. 1996;15:A612. PMID: No PMID. Excluded: not a study.

Haresh KP, Julka PK, Sharma DN, et al. A prospective study evaluating surgery and chemo radiation in muscle invasive bladder cancer. *J Cancer Res Ther*. 2007;3(2):81-5. PMID: 17998728. Excluded: wrong comparator.

Harland SJ. Electromotive drug delivery and bladder cancer. [Erratum appears in *Lancet Oncol*. 2006 Feb;7(2):105]. *Lancet Oncol*. 2006;7(1):6-7. PMID: 16389175. Excluded: wrong intervention.

Hashine K, Miura N, Numata K, et al. Health-related quality of life after bladder preservation therapy for muscle invasive bladder cancer. *Int J Urol*. 2008;15(5):403-6. PMID: 18384578. Excluded: wrong comparator.

Henningsohn L, Wijkstrom H, Dickman PW, et al. Distressful symptoms after radical radiotherapy for urinary bladder cancer. *Radiother Oncol*. 2002;62(2):215-25. PMID: 11937249. Excluded: wrong outcome.

Henningsohn L, Wijkstrom H, Steven K, et al. Relative importance of sources of symptom-induced distress in urinary bladder cancer survivors. *Eur Urol*. 2003;43(6):651-62. PMID: 12767367. Excluded: wrong population.

Henriksson R, Franzen L, Littbrand B. Prevention of irradiation-induced bowel discomfort by sucralfate: a double-blind, placebo-controlled study when treating localized pelvic cancer. *Am J Med.* 1991;91(2A):151S-7S. PMID: 1882903. Excluded: wrong intervention.

Henriksson R, Franzen L, Littbrand B. Effects of sucralfate on acute and late bowel discomfort following radiotherapy of pelvic cancer. *J Clin Oncol.* 1992;10(6):969-75. PMID: 1588377. Excluded: wrong intervention.

Herr HW, Dotan Z, Donat SM, et al. Defining optimal therapy for muscle invasive bladder cancer. *J Urol.* 2007;177(2):437-43. PMID: 17222605. Excluded: not a study.

Hirabayashi N. [Long-term results of short-course preoperative radiotherapy and radical cystectomy for bladder cancer]. *Nippon Hinyokika Gakkai Zasshi.* 1997;88(5):528-34. PMID: 9184445. Excluded: not English language, but possibly relevant.

Holzbeierlein JM, Lopez-Corona E, Bochner BH, et al. Partial cystectomy: a contemporary review of the Memorial Sloan-Kettering Cancer Center experience and recommendations for patient selection. *J Urol.* 2004;172(3):878-81. PMID: 15310988. Excluded: wrong comparator.

Honma I, Masumori N, Sato E, et al. Removal of more lymph nodes may provide better outcome, as well as more accurate pathologic findings, in patients with bladder cancer--analysis of role of pelvic lymph node dissection. *Urology.* 2006;68(3):543-8. PMID: 16979723. Excluded: wrong study design for Key Question.

Horstmann M. Bladder cancer: Screening in risk groups or symptom-based urological diagnosis? *Blasenkrebs: Screening in Risikogruppen oder symptombasierte urologische Diagnostik?* 2011;18(1):20-2. PMID: No PMID. Excluded: not English language, but possibly relevant.

Horwich A. Commentary 1. Radiotherapy 1999:236-8. PMID: No PMID. Excluded: not a study.

Housset M, Maulard C, Chretien Y, et al. Combined radiation and chemotherapy for invasive transitional-cell carcinoma of the bladder: a prospective study. *J Clin Oncol.* 1993;11(11):2150-7. PMID: 8229129. Excluded: wrong comparator.

Hsieh C-H, Chung S-D, Chan P-H, et al. Intensity modulated radiotherapy for elderly bladder cancer patients. *Radiat.* 2011;6:75. PMID: 21679408. Excluded: wrong comparator.

Huang GJ, Stein JP. Open radical cystectomy with lymphadenectomy remains the treatment of choice for invasive bladder cancer. *Curr Opin Urol.* 2007;17(5):369-75. PMID: 17762633. Excluded: not a study.

Huddart RA, Hall E, Hussain SA, et al. Randomized noninferiority trial of reduced high-dose volume versus standard volume radiation therapy for muscle-invasive bladder cancer: results of the BC2001 trial (CRUK/01/004). *Int J Radiat Oncol Biol Phys.* 2013;87(2):261-9. PMID: 23958147. Excluded: wrong comparator.

Huncharek M, Muscat J, Geschwind JF. Planned preoperative radiation therapy in muscle invasive bladder cancer; results of a meta-analysis. *Anticancer Res.* 1998;18(3B):1931-4. PMID: 9677446. Excluded: systematic review or meta-analysis used as source document only to identify individual studies.

Hussain M, Daignault S, Agarwal N, et al. A randomized phase 2 trial of gemcitabine/cisplatin with or without cetuximab in patients with advanced urothelial carcinoma. *Cancer.* 2014;120(17):2684-93. PMID: 24802654. Excluded: wrong population.

Institute of Applied Health S. Systematic review of the clinical and cost-effectiveness, and economic evaluation, of photodynamic diagnosis and novel urine biomarker tests in the detection and follow-up of bladder cancer (Project record). *Health Technology Assessment Database.* 2013(4). PMID: No PMID. Excluded: not a study.

Iwai A, Koga F, Fujii Y, et al. Perioperative complications of radical cystectomy after induction chemoradiotherapy in bladder-sparing protocol against muscle-invasive bladder cancer: a single institutional retrospective comparative study with primary radical cystectomy. *Jpn J Clin Oncol.* 2011;41(12):1373-9. PMID: 21994208. Excluded: wrong intervention.

Izawa JI, Chin JL, Winkquist E. Timing cystectomy and perioperative chemotherapy in the treatment of muscle invasive bladder cancer. *Can J Urol.* 2006;13 Suppl 3:48-53. PMID: 16818012. Excluded: not a study.

Jensen JB, Ulhoi BP, Jensen KM. Lymph node mapping in patients with bladder cancer undergoing radical cystectomy and lymph node dissection to the level of the inferior mesenteric artery. *BJU Int.* 2010;106(2):199-205. PMID: 20002670. Excluded: wrong outcome.

Joung JY, Han KS, Kim TS, et al. Single institutional experience of bladder-preserving trimodality treatment for muscle-invasive bladder cancer. *J Korean Med Sci.* 2008;23(4):598-603. PMID: 18756044. Excluded: wrong study design for Key Question.

Kageyama Y, Yokoyama M, Sakai Y, et al. Favorable outcome of preoperative low dose chemoradiotherapy against muscle-invasive bladder cancer. *Am J Clin Oncol.* 2003;26(5):504-7. PMID: 14528080. Excluded: wrong comparator.

Karl A, Carroll PR, Gschwend JE, et al. The impact of lymphadenectomy and lymph node metastasis on the outcomes of radical cystectomy for bladder cancer. *Eur Urol.* 2009;55(4):826-35. PMID: 19150582. Excluded: not a study.

Kaufman DS, Shipley WU, Griffin PP, et al. Selective bladder preservation by combination treatment of invasive bladder cancer. *N Engl J Med.* 1993;329(19):1377-82. PMID: 8413433. Excluded: wrong comparator.

Kawamura N, Matsushita M, Okada T, et al. [Relative efficacy of neoadjuvant gemcitabine and cisplatin versus methotrexate, vinblastine, adriamycin, and cisplatin in the management for muscle-invasive bladder cancer]. *Hinyokika Kyo.* 2013;59(5):277-81. PMID: 23719134. Excluded: not English language, but possibly relevant.

Kim PH, Cha EK, Sfakianos JP, et al. Genomic Predictors of Survival in Patients with High-grade Urothelial Carcinoma of the Bladder. *Eur Urol.* 2014. PMID: 25092538. Excluded: wrong comparator.

Kinjo M, Okegawa T, Horie S, et al. Detection of circulating MUC7-positive cells by reverse transcription-polymerase chain reaction in bladder cancer patients. *Int J Urol.* 2004;11(1):38-43. PMID: 14678183. Excluded: wrong intervention.

Kitagawa Y, Izumi K, Miwa S, et al. Retrospective analysis of the efficacy of two cycles of M-VAC neoadjuvant chemotherapy followed by radical cystectomy for muscle-invasive bladder cancer. *Anticancer Res.* 2013;33(10):4497-503. PMID: 24123021. Excluded: wrong study design for Key Question.

Koga F, Kihara K, Fujii Y, et al. Favourable outcomes of patients with clinical stage T3N0M0 bladder cancer treated with induction low-dose chemo-radiotherapy plus partial or radical cystectomy vs immediate radical cystectomy: a single-institutional retrospective comparative study. *BJU Int.* 2009;104(2):189-94. PMID: 19154452. Excluded: wrong study design for Key Question.

Kolaczyk W, Dembowski J, Lorenz J, et al. Evaluation of the influence of systemic neoadjuvant chemotherapy on the survival of patients treated for invasive bladder cancer. *BJU Int.* 2002;89(6):616-9. PMID: 11942977. Excluded: wrong study design for Key Question.

Konety BR, Joyce GF, F. W. Bladder and upper tract urothelial cancer. Vol 07-5512. Washington, DC: US Government Printing Office; 2007. PMID: 17437776. Excluded: wrong outcome.

Koppie TM, Vickers AJ, Vora K, et al. Standardization of pelvic lymphadenectomy performed at radical cystectomy: can we establish a minimum number of lymph nodes that should be removed? *Cancer.* 2006;107(10):2368-74. PMID: 17041887. Excluded: wrong study design for Key Question.

Kotb AF, Kovac E, Kassouf W, et al. Radical cystectomy for clinically muscle invasive bladder cancer: does prior non-invasive disease affect clinical outcomes? *World J Urol.* 2012;30(6):761-7. PMID: 22293934. Excluded: wrong intervention.

Kozak KR, Hamidi M, Manning M, et al. Bladder preservation for localized muscle-invasive bladder cancer: the survival impact of local utilization rates of definitive radiotherapy. *Int J Radiat Oncol Biol Phys.* 2012;83(2):e197-204. PMID: 22401916. Excluded: wrong comparator.

Krause FS, Feil G, Zumbargel A, et al. Molecular genetic methods in the diagnosis of invasive bladder cancer. *Anticancer Res.* 2000;20(6D):5015-21. PMID: 11326660. Excluded: wrong intervention.

Krogsbøll LT. Guidelines for screening with urinary dipsticks differ substantially - A systematic review. *Danish Medical Journal.* 2014;61(2). PMID: 24495888. Excluded: wrong population.

Kuten A, Baz M, Rubinov R, et al. Treatment of muscle invasive bladder cancer. Is there a role for neoadjuvant chemotherapy? *Strahlenther Onkol.* 1994;170(9):524-30. PMID: 7524174. Excluded: wrong study design for Key Question.

Larré S, Catto JWF, Cookson MS, et al. Screening for bladder cancer: Rationale, limitations, whom to target, and perspectives. *Eur Urol.* 2013;63(6):1049-58. PMID: 23313034. Excluded: wrong population.

Lee CT, Dunn RL, Ingold C, et al. Early-stage bladder cancer surveillance does not improve survival if high-risk patients are permitted to progress to muscle invasion. *Urology.* 2007;69(6):1068-72. PMID: 17572188. Excluded: wrong comparator.

Lehmann J, Retz M, Wiemers C, et al. Adjuvant cisplatin plus methotrexate versus methotrexate, vinblastine, epirubicin, and cisplatin in locally advanced bladder cancer: results of a randomized, multicenter, phase III trial (AUO-AB 05/95). *J Clin Oncol.* 2005;23(22):4963-74. PMID: 15939920. Excluded: wrong comparator.

Leibovici D, Kassouf W, Pisters LL, et al. Organ preservation for muscle-invasive bladder cancer by transurethral resection. *Urology.* 2007;70(3):473-6. PMID: 17905099. Excluded: sample size too small.

Leissner J, Ghoneim MA, Abol-Enein H, et al. Extended radical lymphadenectomy in patients with urothelial bladder cancer: results of a prospective multicenter study. *J Urol.* 2004;171(1):139-44. PMID: 14665862. Excluded: wrong outcome.

- Leliveld AM, Doornweerd BJJ, Bastiaannet E, et al. Treatment and outcome in muscle invasive bladder cancer: a population-based survey. *World J Urol.* 2010;28(4):439-44. PMID: 20383640. Excluded: wrong comparator.
- Lerner SP, Skinner DG, Lieskovsky G, et al. The rationale for en bloc pelvic lymph node dissection for bladder cancer patients with nodal metastases: long-term results. *J Urol.* 1993;149(4):758-64; discussion 64-5. PMID: 8455238. Excluded: wrong population.
- Li Y-J, Zheng B-Z, Zhou Z-L. [Association of uPA and uPAR expression with invasive behaviors of urinary transitional cell carcinoma]. *Ai Zheng.* 2004;23(6):704-6. PMID: 15191676. Excluded: not English language, but possibly relevant.
- Liedberg F, Anderson H, Mansson W. Treatment delay and prognosis in invasive bladder cancer. *J Urol.* 2005;174(5):1777-81; discussion 81. PMID: 16217282. Excluded: wrong comparator.
- Liew MS, Azad A, Tafreshi A, et al. USANZ: Time-trends in use and impact on outcomes of perioperative chemotherapy in patients treated with radical cystectomy for urothelial bladder cancer. *BJU Int.* 2013;112 Suppl 2:74-82. PMID: 24127680. Excluded: sample size too small.
- Lin C-C, Hsu C-H, Cheng JC, et al. Induction cisplatin and fluorouracil-based chemotherapy followed by concurrent chemoradiation for muscle-invasive bladder cancer. *Int J Radiat Oncol Biol Phys.* 2009;75(2):442-8. PMID: 19307067. Excluded: wrong comparator.
- Lin YL, Sun G, Liu XQ, et al. Clinical significance of CDH13 promoter methylation in serum samples from patients with bladder transitional cell carcinoma. *J Int Med Res.* 2011;39(1):179-86. PMID: 21672320. Excluded: wrong intervention.
- Lin Y-L, Liu X-Q, Li W-P, et al. Promoter methylation of H-cadherin is a potential biomarker in patients with bladder transitional cell carcinoma. *Int Urol Nephrol.* 2012;44(1):111-7. PMID: 21516472. Excluded: wrong intervention.
- Loo RK, Lieberman SF, Slezak JM, et al. Stratifying risk of urinary tract malignant tumors in patients with asymptomatic microscopic hematuria. *Mayo Clin Proc.* 2013;88(2):129-38. PMID: 23312369. Excluded: wrong population.
- Lorusso V. A phase II randomized trial of paclitaxel, gemcitabine and cisplatin versus gemcitabine - cisplatin in advanced transitional cell carcinoma of the urinary tract (TCC). A cooperative study of the IBCG (Italian Bladder Cancer Group). *Genito-urinary tumours.* 2002;93-4. PMID: No PMID. Excluded: not a study.
- Mameghan H, Fisher RJ, Watt WH, et al. The management of invasive transitional cell carcinoma of the bladder. Results of definitive and preoperative radiation therapy in 390 patients treated at the Prince of Wales Hospital, Sydney, Australia. *Cancer.* 1992;69(11):2771-8. PMID: 1571908. Excluded: wrong study design for Key Question.
- Managadze GL, Khvadagiani GG, Tsintsadze OV, et al. [Extended lymphadenectomy in radical cystectomy: margins, scope, methodology]. *Urologiia.* 2006(3):31-6. PMID: 16889087. Excluded: not English language, but possibly relevant.
- Manoharan M, Katkooi D, Kishore TA, et al. Outcome after radical cystectomy in patients with clinical T2 bladder cancer in whom neoadjuvant chemotherapy has failed. *BJU Int.* 2009;104(11):1646-9. PMID: 19466944. Excluded: wrong comparator.
- March Villalba JA, Martinez Jabaloyas JM, Pastor Hernandez F, et al. [Radical cystectomy as a muscle-invasive bladder cancer treatment in elderly patients]. *Actas Urol Esp.* 2008;32(7):696-704. PMID: 18788485. Excluded: not English language, but possibly relevant.
- Martinez-Pineiro JA, Gonzalez Martin M, Arocena F, et al. Neoadjuvant cisplatin chemotherapy before radical cystectomy in invasive transitional cell carcinoma of the bladder: a prospective randomized phase III study. *J Urol.* 1995;153(3 Pt 2):964-73. PMID: 7853584. Excluded: wrong comparator.
- Martini T, Mayr R, Wehrberger C, et al. Comparison of radical cystectomy with conservative treatment in geriatric (>80) patients with muscle-invasive bladder cancer. *Int Braz J Urol.* 2013;39(5):622-30. PMID: 24267105. Excluded: wrong intervention.
- Matsui Y, Nishiyama H, Watanabe J, et al. The current status of perioperative chemotherapy for invasive bladder cancer: a multiinstitutional retrospective study in Japan. *Int J Clin Oncol.* 2005;10(2):133-8. PMID: 15864700. Excluded: wrong study design for Key Question.
- May M, Fritsche HM, Gilfrich C, et al. [Influence of older age on survival after radical cystectomy due to urothelial carcinoma of the bladder: survival analysis of a German multi-centre study after curative treatment of urothelial carcinoma of the bladder]. *Urologe A.* 2011;50(7):821-9. PMID: 21340593. Excluded: not English language, but possibly relevant.
- May M, Herrmann E, Bolenz C, et al. Association between the number of dissected lymph nodes during pelvic lymphadenectomy and cancer-specific survival in patients with lymph node-negative urothelial carcinoma of the bladder undergoing radical cystectomy. *Ann Surg Oncol.* 2011;18(7):2018-25. PMID: 21246405. Excluded: wrong study design for Key Question.

- May M, Herrmann E, Bolenz C, et al. Lymph node density affects cancer-specific survival in patients with lymph node-positive urothelial bladder cancer following radical cystectomy. *Eur Urol*. 2011;59(5):712-8. PMID: 21296488. Excluded: wrong comparator.
- Meeks JJ, Bellmunt J, Bochner BH, et al. A systematic review of neoadjuvant and adjuvant chemotherapy for muscle-invasive bladder cancer. *Eur Urol*. 2012;62(3):523-33. PMID: 22677572. Excluded: systematic review or meta-analysis used as source document only to identify individual studies.
- Mian C, Lodde M, Comploj E, et al. The value of the ImmunoCyt/uCyt+ test in the detection and follow-up of carcinoma in situ of the urinary bladder. *Anticancer Res*. 2005;25(5):3641-4. PMID: 16101194. Excluded: wrong population.
- Mian C, Lodde M, Haitel A, et al. Comparison of the monoclonal UBC-ELISA test and the NMP22 ELISA test for the detection of urothelial cell carcinoma of the bladder. *Urology*. 2000;55(2):223-6. PMID: 10688083. Excluded: wrong population.
- Mills RD, Fleischmann A, Studer UE. Radical cystectomy with an extended pelvic lymphadenectomy: rationale and results. *Surg Oncol Clin N Am*. 2007;16(1):233-45. PMID: 17336246. Excluded: not a study.
- Milonas D, Mickevicius J, Mickevicius R, et al. [Treatment of superficial transitional cell bladder carcinoma. Long-term results of trial comparing transurethral resection alone and adjuvant chemotherapy with Doxorubicin]. *Medicina (Kaunas)*. 2002;38 Suppl 1:79-83. PMID: 12556642. Excluded: not English language, but possibly relevant.
- Mitin T, Hunt D, Shipley WU, et al. Transurethral surgery and twice-daily radiation plus paclitaxel-cisplatin or fluorouracil-cisplatin with selective bladder preservation and adjuvant chemotherapy for patients with muscle invasive bladder cancer (RTOG 0233): a randomised multicentre phase 2 trial. *Lancet Oncol*. 2013;14(9):863-72. PMID: 23823157. Excluded: wrong comparator.
- Monica B, Larosa M, Frattini A, et al. [Neoadjuvant chemotherapy in advanced-stage bladder carcinoma. A randomized prospective study comparing MVAC and MVEEC]. *Arch Ital Urol Androl*. 1994;66(5):235-43. PMID: 7812302. Excluded: not English language, but possibly relevant.
- Monzo Gardiner JI, Herranz Amo F, Cabello Benavente R, et al. [Response to adjuvant chemotherapy after radical cystectomy in patients with infiltrative bladder: Analysis of 397 cases]. *Arch Esp Urol*. 2009;62(4):275-82. PMID: 19717877. Excluded: wrong study design for Key Question.
- Morales A, Nickel JC, Wilson JW. Dose-response of bacillus Calmette-Guerin in the treatment of superficial bladder cancer. *J Urol*. 1992;147(5):1256-8. PMID: 1569662. Excluded: wrong population.
- Mori Y, Arima M, Shimada K, et al. [Treatment of 300 patients with bladder cancer]. *Hinyokika Kyo*. 1991;37(10):1235-41. PMID: 1755417. Excluded: not English language, but possibly relevant.
- Moskovitz B, Halachmi S, Moskovitz M, et al. 10-year single-center experience of combined intravesical chemohyperthermia for nonmuscle invasive bladder cancer. *Fut Oncol*. 2012;8(8):1041-9. PMID: 22894675. Excluded: wrong population.
- Moskovitz B, Meyer G, Kravtsov A, et al. Thermo-chemotherapy for intermediate or high-risk recurrent superficial bladder cancer patients. *Ann Oncol*. 2005;16(4):585-9. PMID: 15734775. Excluded: wrong population.
- Moussa O, Abol-Enein H, Bissada NK, et al. Evaluation of survivin reverse transcriptase-polymerase chain reaction for noninvasive detection of bladder cancer. *J Urol*. 2006;175(6):2312-6. PMID: 16697865. Excluded: wrong population.
- Moyano Calvo JL, Romero Diaz JA, Ortiz Gamiz A, et al. [Randomized prospective study comparing BCG and BCG plus oral tegafur in the prevention of stage T1 superficial tumors of the bladder. Results after 2.5 years]. *Actas Urol Esp*. 1999;23(10):843-7. PMID: 10670125. Excluded: not English language, but possibly relevant.
- Moyer VA. Screening for bladder cancer: U.S. preventive services task force recommendation statement. *Annals of Internal Medicine*. 2011;155(4):246-51. PMID: 21844550. Excluded: wrong population.
- Mulders PF, Meyden AP, Doesburg WH, et al. Prognostic factors in pTa-pT1 superficial bladder tumours treated with intravesical instillations. The Dutch South-Eastern Urological Collaborative Group. *Br J Urol*. 1994;73(4):403-8. PMID: 8199828. Excluded: wrong population.
- Natale RB. Randomized Phase III Trial of Neoadjuvant MVAC + Cystectomy Versus Cystectomy Alone in Patients with Locally Advanced Bladder Cancer. Paper presented at: Plenary Presentation, Mon 1:00 pm - 3:30 pm 2011; U Colorado, Denver, CO. Excluded: not a study.
- National Institute for Health and Clinical Excellence. Laparoscopic cystectomy (of the urinary bladder) (Structured abstract). *Health Technology Assessment Database*. 2013(4). PMID: No PMID. Excluded: not a study.

- Nazeri N. Incidental sonographic detection of non-muscle-invasive papillary urothelial carcinoma in a low-risk patient. *Journal of Diagnostic Medical Sonography*. 2014;30(1):34-8. PMID: No PMID. Excluded: wrong study design for Key Question.
- Neulander EZ, Kaneti J. Long-term outcomes of a randomized controlled trial comparing thermochemotherapy with mitomycin-C alone as adjuvant treatment for non-muscle-invasive bladder cancer (NMIBC). *BJU Int*. 2011;107(10):1685; author reply -6. PMID: 21518420. Excluded: not a study.
- NHSC. NMP22 BladderChek proteomic assay for the detection of bladder cancer - horizon scanning technology note (Structured abstract). *Health Technology Assessment Database*. 2013(4). PMID: No PMID. Excluded: not a study.
- Niedersuss-Beke D. [Systemic therapy of muscle invasive bladder cancer - an update]. *Wien Med Wochenschr*. 2011;161(15-16):371-3. PMID: 21953426. Excluded: not English language, but possibly relevant.
- Nilsson S, Ragnhammar P, Glimelius B, et al. A systematic overview of chemotherapy effects in urothelial bladder cancer. *Acta Oncol*. 2001;40(2-3):371-90. PMID: 11441942. Excluded: systematic review or meta-analysis used as source document only to identify individual studies.
- Nomi M, Gohji K, Okamoto M, et al. Results of transurethral resection plus adjuvant intravesical chemotherapy for superficial bladder cancer. *Int J Urol*. 1998;5(6):534-9. PMID: 9855120. Excluded: wrong population.
- O'Connor RC, Alsikafi NF, Steinberg GD. Therapeutic options and treatment of muscle invasive bladder cancer. *Expert Rev Anticancer Ther*. 2001;1(4):511-22. PMID: 12113083. Excluded: not a study.
- Oeda T, Manabe D. [The usefulness of urinary FDP in the diagnosis of bladder cancer: comparison with NMP22, BTA and cytology]. *Nippon Hinyokika Gakkai Zasshi*. 2001;92(1):1-5. PMID: 11235137. Excluded: not English language, but possibly relevant.
- Ogawa H, Nishimura T, Hori N, et al. 10-year survival rate in 92 patients with invasive bladder carcinoma treated by bladder sparing methods. *Nippon Ika Daigaku Zasshi*. 1997;64(5):446-54. PMID: 9366149. Excluded: wrong comparator.
- Ohlmann CH, De Santis M. [Neoadjuvant, inductive or adjuvant chemotherapy of bladder cancer]. *Urologe A*. 2013;52(11):1534-8, 40. PMID: 24197083. Excluded: not English language, but possibly relevant.
- Okegawa T, Kinjo M, Horie S, et al. Detection of mucin 7 gene expression in exfoliated cells in urine from patients with bladder tumor. *Urology*. 2003;62(1):182-6. PMID: 12837463. Excluded: wrong population.
- Oliva E, Pinheiro NF, Heney NM, et al. Immunohistochemistry as an adjunct in the differential diagnosis of radiation-induced atypia versus urothelial carcinoma in situ of the bladder: a study of 45 cases. *Hum Pathol*. 2013;44(5):860-6. PMID: 23199526. Excluded: wrong population.
- Ollesch J, Drees SL, Heise HM, et al. FTIR spectroscopy of biofluids revisited: an automated approach to spectral biomarker identification. *Analyst*. 2013;138(14):4092-102. PMID: 23712384. Excluded: wrong population.
- Ondrus D, Hornak M, Bardos A, et al. Systemic chemotherapy for muscle invasive bladder cancer. *Neoplasma*. 1994;41(5):263-8. PMID: 7854496. Excluded: wrong comparator.
- Onishi T, Sasaki T, Hoshina A, et al. Continuous saline bladder irrigation after transurethral resection is a prophylactic treatment choice for non-muscle invasive bladder tumor. *Anticancer Res*. 2011;31(4):1471-4. PMID: 21508405. Excluded: wrong population.
- Orsola A, Cecchini L, Raventos CX, et al. Risk factors for positive findings in patients with high-grade T1 bladder cancer treated with transurethral resection of bladder tumour (TUR) and bacille Calmette-Guerin therapy and the decision for a repeat TUR. *BJU Int*. 2010;105(2):202-7. PMID: 19558557. Excluded: wrong population.
- Panteliadou M, Touloupidis S, Giatromanolaki A, et al. Concurrent administration of liposomal doxorubicin improves the survival of patients with invasive bladder cancer undergoing hypofractionated accelerated radiotherapy (HypoARC). *Med Oncol*. 2011;28(4):1356-62. PMID: 20424934. Excluded: wrong comparator.
- Parkinson JP, Konety BR. Health related quality of life assessments for patients with bladder cancer. *J Urol*. 2004;172(6 Pt 1):2130-6. PMID: 15538218. Excluded: systematic review or meta-analysis used as source document only to identify individual studies.
- Perdona S, Autorino R, Damiano R, et al. Bladder-sparing, combined-modality approach for muscle-invasive bladder cancer: a multi-institutional, long-term experience. *Cancer*. 2008;112(1):75-83. PMID: 18008364. Excluded: wrong comparator.
- Peyromaure M, Slama J, Beuzeboc P, et al. Concurrent chemoradiotherapy for clinical stage T2 bladder cancer: report of a single institution. *Urology*. 2004;63(1):73-7. PMID: 14751352. Excluded: wrong comparator.

Philip J, Manikandan R, Venugopal S, et al. Orthotopic neobladder versus ileal conduit urinary diversion after cystectomy--a quality-of-life based comparison. *Ann R Coll Surg Engl*. 2009;91(7):565-9. PMID: 19558757. Excluded: wrong outcome.

Plimack ER. Next-generation sequencing to identify molecular alterations in DNA repair and chromatin maintenance genes associated with pathologic complete response (pT0) to neoadjuvant accelerated methotrexate, vinblastine, doxorubicin, and cisplatin (AMVAC) in muscle-invasive bladder cancer (MIBC). *J Clin Oncol*. 2014;35(5s):abstr 4538. PMID. Excluded: not a study.

Plimack ER, Hoffman-Censits JH, Viterbo R, et al. Accelerated methotrexate, vinblastine, doxorubicin, and cisplatin is safe, effective, and efficient neoadjuvant treatment for muscle-invasive bladder cancer: results of a multicenter phase II study with molecular correlates of response and toxicity. *J Clin Oncol*. 2014;32(18):1895-901. PMID: 24821881. Excluded: wrong comparator.

Porpiglia F, Renard J, Billia M, et al. Open versus laparoscopy-assisted radical cystectomy: results of a prospective study. *J Endourol*. 2007;21(3):325-9. PMID: 17444780. Excluded: wrong comparator.

Raj GV, Karavadia S, Schlomer B, et al. Contemporary use of perioperative cisplatin-based chemotherapy in patients with muscle-invasive bladder cancer. *Cancer*. 2011;117(2):276-82. PMID: 20830767. Excluded: wrong comparator.

Resorlu B, Turkolmez K, Ergun G, et al. The role of adjuvant chemotherapy in patients with locally advanced (pT3, pT4a) and/or lymph node-positive bladder cancer. *Int Urol Nephrol*. 2010;42(4):959-64. PMID: 20405206. Excluded: wrong study design for Key Question.

Richards B, Bastable JR, Freedman L, et al. Adjuvant chemotherapy with doxorubicin (Adriamycin) and 5-fluorouracil in T3, NX, MO bladder cancer treated with radiotherapy. *Br J Urol*. 1983;55(4):386-91. PMID: CN-00031935 UPDATE. Excluded: wrong comparator.

Rink M, Zabor EC, Furberg H, et al. Impact of smoking and smoking cessation on outcomes in bladder cancer patients treated with radical cystectomy. *Eur Urol*. 2013;64(3):456-64. PMID: 23206854. Excluded: wrong comparator.

Rodel C, Grabenbauer GG, Kuhn R, et al. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. *J Clin Oncol*. 2002;20(14):3061-71. PMID: 12118019. Excluded: wrong comparator.

Rosenblatt R, Sherif A, Rintala E, et al. Pathologic downstaging is a surrogate marker for efficacy and increased survival following neoadjuvant chemotherapy and radical cystectomy for muscle-invasive urothelial bladder cancer. *Eur Urol*. 2012;61(6):1229-38. PMID: 22189383. Excluded: systematic review or meta-analysis used as source document only to identify individual studies.

Ruggeri EM, Giannarelli D, Bria E, et al. Adjuvant chemotherapy in muscle-invasive bladder carcinoma: a pooled analysis from phase III studies. *Cancer*. 2006;106(4):783-8. PMID: 16419069. Excluded: systematic review or meta-analysis used as source document only to identify individual studies.

Ruoppolo M, Bellorofonte C, Gritti A, et al. [Neoadjuvant chemotherapy of locally advanced tumors of the bladder: preliminary experience]. *Arch Ital Urol Nefrol Androl*. 1990;62(2):243-8. PMID: 2142808. Excluded: not English language, but possibly relevant.

Sagaster P, Flamm J, Flamm M, et al. Neoadjuvant chemotherapy (MVAC) in locally invasive bladder cancer. *Eur J Cancer*. 1996;32A(8):1320-4. PMID: 8869093. Excluded: wrong study design for Key Question.

Sangar VK, McBain CA, Lyons J, et al. Phase I study of conformal radiotherapy with concurrent gemcitabine in locally advanced bladder cancer. *Int J Radiat Oncol Biol Phys*. 2005;61(2):420-5. PMID: 15667962. Excluded: wrong comparator.

Sapre N, Anderson P, Foroudi F. Management of local recurrences in the irradiated bladder: a systematic review. *BJU Int*. 2012;110 Suppl 4:51-7. PMID: 23194126. Excluded: not a study.

Sarkis AS, Bajorin DF, Reuter VE, et al. Prognostic value of p53 nuclear overexpression in patients with invasive bladder cancer treated with neoadjuvant MVAC. *J Clin Oncol*. 1995;13(6):1384-90. PMID: 7751883. Excluded: wrong intervention.

Sauer R, Birkenhake S, Kuhn R, et al. Efficacy of radiochemotherapy with platin derivatives compared to radiotherapy alone in organ-sparing treatment of bladder cancer. *Int J Radiat Oncol Biol Phys*. 1998;40(1):121-7. PMID: 9422567. Excluded: wrong comparator.

Scattoni V, Da Pozzo L, Nava L, et al. Five-year results of neoadjuvant cisplatin, methotrexate and vinblastine chemotherapy plus radical cystectomy in locally advanced bladder cancer. *Eur Urol*. 1995;28(2):102-7. PMID: 8529731. Excluded: wrong study design for Key Question.

Schrag D, Mitra N, Xu F, et al. Cystectomy for muscle-invasive bladder cancer: patterns and outcomes of care in the Medicare population. *Urology*. 2005;65(6):1118-25. PMID: 15922428. Excluded: wrong comparator.

Scrimger RA, Murtha AD, Parliament MB, et al. Muscle-invasive transitional cell carcinoma of the urinary bladder: a population-based study of patterns of care and prognostic factors. *Int J Radiat Oncol Biol Phys*. 2001;51(1):23-30. PMID: 11516847. Excluded: wrong study design for Key Question.

See WA, Dreicer R, Forest PK, et al. Continuous infusion, intravesical doxorubicin for the treatment of regionally advanced bladder cancer: a phase I-II trial. *Am J Clin Oncol*. 1997;20(4):331-7. PMID: 9256884. Excluded: wrong study design for Key Question.

Segal R, Winquist E, Lukka H, et al. Adjuvant chemotherapy for deep muscle-invasive transitional cell bladder carcinoma - a practice guideline. *Can J Urol*. 2002;9(5):1625-33. PMID: 12431323. Excluded: systematic review or meta-analysis used as source document only to identify individual studies.

Segati R, Bari M, Azzarello G, et al. Carboplatin monochemotherapy in elderly patients with nonoperable transitional cell carcinoma of the bladder: a two-stage, phase II study. *Eur Urol*. 1996;29(3):312-6; discussion 7. PMID: 8740038. Excluded: wrong population.

Serretta V, Lo Greco G, Pavone C, et al. The fate of patients with locally advanced bladder cancer treated conservatively with neoadjuvant chemotherapy, extensive transurethral resection and radiotherapy: 10-year experience. *J Urol*. 1998;159(4):1187-91. PMID: 9507829. Excluded: wrong study design for Key Question.

Sharp VJ, Barnes KT, Erickson BA. Assessment of asymptomatic microscopic hematuria in adults. *Am Fam Physician*. 2013;88(11):747-54. PMID: 24364522. Excluded: not a study.

Shelley M, Barber J, Wilt TJ, et al. Surgery versus radiotherapy for muscle invasive bladder cancer. *Cochrane Database Syst Rev*. 2012(4). PMID: No PMID. Excluded: systematic review or meta-analysis used as source document only to identify individual studies.

Shelley M, Cleves A, Wilt TJ, et al. Gemcitabine for unresectable, locally advanced or metastatic bladder cancer. *Cochrane Database Syst Rev*. 2011(4). PMID: 21491413. Excluded: systematic review or meta-analysis used as source document only to identify individual studies.

Shelley MD, Barber J, Wilt T, et al. Surgery versus radiotherapy for muscle invasive bladder cancer. *Cochrane Database Syst Rev*. 2002(1):CD002079. PMID: 11869621. Excluded: systematic review or meta-analysis used as source document only to identify individual studies.

Shelley MD, Jones G, Cleves A, et al. Intravesical gemcitabine therapy for non-muscle invasive bladder cancer (NMIBC): a systematic review. *BJU Int*. 2012;109(4):496-505. PMID: 22313502. Excluded: systematic review or meta-analysis used as source document only to identify individual studies.

Shelley MD, Wilt TJ, Barber J, et al. A meta-analysis of randomised trials suggests a survival benefit for combined radiotherapy and radical cystectomy compared with radical radiotherapy for invasive bladder cancer: are these data relevant to modern practice? *Clin Oncol (R Coll Radiol)*. 2004;16(3):166-71. PMID: 15191002. Excluded: systematic review or meta-analysis used as source document only to identify individual studies.

Sherif A, Holmberg L, Rintala E, et al. Neoadjuvant cisplatin based combination chemotherapy in patients with invasive bladder cancer: a combined analysis of two Nordic studies. *Eur Urol*. 2004;45(3):297-303. PMID: 15036674. Excluded: no original data, duplicate data.

Shiba M, Takatera H, Fujii T, et al. [Intraarterial chemotherapy with bladder preservation in patients with invasive bladder carcinoma]. *Hinyokika Kyo*. 2004;50(1):15-9. PMID: 15032009. Excluded: not English language, but possibly relevant.

Shibley WU, Winter KA, Kaufman DS, et al. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. *J Clin Oncol*. 1998;16(11):3576-83. PMID: 9817278. Excluded: wrong comparator.

Shibley WU, Zietman AL, Kaufman DS, et al. Invasive bladder cancer: treatment strategies using transurethral surgery, chemotherapy and radiation therapy with selection for bladder conservation. *Int J Radiat Oncol Biol Phys*. 1997;39(4):937-43. PMID: 9369144. Excluded: not a study.

Siefker-Radtke AO, Dinney CP, Shen Y, et al. A phase 2 clinical trial of sequential neoadjuvant chemotherapy with ifosfamide, doxorubicin, and gemcitabine followed by cisplatin, gemcitabine, and ifosfamide in locally advanced urothelial cancer: final results. *Cancer*. 2013;119(3):540-7. PMID: 22914978. Excluded: wrong intervention.

Skinner DG, Daniels JR, Russell CA, et al. Adjuvant chemotherapy following cystectomy benefits patients with deeply invasive bladder cancer. *Semin Urol*. 1990;8(4):279-84. PMID: 2284533. Excluded: wrong intervention.

- Soga N, Arima K, Sugimura Y. Adjuvant methotrexate, vinblastine, adriamycin, and cisplatin chemotherapy has potential to prevent recurrence of bladder tumors after surgical removal of upper urinary tract transitional cell carcinoma. *Int J Urol*. 2008;15(9):800-3. PMID: 18651862. Excluded: wrong population.
- Sonpavde G, Goldman BH, Speights VO, et al. Quality of pathologic response and surgery correlate with survival for patients with completely resected bladder cancer after neoadjuvant chemotherapy. *Cancer*. 2009;115(18):4104-9. PMID: 19517476. Excluded: wrong outcome.
- Sonpavde G, Khan MM, Lerner SP, et al. Disease-free survival at 2 or 3 years correlates with 5-year overall survival of patients undergoing radical cystectomy for muscle invasive bladder cancer. *J Urol*. 2011;185(2):456-61. PMID: 21167527. Excluded: wrong study design for Key Question.
- Soukup V, Babjuk M, Bellmunt J, et al. Follow-up after surgical treatment of bladder cancer: a critical analysis of the literature. *Eur Urol*. 2012;62(2):290-302. PMID: 22609313. Excluded: systematic review or meta-analysis used as source document only to identify individual studies.
- Splinter TA, Pavone-Macaluso M, Jacqmin D, et al. A European Organization for Research and Treatment of Cancer--Genitourinary Group phase 2 study of chemotherapy in stage T3-4N0-XM0 transitional cell cancer of the bladder: evaluation of clinical response. *J Urol*. 1992;148(6):1793-6. PMID: 1433610. Excluded: wrong study design for Key Question.
- Stadler WM, Lerner SP, Groshen S, et al. Phase III study of molecularly targeted adjuvant therapy in locally advanced urothelial cancer of the bladder based on p53 status. *J Clin Oncol*. 2011;29(25):3443-9. PMID: 21810677. Excluded: wrong intervention.
- Startsev VI, Karelin MI. [Combined therapy for patients with invasive bladder cancer]. *Vopr Onkol*. 2003;49(2):235-8. PMID: 12785212. Excluded: not English language, but possibly relevant.
- Startsev VY. The role of combined method in organ-sparing treatment of muscle-invasive bladder cancer recurrences. *Arch Ital Urol Androl*. 2002;74(2):54-6. PMID: 12161935. Excluded: wrong comparator.
- Stein JP. The role of lymphadenectomy in patients undergoing radical cystectomy for bladder cancer. *Curr Oncol Rep*. 2007;9(3):213-21. PMID: 17430693. Excluded: not a study.
- Stejskal D, Fiala RR. Evaluation of serum and urine clusterin as a potential tumor marker for urinary bladder cancer. *Neoplasma*. 2006;53(4):343-6. PMID: 16830064. Excluded: wrong population.
- Stejskal D, Humenanska V, Hanulova Z, et al. Evaluation of urine N1,N12-Diacetylspermine as potential tumor marker for urinary bladder cancer. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2006;150(2):235-7. PMID: 17426784. Excluded: wrong population.
- Sternberg CN. Perioperative chemotherapy in muscle-invasive bladder cancer to enhance survival and/or as a strategy for bladder preservation. *Semin Oncol*. 2007;34(2):122-8. PMID: 17382795. Excluded: not a study.
- Sternberg CN, Apolo AB. Everything old is new again! Neoadjuvant chemotherapy in the treatment of muscle-invasive bladder cancer. *J Clin Oncol*. 2014;32(18):1868-70. PMID: 24821880. Excluded: no original data, duplicate data.
- Sternberg CN, Pansadoro V, Calabro F, et al. Neo-adjuvant chemotherapy and bladder preservation in locally advanced transitional cell carcinoma of the bladder. *Ann Oncol*. 1999;10(11):1301-5. PMID: 10631456. Excluded: wrong study design for Key Question.
- Stewart AB, Mostafid H. Re: A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. *J Urol*. 2005;173(4):1433; author reply PMID: 15758827. Excluded: not a study.
- Stockle M, Meyenburg W, Wellek S, et al. Adjuvant polychemotherapy of nonorgan-confined bladder cancer after radical cystectomy revisited: long-term results of a controlled prospective study and further clinical experience. *J Urol*. 1995;153(1):47-52. PMID: 7966789. Excluded: wrong population.
- Stockle M, Wellek S, Meyenburg W, et al. Radical cystectomy with or without adjuvant polychemotherapy for non-organ-confined transitional cell carcinoma of the urinary bladder: prognostic impact of lymph node involvement. *Urology*. 1996;48(6):868-75. PMID: 8973669. Excluded: wrong population.
- Studer UE, Bacchi M, Biedermann C, et al. Adjuvant cisplatin chemotherapy following cystectomy for bladder cancer: results of a prospective randomized trial. *J Urol*. 1994;152(1):81-4. PMID: 8201695. Excluded: wrong intervention.
- Sumiyoshi Y, Yano M, Yokota K, et al. [Intra-arterial infusion chemotherapy in bladder cancer]. *Gan To Kagaku Ryoho*. 1990;17(8 Pt 2):1697-700. PMID: 2389958. Excluded: not English language, but possibly relevant.
- Sun X, Hu J, Yang Q. Combined modality therapy following bladder conservation surgery for bladder cancers. *Chin Med J*. 2002;115(10):1548-51. PMID: 12490108. Excluded: wrong comparator.

- Svatek RS, Karam J, Karakiewicz PI, et al. Role of urinary cathepsin B and L in the detection of bladder urothelial cell carcinoma. *J Urol*. 2008;179(2):478-84; discussion 84. PMID: 18076936. Excluded: wrong population.
- Sylvester R, Sternberg C. The role of adjuvant combination chemotherapy after cystectomy in locally advanced bladder cancer: what we do not know and why. *Ann Oncol*. 2000;11(7):851-6. PMID: 10997813. Excluded: systematic review or meta-analysis used as source document only to identify individual studies.
- Tanaka T, Miyazawa K, Tsukamoto T, et al. Pathobiology and chemoprevention of bladder cancer. *Journal of Oncology*. 2011. PMID: 21941546. Excluded: not a study.
- Tilki D, Brausi M, Colombo R, et al. Lymphadenectomy for bladder cancer at the time of radical cystectomy. *Eur Urol*. 2013;64(2):266-76. PMID: 23648149. Excluded: systematic review or meta-analysis used as source document only to identify individual studies.
- Tsuji H, Akaza H, Ohtani M, et al. Preliminary results of bladder-preserving therapy with definitive radiotherapy and intraarterial infusion of chemotherapy. *Strahlenther Onkol*. 1994;170(9):531-7. PMID: 7940124. Excluded: wrong comparator.
- Tunio MA, Hashmi A, Qayyum A, et al. Whole-pelvis or bladder-only chemoradiation for lymph node-negative invasive bladder cancer: single-institution experience. *Int J Radiat Oncol Biol Phys*. 2012;82(3):e457-62. PMID: 21945107. Excluded: wrong comparator.
- Tunio MA, Hashmi A, Rafi M, et al. Bladder preservation by neoadjuvant chemotherapy followed by concurrent chemoradiation for muscle-invasive bladder cancer: experience at Sindh Institute of Urology & Transplantation (SIUT). *JPM J Pak Med Assoc*. 2011;61(1):6-10. PMID: 22368893. Excluded: wrong comparator.
- Vale CL. Adjuvant chemotherapy for invasive bladder cancer (individual patient data). *Cochrane Database Syst Rev*. 2011(4). PMID: No PMID. Excluded: systematic review or meta-analysis used as source document only to identify individual studies.
- Van Allen EM, Mouw KW, Kim P, et al. Somatic ERCC2 mutations correlate with cisplatin sensitivity in muscle-invasive urothelial carcinoma. *Cancer Discov*. 2014;4(10):1140-53. PMID: 25096233. Excluded: wrong comparator.
- van der Steen-Banasik E, Ploeg M, Witjes JA, et al. Brachytherapy versus cystectomy in solitary bladder cancer: a case control, multicentre, East-Netherlands study. *Radiother Oncol*. 2009;93(2):352-7. PMID: 19457565. Excluded: wrong population.
- van Hemelrijck M, Thorstenson A, Smith P, et al. Risk of in-hospital complications after radical cystectomy for urinary bladder carcinoma: population-based follow-up study of 7608 patients. *BJU Int*. 2013;112(8):1113-20. PMID: 23906011. Excluded: wrong comparator.
- von der Masse H. Long-Term Survival Results of a Randomized Trial Comparing Gemcitabine Plus Cisplatin, With Methotrexate, Vinblastine, Doxorubicin, Plus Cisplatin in Patients with Bladder Cancer. *J Clin Oncol*. 2005;23(21):4602-8. PMID: 16034041. Excluded: wrong population.
- Wallace DM, Bloom HJ. The management of deeply infiltrating (T3) bladder carcinoma: controlled trial of radical radiotherapy versus preoperative radiotherapy and radical cystectomy (first report). *Br J Urol*. 1976;48(7):587-94. PMID: CN-00015542 UPDATE. Excluded: wrong study design for Key Question.
- Wallace DM, Raghavan D, Kelly KA, et al. Neo-adjuvant (pre-emptive) cisplatin therapy in invasive transitional cell carcinoma of the bladder. *Br J Urol*. 1991;67(6):608-15. PMID: 2070206. Excluded: wrong intervention.
- Walz J, Shariat SF, Suardi N, et al. Adjuvant chemotherapy for bladder cancer does not alter cancer-specific survival after cystectomy in a matched case-control study. *BJU Int*. 2008;101(11):1356-61. PMID: 18454792. Excluded: wrong population.
- Washino S, Hirai M, Terauchi F, et al. [Intra-arterial chemotherapy for bladder preservation in patients with locally advanced bladder cancer]. *Nippon Hinyokika Gakkai Zasshi*. 2009;100(3):486-94. PMID: 19348188. Excluded: not English language, but possibly relevant.
- Winqvist 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;171(2 Pt 1):561-9. PMID: 14713760. Excluded: systematic review or meta-analysis used as source document only to identify individual studies.
- Woolcott CG, Kolonel LN. Regarding measures of impact: Diabetes and urothelial cancer. *Cancer Epidemiology*. 2012;36(6):581. PMID: No PMID. Excluded: not a study.
- 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;112(11):2401-8. PMID: 18383515. Excluded: wrong population.
- Yuh BE, Ruel N, Wilson TG, et al. Pooled analysis of clinical outcomes with neoadjuvant cisplatin and gemcitabine chemotherapy for muscle invasive bladder cancer. *J Urol*. 2013;189(5):1682-6. PMID: 23123547. Excluded: systematic review or meta-analysis used as source document only to identify individual studies.

Zaid HB, Patel SG, Stimson CJ, et al. Trends in the utilization of neoadjuvant chemotherapy in muscle-invasive bladder cancer: results from the National Cancer Database. *Urology*. 2014;83(1):75-80. PMID: 24231210. Excluded: wrong comparator.

Zapatero A, Martin de Vidales C, Arellano R, et al. Updated results of bladder-sparing trimodality approach for invasive bladder cancer. *Urol*. 2010;28(4):368-74. PMID: 19362865. Excluded: wrong comparator.

Zapatero A, Martin De Vidales C, Arellano R, et al. Long-term results of two prospective bladder-sparing trimodality approaches for invasive bladder cancer: neoadjuvant chemotherapy and concurrent radio-chemotherapy. *Urology*. 2012;80(5):1056-62. PMID: 22999456. Excluded: wrong comparato

Appendix E. Evidence Tables

Table E1. Key Question 1: Included studies

Author, Year Study Name Country Study Design Risk of Bias	Setting and Study Years	Single- or Multi- Center	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup
Bekelman, 2013 ² Retrospective cohort Medium	US Population-based SEER-Medicare data 1995-2005	Multi, population- based data	1995-2005 Stages T2 and T3 urothelial cell carcinoma Medicare FFS only, no HMO	Unstaged, combination radical cystectomy with EBRT or chemotherapy, use of non-platinum- based chemotherapy with EBRT, chemotherapy alone, EBRT alone, non- concurrent chemoradiation. Also excluded deaths within 3 months of diagnosis	A: TURBT, EBRT, and concurrent platinum-based chemotherapy B: Radical cystectomy with or without lymphadenectomy	Not reported
Goossens-Laan, 2014 ³ Retrospective cohort study High	Netherlands Population-based cancer registry data 1995-2009	Multi, population- based data	1995-2009 Stages T2, T3, T4a (presumed)	Missing comorbidity, socioeconomic status	A: Radical cystectomy B: EBRT C: Interstitial radiotherapy/brachytherapy D: Maximal TURBT	Not reported

Author, Year Study Name Country Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results
Bekelman, 2013 ² Retrospective cohort Medium	Screened: 54,402 Eligible: 6,486 Enrolled: 1,843 Total Analyzed: 1,843 Per Group Analyzed: A: 417; B: 1,426	Age: A: mean 79.3 ± 6.0 years; B: mean 75.4 ± 6.2 years Sex: A: 300/417 male; B: 892/1426 male Stage: Not reported Functional Status: Not reported	Unadjusted 5-year survival, A vs. B, log-rank test p-value: Overall: 27.9% vs. 46.5%, p<0.001 Disease-specific: 52.2% vs. 64.5%, p<0.001 Unadjusted Cox models: HR overall mortality A vs. B 1.54, 95% CI 1.33-1.77 Propensity-score adjusted model with propensity score derived from demographic and hospital characteristics not further specified: HR for overall mortality, A vs. B, 1.26, 95% CI 1.05-1.53 IVA with area cystectomy rate as instrument, HR for overall mortality, A vs. B: 1.06, 95% CI 0.78-1.31
Goossens-Laan, 2014 ³ Retrospective cohort study High	Screened: Not reported Eligible: 2,610 Enrolled: 2,455 Total Analyzed: 2,455 Per Group Analyzed: A: 835; B: 859; C: 172; D: 417	Age: crossover between groups allows total for each group to equal >100%. A: 52% <60, 43% 61-74, 13% 75+; B: 15% <60, 31% 61-74, 48% 75+; C: 10% <60, 9% 61-74, 3% 75+; D: 10% <60, 12% 61-74, 28% 75+ Sex: A: 34% of males, 32% of females; B: 35% of males, 33% of females; C: 7% of males, 5% of females; D: 17% of males, 20% of females Stage: A: 25% stage 2, 59% stage 3, 30% stage 4; B: 43% stage 2, 24% stage 3, 23% stage 4; C: 10% stage 2, 3% stage 3, 1% stage 4; D: 23% stage 2, 8% stage 3, 16% stage 4 Functional Status: Not reported	Unadjusted 5-year survival: A vs. B vs. C vs. D: "Relative": 48% vs. 29% vs. 70% vs. 19%, no significance test

Author, Year Study Name Country Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Adjustment for Confounding	Sponsor	Comments
Bekelman, 2013 ² Retrospective cohort Medium	Withdrawals due to AE: Not reported Death during post-operative period: excluded Death within 1st year: Not reported	Propensity scores and IVA		Compared to other observational studies, rigorous definition of bladder- preserving therapy
Goossens-Laan, 2014 ³ Retrospective cohort study High	Withdrawals due to AE: Not reported Death during post-operative period: Not reported Death within 1st year: Not reported			

Author, Year Study Name Country Study Design Risk of Bias	Setting and Study Years	Single- or Multi- Center	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup
Holmang, 1997 ⁴ Retrospective cohort High	Sweden Population-based Swedish cancer registry data 1987-1988	Multi	1987-1988 Stage T2 or greater Included patients diagnosed at autopsy	Metastatic disease at presentation	A: EBRT with 3-field box, 60 Gy or more B: Radical TURBT alone C: Radical cystectomy, some of whom received preoperative radiotherapy, 2 of whom received preoperative chemotherapy, no routine lymphadenectomy	≥ 5 years
James, 2012 ⁵ Randomized trial Medium	United Kingdom 45 centers 2001-2011	Multi	2001-2011 Stage T2, T3, or T4a bladder cancer, WHO performance status 0-2	Clinical lymph node involvement or metastasis, abnormal hematologic, renal, or hepatic labs, pregnant, previous cancer, inflammatory bowel disease	A: EBRT 55 Gy in 20 fractions over 4 weeks or 64 Gy in 32 fractions over 6.5 weeks, fluorouracil 500 mg/m ² during fraction 1 to 5 and 16 to 20 and mitomycin c 12 mg/m ² on day 1; 18 patients underwent modified volume radiotherapy B: EBRT alone	Median 70 months in group A
Kalogeras, 2008 ⁶ Retrospective cohort High	Greece Single institution 1995-2006	Single	1995-2006 Stage T2N0M0	None noted	A: EBRT with box configuration, 64 Gy, no reported of percent that underwent cystectomy B: Radical cystectomy, no perioperative radiotherapy, no note of lymphadenectomy	A: mean 38 months (range 5-125 months) B: mean 37 months (range 8-89 months)

Author, Year Study Name Country Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results
Holmang, 1997 ⁴ Retrospective cohort High	Screened: Not reported Eligible: Not reported Enrolled: Not reported Total Analyzed: 148 Per Group Analyzed: A: 42; B: 70; C: 36	Age: Not reported Sex: Not reported Stage: 79% vs. 63% vs. 83% T2 or T3, 21% vs. 37% vs. 17% T4a Functional Status: Not reported	Survival at study endpoint (~ 5 years after diagnosis), A vs. B vs. C, log-rank test p-value: Overall: T2/T3, A: 17/30 deaths within 5 years, B: 38/44 deaths within 5 years, C: 28/33 deaths within 5 years; T4a, A: 6/6 dead from bladder cancer within 5-26 months, B: all dead C: 9/9 dead from bladder cancer
James, 2012 ⁵ Randomized trial Medium	Screened: 458 Eligible: Not reported Enrolled: 360 Total analyzed: 360 Per Group Analyzed: A: 178; B: 182	Age (median): 72 vs. 71 years Male: 82% vs. 79% T2: 85% vs. 80% T3a: 5.5% vs. 8.4% T3b: 3.8% vs. 3.9% T4a: 3.8% vs. 3.9% WHO performance status 0-1: 97% vs. 97%	2-year locoregional recurrence: 33% vs. 46%, HR 0.68 (95% CI 0.48- 0.96) 2-year invasive locoregional disease: 18% vs. 32%, HR 0.57 (95% CI 0.37 to 0.89) 2-year cystectomy rate: 11.4% vs. 16.8% (p=0.07) Overall mortality: 55% (98/178) vs. 60% (110/182), RR 0.91 (95% CI 0.76 to 1.09) 5-year mortality: 52% vs. 65%, HR 0.82 (95% CI 0.63 to 1.09) favoring A Bladder cancer mortality: 42% (74/178) vs. 51% (92/182), HR 0.77 (95% CI 0.57 to 1.05) 5-year metastasis rate: difference 11%, HR 0.72 (95% CI 0.53 to 0.99) 5-year disease-free survival: difference 8.9% (favors A), HR 0.78 (95% CI 0.60 to 1.03) Estimates similar for locoregional recurrence in subgroups based on type or radiotherapy, radiotherapy dose fractionation, use of neoadjuvant chemotherapy
Kalogeris, 2008 ⁶ Retrospective cohort High	Screened: Not reported Eligible: Not reported Enrolled: Not reported Total Analyzed: 145 Per Group Analyzed: A: 119; B: 26	Age: A: < 70, 39 patients; > 70, 80 patients B: < 70, 10 patients; > 70. 16 patients Sex: Not reported Stage: all T2 Functional Status: Not reported	3-year survival, A vs. B, log-rank test p-value: Overall: 39% vs. 69%, p=0.032 Disease-specific: Not reported Local recurrences: A vs. B Local "disease control" reported as 42% for A, 88% for B

Author, Year Study Name Country Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Adjustment for Confounding	Sponsor	Comments
Holmang, 1997 ⁴ Retrospective cohort High	2 cystectomy perioperative deaths 3 EBRT peri-procedure deaths	None	Western Sweden Oncology Centre and Medical Society of Goteborg	
James, 2012 ⁵ Randomized trial Medium	Any grade 3-5 adverse event: 36% vs. 28%, OR 1.51 (95% CI 0.83 to 2.74) Grade 3-5 genitourinary adverse event: 21% vs. 21%, OR 1.00 (95% CI 0.52 to 1.95) Grade 3-5 gastrointestinal adverse event: 9.6% vs. 2.7%, OR 3.84 (95% CI 0.97 to 15.19)	Analysis of locoregional recurrence (primary end point) adjusted for neoadjuvant chemotherapy, age, radiotherapy dose, tumor stage, performance status, tumor grade (no difference in estimate)	Cancer Research UK and National Institute for Health Research	
Kalogeris, 2008 ⁶ Retrospective cohort High	Withdrawals due to AE: 0 Death during post-operative period: 0 Grade 3 toxicities in A: 8/119 diarrhea, 8/119 leukopenia, 3/119 anemia Postoperative complications in B: 46% (most of which were surgical site infections)	None	None	No adjustment of case-mix differences between study groups

Author, Year Study Name Country Study Design Risk of Bias	Setting and Study Years	Single- or Multi- Center	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup
Kotwal, 2008 ⁷ Retrospective cohort High	UK Single institution 1996-2000	Single	1996-2000 (sub analysis on 2002-2005) Stages Tis, T1, T2, T3 or T4a urothelial cell carcinoma, complete clinical information available	None reported. Excluded patients found to undergo cystectomy for benign indications	A: Radical radiotherapy with 50-55 Gy in 20 fractions B: Radical cystectomy, including lymphadenectomy in 52/72 patients	Not reported. Did include 5- year survival estimates
Nieuwenhuijzen 2005 ⁸ Retrospective cohort Medium	Netherlands Single institution 1988-2003	Single	1988-2003 Stages T1 high grade and T2 urothelial cell carcinoma < 5 cm	Previous EBRT, size of tumor not described For Group A, multiple tumors	A: EBRT with 30 Gy in 15 fractions followed by brachytherapy through suprapubic cystotomy, combined with partial cystectomy in 24 patients B: Radical cystectomy with lymphadenectomy	Not reported, included 5-year and 10-year survival estimates

Author, Year Study Name Country Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results
Kotwal, 2008 ⁷ Retrospective cohort High	Screened: Not reported Eligible: Not reported Enrolled: Not reported Total Analyzed: 169 Per Group Analyzed: A: 97; B: 72	Age (median): 75 years (range: 42-99) vs. 68 years (range: 37-85 years) Male: 75% vs. 65% Stage: 9% vs. 19% Tis or T1, 38% vs. 31% T2, 49% vs. 43% T3 or T4a, 3% vs. 7% unknown Functional Status: Not reported	5-year survival, A vs. B, log-rank test p-value: Overall: 34.6% vs. 41.3%, p=0.39 Disease-specific: 56.8% vs. 53.4%, p=0.376 8-year survival, A vs B, log-rank test p-value: Overall: 17.8% vs. 36.4%, p=Not reported Disease-specific: Not reported Local recurrences: A vs. B 31/97 vs 27/72 regional or distant recurrences Need for cystectomy Not reported, commented on 31 local failures and 9 cystectomy patients
Nieuwenhuijzen 2005 ⁸ Retrospective cohort Medium	Screened: Not reported Eligible: Not reported Enrolled: Not reported Total Analyzed: 185 Per Group Analyzed: A: 108; B: 77	Age: A: Median: 63 years, range 31-88; B: Median: 63 years, range 36-84 Sex: A: 89/108 male; B: 62/77 male Stage: A: T1: 17/108, T2: 91/108 B: T1: 28/77, T2: 49/77 Functional Status: Not reported Discrepancy in reporting of tumor sizes, A vs. B: < 3 cm: A 77/108, B 12/77 3-5 cm: A 26/108, B 11/77 Unknown: A 5/108, B 54/77	5-year survival, A vs. B, log-rank test p-value: Overall: 62% vs. 67%, p=0.67 Disease-specific: 73% vs. 72%, p=0.28 10-year survival, A vs. B, log-rank test p-value: Overall: 50% vs. 58%, p=0.67 (only p recorded likely from log-rank) Disease-specific: 67% vs. 72%, p=0.28 (only p recorded likely from log-rank) Local recurrences: A 23/108 with bladder recurrences Multivariable model: Cox proportional hazards model adjusted for age, T stage, grade, number of tumors Overall: HR 1.6 (0.7-3.6) favoring group B Disease-specific: HR 2.0 (0.8-5.1) favoring group B

Author, Year Study Name Country Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Adjustment for Confounding	Sponsor	Comments
Kotwal, 2008 ⁷ Retrospective cohort High	Withdrawals due to AE: Not reported Death during post-operative period: 4 Death within 1st year: 21.6% vs. 34.7%, p=Not reported	Cox proportional hazards methods adjusting for tumor stage, grade, hydronephrosis, age, sex, and treatment	None	
Nieuwenhuijzen 2005 ⁸ Retrospective cohort Medium	Withdrawals due to AE: 0 Death during post-operative period: 0 Death within 1st year: Not reported	Cox proportional hazards methods adjusting for T-category (T1 vs. T2), grade of differentiation (G2 vs. G3 vs. Gx), N-stage (N0 vs. Nx), age (linear) and tumor multiplicity (solitary vs. multiple).		

Author, Year Study Name Country Study Design Risk of Bias	Setting and Study Years	Single- or Multi- Center	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup
Rincon Mayans, 2010 ⁹ Retrospective cohort High	Spain Single institution 1994-2007	Single	1994-2007 Stage T2-4N0M0	None noted	A: EBRT with two regimens: 1997-2003 patients received Taxol®-methotrexate-5-fluorouracil-cisplatin, 45-65 Gy concurrent with 5-fluorouracil-cisplatin, and 2 subsequent cycles of chemotherapy; from 2003-2007, patients received Taxol®-gemcitabine-cisplatin, IMRT 55-65 Gy B: Radical cystectomy, no perioperative radiotherapy, no note of lymphadenectomy or other surgical details	A: mean follow-up 51 months, median follow-up 39 months B: mean follow-up 29 months, median follow-up 18 months
Sell, 1991 ¹⁰ Randomized controlled trial High	Denmark Multicenter 1983-1986	Multi	1983-1986 Stages T2, T3, T4a	Age > 70 years Previous EBRT Other malignancies	A: Radical EBRT with 60 Gray B: Preoperative ERBT with 40 Gray followed by radical cystectomy, including lymphadenectomy in 40/61 patients	Median follow-up 50 months, not further stratified
Solsona, 2009 ¹¹ Nonrandomized clinical trial High	Spain Multicenter 1980-1990	Multi	1989-2005 MIBC Positive biopsy 3 months after radical TURBT	Lymph node involvement, hydronephrosis, residual tumor after TURBT	A: Bladder-sparing chemotherapy with CMV, MVAC, or GC B: Radical cystectomy with lymphadenectomy	Partially reported, reported 84 months among those with a cR to chemotherapy

Author, Year Study Name Country Study Design Risk of Bias	Number of Treatment and Control Subjects (screened, eligible, enrolled, total and per group analyzed)	Population Characteristics by Treatment Group (age, race, sex, stage of disease, functional status)	Results
Rincon Mayans, 2010 ⁹ Retrospective cohort High	Screened: Not reported Eligible: Not reported Enrolled: Not reported Total Analyzed: 188 Per Group Analyzed: A: 43; B: 145	Age: Not reported Sex: Not reported Stage: A: T1/T2 20 patients, T3/T4 23 patients B: Not reported Functional Status: Not reported	3-year progression-free survival, A vs. B, log-rank test p-value: 69±7% vs. 72±5%, p=0.83 5-year progression-free survival, A vs. B, log-rank test p-value: 61±7% vs. 63±7%. p=0.83 Complete response in A in 31 patients (72%)
Sell, 1991 ¹⁰ Randomized controlled trial High	Screened: Not reported Eligible: Not reported Enrolled: Not reported Total Analyzed: 183 Per Group Analyzed ITT: A: 95; B: 88 Per Group Analyzed Actual: A: 88; B: 66	Age: A: Mean: 61.3 years, B: Mean: 61.3 years Sex: A: 80 vs. 82% Stage: 37% vs. 42% T2, 63 vs. 58% T3 or T4 Functional Status: Not reported	Median Survival (months), A vs. B, log-rank test p-value: Overall ITT: 20 vs. 18, Overall Actual: p=0.08 trend favoring Group A Survival of salvage cystx patients did not differ from Group B Local recurrence, A vs B: 6.8% vs. 35.8% Distant recurrence, A vs. B: 34% vs. 31.5%
Solsona, 2009 ¹¹ Nonrandomized clinical trial High	Screened: Not reported Eligible: Not reported Enrolled: 146 Total Analyzed: 146 Per Group Analyzed: A: 75; B: 71	Age: A: median 62 years; B: median 64 years Sex: A: 68/75 male; B: 62/71 male Stage: Not reported Functional Status: Not reported	5-year survival, A vs. B, log-rank test p-value: Disease-specific: 64.5% vs. Not reported, p=NS but Not reported Need for cystectomy in 54/75 Group A patients

Author, Year Study Name Country Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Adjustment for Confounding	Sponsor	Comments
Rincon Mayans, 2010 ⁹ Retrospective cohort High	Withdrawals due to AE: Not reported Death during post-operative period: Not reported Toxicities in A: Not reported Postoperative complications in B: Not reported	None	None	No adjustment of case-mix differences between study groups
Sell, 1991 ¹⁰ Randomized controlled trial High	Withdrawals due to AE: Not reported Death during post-operative period: 0 Death within 1st year: Not reported Moderate or greater GI side effects, A vs. B: 19/95 vs. 22/88 Contracted bladder in 9/61 Group A patients		Danish Cancer Society	Antiquated clinical regimen
Solsona, 2009 ¹¹ Nonrandomized clinical trial High	Withdrawals due to AE: Not reported Death during post-operative period: Not reported Death within 1st year: Not reported Table 5 reports Group A chemo-related toxicity including Grade \geq 3 leucopenia in 32%, neutropenia in 66%, anemia in 13%, thrombocytopenia in 25%	Cox proportional hazards methods adjusting for age, sex, presence of bladder Tis, antecedents, size, clinical response, and chemotherapy modality		

AE, Adverse events; CI, Confidence Intervals; cm, centimeters; CMV, cisplatin, methotrexate, vinblastine ; cR, Clinical response; EBRT, external beam radiation therapy; FFS, Fee-for-service;; G2, grade 2; G3, grade 3; GC, gemcitabine plus cisplatin; GI, Gastrointestinal; Gy, Gray; HMO, Health maintenance organization; HR, Hazard ratio; IMRT, Intensity Modulated Radiation Therapy; ITT, intention-to-treat analysis; IVA, instrumental variable analysis; M0, Metastasis stage 0; mg/m2, milligrams per meter squared ;MIBC, Muscle Invasive Bladder Cancer; ;MVAC, Methotrexate, Vinblastine, Doxorubicin, Cisplatin; N0, Node stage 0;; NR, Not reported; NS, Not significant; Nx, Nodes not removed or unknown; OR, odds ratio;; ; SEER, Surveillance, Epidemiology and End Results; T1, Tumor stage 1; T2, Tumor stage 2; T3, Tumor stage 3; T4, Tumor stage 4; T4a, Tumor stage 4a; Tis, carcinoma in situ; TURBT, Transurethral resection of bladder tumor; UK, United Kingdom; WHO, World Health Organization.

Table E2. Key Question 2: Included studies

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Abdollah, 2012 ¹² Retrospective Cohort Medium	US 1988-2006	Radical cystectomy for non-metastatic transitional cell carcinoma of the urinary bladder	Unknown tumor stage or grade	A: Cystectomy with extended lymph node dissection (≥10 lymph nodes removed and examined) B: Cystectomy with limited lymph node dissection (<10 lymph nodes removed and examined) C: Cystectomy without pelvic lymph node dissection	Not reported

Author, Year Study Name Study Design Risk of Bias	Number of Subjects Per Group	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Abdollah, 2012 ¹² Retrospective Cohort Medium	A+B: 8394 C: 2789	<p>A+B vs. C</p> <p>Age (mean): 67.1 vs. 68.8, p<0.001</p> <p>Male: 6285/8394 vs. 2025/2789 , p<0.01</p> <p>Caucasian:7533/8394 vs. 2508/2789</p> <p>Smoking status: Not reported</p> <p>Recurrent bladder cancer: Not reported</p> <p>Stage: Ta/Tis:159/8394 vs. 161/2789</p> <p>T1: 807/8394 vs. 4332789</p> <p>T2: 3191/8394 vs. 1193/2789</p> <p>T3: 2578/8394 vs. 495/2789</p> <p>T4: 1659/8394 vs. 507/2789; p<0.001</p> <p>Grade: G1/G2: 599/8394 vs. 326/2789</p> <p>G3: 4466/8394 vs. 1559/2789</p> <p>G4: 3329/8394 vs. 904/2789; p<0.001</p> <p>Functional status: Not reported</p>	<p><u>A+B vs. C</u></p> <p>HRs adjusted for age, sex, race, tumor stage, tumor grade and year of surgery</p> <p>10-year cancer-specific mortality: 57.5% vs. 52.5% (log rank p <0.001), HR 1.33 (95% CI: 1.24-1.44)</p> <p>Ta/Tis: 80.4% vs. 71.9% (p=0.02), HR 2.09 (95% CI 1.16-3.79)</p> <p>T1: 81.7% vs. 70.0% (p<0.001), HR 1.60 (95% CI 1.18-2.17)</p> <p>T2: 71.5% vs. 56.1% (p<0.001), HR 1.68 (95% CI 1.47-1.91)</p> <p>T3: 43.7% vs. 38.8% (p=0.006), HR 1.15 (95% CI 1.01-1.33)</p> <p>T4: 35.1% vs. 32.0% (p=0.1), HR 1.11 (95% CI 0.9-1.28)</p> <p>10-year overall mortality: 34.1% vs. 27.2% (log rank p<0.001), HR 1.29 (95% CI 1.22-1.37)</p> <p>Ta/Tis:53.4% vs. 48.1% (p=0.07), HR 1.49 (95% CI 1.02-2.17)</p> <p>T1: 57.7% vs. 41.4% (p=0.001), HR 1.29 (95% CI 1.06-1.57)</p> <p>T2: 44.6% vs. 29.4% (p<0.001), HR 1.44 (95% CI 1.31-1.58)</p> <p>T3: 23.4% vs. 18.5% (p<0.001), HR 1.13 (95% CI 1.01-1.28)</p> <p>T4: 17.5% vs. 11.8% (p<0.001), HR 1.24 (95% CI 1.11-1.39)</p> <p><u>A vs. B</u></p> <p>10-year cancer-specific mortality: 62.2% vs. 54.0% (log rank p<0.001)</p> <p>Ta/Tis: 70.8% vs. 85.7% (p=0.1)</p> <p>T1: 85.8% vs. 78.% (p=0.01)</p> <p>T2: 76.1% vs. 67.7% (p<0.001)</p> <p>T3: 48.7% vs. 39.7% (p<0.001)</p> <p>T4: 38.6% vs. 32.5% (p=0.02)</p> <p>10-year overall mortality: 39.4% vs. 30.3% (log rank p<0.001)</p> <p>Ta/Tis: 39.1% vs. 63.3% (p=0.05)</p> <p>T1: 66.7% vs. 51.2% (p<0.001)</p> <p>T2: 50.0% vs. 40.4% (p<0.001)</p> <p>T3: 28.2% vs. 19.7% (p<0.001)</p> <p>T4: 21.5% vs. 14.8% (p<0.001)</p>

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Abdollah, 2012 ¹² Retrospective Cohort Medium	Not reported	Not reported	

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Brossner, 2004 ¹³ Retrospective Cohort High	Austria and Italy Two centers 1998-2002	Patients undergoing radical cystectomy, American Society of Anesthesiologists grade 2 or 3	Not reported	A: (Italian Cohort): Cystoprostatectomy in men or pelvectomy in women, with "extended" lymphadenectomy, including the perivesical, hypogastric, obturator, external iliac, common iliac and aortal lymph nodes, into the region of the inferior mesenteric artery. B: (Australian cohort): Cystoprostatectomy in men or pelvectomy in women, with "minimal" lymphadenectomy, including perivesical lymph nodes and lymphatic tissue of the obturator fossa, confined laterally by the external iliac vein and medial by the obturator nerve.	30 days Unclear method of followup

Author, Year Study Name Study Design Risk of Bias	Number of Subjects Per Group	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Brossner, 2004 ¹³ Retrospective Cohort High	A: 46 B: 46	Age (mean): 66.3 vs. 68.2 years Male: Not reported Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage: pT1: 4 vs. 6; pT2-3a: 24 vs. 18; pT3b-4: 18 vs. 22; Node positive: 18 vs. 10 Grade: Not reported Functional Status: Not reported	Median operative duration (minutes): 330 vs. 227

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Brossner, 2004 ¹³ Retrospective Cohort High	Median ICU stay (days): 4.5 vs. 5.1, P-value Not reported Median hospital stay (days): 16.3 vs. 14.2, P-value Not reported Median blood units received during surgery: 0.8 vs. 1.15, P=0.37 Median blood units received within 30 days: 0.7 vs. 3.2, P=0.067 Complications within 30 days: Overall surgical complications: 20/46 vs. 17/46, P=0.08 Perioperative mortality: 4.3% (2/46) (pneumonia) vs. 2.2% (1/46) (pulmonary embolus), RR 0.50 (95% CI 0.047 to 5.32) Complications requiring surgery: 5/46 vs. 4/46, P=0.28 Cardiac arrhythmia: 5/46 vs. 3/46, P=0.16 Pulmonary embolus: 1/46 vs. 2/46 Pneumonia: 2/46 vs. 7/46, P=0.02 Prolonged ileus >6 days: 1/46 vs. 2/46 Hydronephrosis: 3/46 vs. 6/46 Pyelonephritis: 4/46 vs. 4/46 Acute renal failure: 1/46 vs. 0/46 Transient cerebrovascular accident: 3/46 vs. 1/46	Not reported	

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Brunocilla, 2013 ¹⁴ Retrospective Cohort Medium	Italy 1995-2011	Radical cystectomy for muscle-invasive or high-grade superficial bladder cancer with curative intent	Neoadjuvant or adjuvant chemotherapy and/or radiation; incomplete clinical, pathological, and followup data	<p>A: Limited template: Cystectomy including external and obturator lymph nodes; or no lymphadenectomy</p> <p>B: Standard template: Cystectomy including external, obturator, internal iliac, and 2 cm common iliac lymph nodes up to the cross with the ureters</p> <p>C: Extended template: Cystectomy including external, obturator, internal iliac, presacral, and complete common iliac lymph nodes up to the aortic bifurcation</p> <p>D: Super-extended template: Cystectomy including external, obturator, internal iliac, presacral, complete common iliac lymph nodes up to the aortic bifurcation, preaortic and precaval lymph nodes up to inferior mesenteric artery</p> <p>Selection of template was based on preference and skills of the surgeons</p>	Mean: 59.2±44.3 months

Author, Year Study Name Study Design Risk of Bias	Number of Subjects Per Group	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Brunocilla, 2013 ¹⁴ Retrospective Cohort Medium	A: 116 B: 94 C: 39 D: 23	<p>Reported for 0-14 lymph nodes removed (n=128) vs. ≥14 lymph nodes removed (n=154):</p> <p>Age (mean): 69.6±8.4 vs. 667.3±8.1; p=0.010</p> <p>Male: 82.8% vs. 83.1%</p> <p>Race: Not reported</p> <p>Smoking status: Not reported</p> <p>Recurrent bladder cancer: Not reported</p> <p>Stage: T0: 23/128 vs. 18/154 T1: 21/128 vs. 20/154 T2: 24/128 vs. 41/154 T3: 37/128 vs. 50/154 T4: 23/128 vs. 25/154</p> <p>Tumor Grade: G1-G2: 32/128 vs. 34/154 G3: 96/128 vs. 120/154</p> <p>Functional status: Not reported</p>	<p>Cancer-specific survival, hazard ratio (95%CI)</p> <p>Univariable: B vs. A: 0.828 (0.547-1.255) C vs. A: 0.350 (0.221-0.740) ≥14 lymph nodes removed vs. 0-14 lymph nodes removed: 0.576 (0.382-0.847)</p> <p>Multivariable: B vs. A: 0.986 (0.547-1.354) C vs. A: 0.455 (0.365-0.894) ≥14 lymph nodes removed vs. 0-14 lymph nodes removed: 0.556 (0.282-0.995)</p>

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Brunocilla, 2013 ¹⁴ Retrospective Cohort Medium	Not reported	Not reported	

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Dhar, 2008 ¹⁵ Retrospective cohort High	US and Switzerland Two centers 1987-2000	TCC of bladder (preoperative stage N0M0) who underwent curative intent radical cystectomy	Neoadjuvant treatment, positive pathological margins, stages pTa, pT1, and pT4 cancer	A (Switzerland cohort): Cystectomy with extended lymphadenectomy, with cephalad dissection extended to the crossing of the ureters with the common iliac arteries and removal of all tissue along the lateral and medial portion of internal iliac vessels. B: (US cohort): Cystectomy with limited lymphadenectomy, with boundaries of the pelvic sidewall between the genitofemoral and obturator nerves, and bifurcation of the iliac vessels to the circumflex iliac vein.	5 years A: Every 6 months for 2 years and annually thereafter. B: 3 and 6 months after surgery, 6-month intervals until 5 years and annually thereafter.

Author, Year Study Name Study Design Risk of Bias	Number of Subjects Per Group	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Dhar, 2008 ¹⁵ Retrospective cohort High	A: 322 B: 336	Age (median): 66.9 vs. 61.6 years, p<0.001 Male: 78% vs. 79% Race: Not reported Smoking status: Not reported Recurrent bladder cancer: Not reported Stage: Not reported Tumor grade: Not reported Functional status: Not reported	<p>A vs. B</p> <p><u>Lymph Nodes</u> Number of nodes examined, median (range): 12 (2-31) vs. 22 (10-43) Number of positive nodes, median (range): 1 (1-5) vs. 2 (1-26) Lymph node positive rate: overall, 13% vs. 26%; pT2, 15/200 vs. 24/150; pT3, 29/136 vs. 59/172</p> <p><u>5 year recurrence-free survival</u> (median followup: 25 vs. 40, p<0.001) pT2: 71% vs. 63%, p=0.10 pT3: 19% vs 49%, p<0.0001</p> <p><u>5 year overall survival</u> (median followup: 36 vs. 51, p<0.001) pT2: 64% vs. 61%, p=0.10 pT3: 22% vs. 42%, p=0.0002</p> <p><u>Progression:</u> local or systemic: 55% (184/336) vs. 40% (130/322) RR 0.74 (95% CI 0.63 to 0.87) Local progression (p for log-rank test):: pT2: 24% vs 44%, p<0.0001 pT3: 60% vs. 10%, p<0.0001 Systemic progression (includes those with both local and systemic progression): pT2: 14% vs. 27%, p=0.0048 pT3: 20% vs. 45%, p=0.0012</p>

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Dhar, 2008 ¹⁵ Retrospective cohort High	Not reported	Not reported	Numbers in table do not correspond to percentages reported in the paper. Percentages are presented here for RFS and OS. Should we do the same for progression. I am unclear as to what denominator was used when calculating p-values.

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Herr, 2002 ¹⁶ Retrospective cohort High	US Single center 1980-1990	Bilateral pelvic lymphadenectomy and radical cystectomy, pathological muscle invasive transitional cell carcinoma, followup greater than 10 years	Preoperative radiation, neoadjuvant or adjuvant chemotherapy	A: Radical cystectomy with standard lymphadenectomy, including the distal common iliac, external iliac, hypogastric, obturator, presacral and perivesical lymph nodes (n=Not reported) B: Cystectomy with limited lymphadenectomy, with obturator and perivesical lymph nodes removed en bloc with the bladder. (n=Not reported)	Minimum followup 10 years

Author, Year Study Name Study Design Risk of Bias	Number of Subjects Per Group	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Herr, 2002 ¹⁶ Retrospective cohort High	Not reported, Overall N=322	Age: Not reported Male: Not reported Race: Not reported Smoking status: Not reported Recurrent bladder cancer: Not reported Stage: 188 T2, 134 T2-T3 Tumor grade: Not reported Functional status: Not reported	<p>Local recurrence (uncertain followup): N0 patients: 5% (7/131) when 8 or more nodes, 24% (31/127) when 1-8 nodes, p=0.001; N+ patients, 9% (3/34) when 11 or more nodes, 30% (10/30) when 1-11 nodes, p=0.002</p> <p>5-year recurrence-free survival: Stage ≤T3a: 85% vs. 64%, p<0.02; Stage ≥T3b: 27% vs. 39%, p=0.87</p> <p>10-year survival N0 patients (n=258): 82% when 8 or more nodes, 63% when 4-7 nodes, 23% when 0-3 nodes, p=0.004. 59% (75/127) ≥ 8 vs. 18% (23/131) <8 lymph nodes</p> <p>N+ patients (n=64): 45% when > 14 nodes, 39% when 9-14 nodes, 16% when 1-8 nodes, p=0.02. 56% (19/34) ≥ 11 vs. 80% (24/30) for < 11 lymph nodes, p=0.004</p>

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Herr, 2002 ¹⁶ Retrospective cohort High	Not reported	Not reported	

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Herr, 2004 ¹⁷ Reanalysis of RCT Medium	US Multiple centers 1987-1998 Reanalysis of RCT	Muscle invasive bladder cancer, T2-T4a, N0, M0, candidate for radical cystectomy, SWOG performance status 0-1	Prior pelvic radiation	A: Cystectomy with standard lymphadenectomy (n=146), median 15 LN B: Cystectomy with limited lymphadenectomy (n=98), median 7 LN C: Cystectomy with no lymphadenectomy (n=24)	Minimum followup 5 years
Konety, 2003 ¹⁸ Retrospective cohort Medium	US Population based study (SEER data) 1988-1996	primary bladder cancer; subset with radical cystectomy with or without lymph node dissection	Not reported	Patients with bladder cancer who underwent cystectomy, number of lymph nodes examined: 0 (n=645), 1-3 (n=203), 4-6 (n=239), 7-9 (n=164), 10-14 (n=163), 15-19 (n=106), ≥20 (n=81), missing data.	Minimum 2 years; Median in surviving post-cystectomy patients: 63.5 months

Author, Year Study Name Study Design Risk of Bias	Number of Subjects Per Group	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Herr, 2004 ¹⁷ Reanalysis of RCT Medium	A: 146 B: 98 C: 24	Overall characteristics, not reported by treatment group: Age: 148/268 <65 years, 120/268 ≥ 65 years Male 81% (216/268) Race: Not reported Smoking status: Not reported Recurrent bladder cancer: Not reported Stage: 69% (184/268) T0-T2 31% (84/268) T3-T4 Tumor grade: Not reported Functional status: 100% SWOG 0 or 1	A vs. B vs. C Local Recurrence (no median followup reported): 7/146 (5%) vs. 22/98 (22%) vs. 12/24 (50%), p<0.0001 RR 0.21, 95% CI 0.09 to 0.48 ≥10 nodes removed vs. <10 nodes removed: 6% vs. 25%, p<0.0001, multivariate Cox proportional hazards model <10 nodes (HR 0.20, 95% CI 0.07 to 0.56) 5-year overall survival: 60% vs. 46% vs. 33%, p=0.01 ≥10 nodes removed vs. <10 nodes removed: 5-year overall survival: 61% vs. 44%, p=0.0007, multivariate Cox proportional hazards model <10 nodes HR 0.50, 95% CI 0.36 to 0.71 A vs. B Risk of mortality: 52% (59/146) vs. 64% (63/98), RR 0.94, 95% CI 0.68 to 1.04
Konety, 2003 ¹⁸ Retrospective cohort Medium	Cystectomy subset: N=1923 0 lymph nodes, n=645 ≥1 lymph node, n=956 unknown lymph nodes, n=322	Age: <35: 70 (3.6%); 35-44: 86 (4.5%); 45-54: 237 (12.3%); 55-64: 476 (24.8%); 65-74: 681 (35.4%); 75-84: 349 (18.2%); ≥85: 24 (1.3%) Male: 1265/1923 (65.8%) Race: White: 1698/1923 (93.6%); Black: 117/1923 (6.5%) Smoking Status: Not reported Recurrent bladder cancer: Not reported Stage: In situ or 1: 150 (12.9%); Stage 2: 249 (21.4%); Stage 3: 300 (25.8%); Stage 4: 465 (39.9%); missing: 759 Tumor grade: Not reported Functional status: Not reported	Risk of death by number of lymph nodes examined; Adjusted hazard ratio (95%CI); p-value: 0: 1 (reference) 1-3: 0.93 (0.69 to 1.27); 4-6: 0.52 (0.36 to 0.76); 7-9: 0.57 (0.39 to 0.81); 10-14: 0.38 (0.25 to 0.57); 15-19: 0.57 (0.39 to 0.85); ≥20: 0.48 (0.30 to 0.76); ≥4: 0.53 (0.36 to 0.76)

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Herr, 2004 ¹⁷ Reanalysis of RCT Medium	Not reported	SWOG	
Konety, 2003 ¹⁸ Retrospective cohort Medium	Not reported	Not reported	

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Leissner, 2000 ¹⁹ retrospective cohort High	Germany 1986-1997	Radical cystectomy with curative intent for pTis, pT1G3, pT2 to pT4 transitional cell carcinoma	previous pelvic lymphadenectomy or irradiation, preoperative chemotherapy for bladder cancer, pTa bladder cancer	Patients with bladder cancer who underwent cystectomy, number of lymph nodes examined: 1-5, 6-10, 11-15, 16-20, and >20	Minimum 2 years; Mean: 38.7 months
Poulsen, 1998 ²⁰ Retrospective cohort High	Denmark Single study 1990-1997	radical cystectomy with lymphadenectomy	pretreatment of bladder cancer	A: Radical cystectomy with extended lymphadenectomy, bounded proximally by bifurcation of the aorta, laterally by the genitofemoral nerve, distally by the circumflex iliac vein and Cloquet's lymph node and posteriorly by the internal iliac vessel, including the presacral nodes and obturator fossa B: Cystectomy with limited lymphadenectomy, bounded proximally by bifurcation of the common iliac vessels, while the lateral, distal and posterior boundaries were the same as for the extended dissection, including dissection of the obturator fossa.	4-month intervals for the first year, then annually.

Author, Year Study Name Study Design Risk of Bias	Number of Subjects Per Group	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Leissner, 2000 ¹⁹ retrospective cohort High	Per group: Not reported, Overall: 302	Age: 62.8 years Male: male: female ratio 4.5:1 Race: Not reported Smoking status: Not reported Recurrent bladder cancer: Not reported Stage of disease (for all patients with radical cystectomy): pTis: 15 (3.4%); pT1: 100 (22.4%); pT2a: 88 (19.7%); pT2b: 51 (11.4%); pT3: 146 (32.7%); pT4: 47 (10.5%) Tumor grade: Not reported Functional status: Not reported	≥16 nodes removed vs. ≤15 nodes removed : 5-year bladder cancer- specific survival: 65% vs. 51%, p<0.013 Local recurrence: 17% vs. 27%, p<0.01 Distant metastasis: 10.5% vs. 17%, p<0.01
Poulsen, 1998 ²⁰ Retrospective cohort High	A: n=126 B: n=68	Age, mean: 61.8 vs. 63.2 years Male: 102/126 vs. 55/68 Race: Not reported Smoking status: Not reported Recurrent bladder cancer: Not reported Stage: T0-Ta: 7.1% vs. 5.9%; Tis: 13.5% vs. 5.9%; T1: 12.7% vs. 25%; T2: 10.3% vs. 13.2%; T3a: 13.5% vs. 16.2%; T3b: 35.7% vs. 29.4%; T4a: 4.0% vs. 1.5%; T4b: 1.6% vs. 1.5%; prostate: 0.8% vs. 1.5%; adenocarcinoma: 0.8% vs. 0% Tumor grade: Not reported Functional status: Not reported	A vs. B: Median number of nodes removed: 25 (range 9-67) vs. 13 (range 6-30), p<0.0001 5-year recurrence-free survival: 62% vs. 56%, p=0.33 5-year risk of distant metastasis: 29% vs. 30%, p not reported 5-year risk of pelvic metastasis: 10% vs. 10%, p not reported 5-year recurrence-free survival: Stage ≤T3a: 85% vs. 64%, p<0.02; Stage ≥T3b: 27% vs. 39%, p=0.87 5-year survival: Stage ≤T3a,N0: 90% vs. 71%, p<0.02; Stage ≥T3b,N0: 38% vs. 67%, p=0.46

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Leissner, 2000 ¹⁹ retrospective cohort High	Inverse relationship between number of complications associated with the lymphadenectomy and the number of lymph nodes removed, data Not reported	Not reported	
Poulsen, 1998 ²⁰ Retrospective cohort High	Not reported	Mauritzen La Fontaine Foundation	

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Shirotake, 2010 ²¹ Retrospective cohort Medium	Japan Single center 1987-2008	refractory non-muscle-invasive or muscle-invasive bladder cancer	noncurative surgery, tumors of nonurothelial origin, unclear medical history	A: Cystectomy with lymphadenectomy B: Cystectomy without lymphadenectomy Neoadjuvant chemotherapy, n=16, mostly T3-4 Adjuvant chemotherapy, n=26, T3-4 or Node positive	3-month intervals for 2 years and every 6 months thereafter
Simone, 2013 ²² Retrospective cohort Medium	Italy Two centers 2002-2010	high-grade urothelial carcinoma	neoadjuvant treatment, salvage cystectomy	A: Cystectomy with extended lymphadenectomy, dissected nodes up to and, in some cases, above the aortic bifurcation including the presacral nodes B: Cystectomy with standard lymphadenectomy, dissected nodes with an upper boundary at the iliac bifurcation (not including presacral and common nodes)	followup method, Not reported

Author, Year Study Name Study Design Risk of Bias	Number of Subjects Per Group	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional)	Results
Shirotake, 2010 ²¹ Retrospective cohort Medium	A: 107 B: 62 (includes those without lymphadenectomy or unknown number of nodes removed)	Age, mean: 67.65 vs. 69.4 years Male: overall 127/169 Race: Not reported Smoking status: Not reported Recurrent bladder cancer: Not reported Stage: ≤T2: 52/107 vs. 34/62; T3-4: 55/107 vs. 28/62 Tumor grade: G1-2: 27/107 vs. 28/62; G3: 80/107 vs. 38/62 Functional status: Not reported	Node positive (N+) vs. Node negative (N-) vs. Nodes not removed or unknown (Nx) 5-year Cancer-specific survival: 40.8% vs. 72.3% vs. 73.5%; N+ vs. N-, p=0.0471, Nx vs. N-, p=0.846 ≥9 nodes removed vs. <9 nodes removed: 5-year Cancer-specific survival, node-positive and node negative patients: 84.3% vs. 52.7%, adjusted HR 3.48 (95%CI 1.50 to 9.31) Node negative patients: adjusted HR 6.94 (95% CI 1.88 to 38.21)
Simone, 2013 ²² Retrospective cohort Medium	A: 349 B: 584	Age, mean: 65.4 years vs. 66.9 years Male: 309/349 vs. 502/584 Race: Not reported Smoking status: Not reported Recurrent bladder cancer: Not reported Stage: T0, a, is, 1: 94/349 vs. 140/584; T2: 98/349 vs. 131/584; T3: 108/349 vs. 235/584; T4: 49/349 vs. 78/584 Tumor grade: Not reported Functional status: Not reported	Number of nodes removed, A vs. B, mean (SD): 32.7 (14.9) vs. 16.6 (11.8), p<0.001 Lymph node invasion found: 111/349 vs. 187/584, p=0.56 Bladder cancer specific survival: Adjusted HR 1.80 (95% CI 1.37 to 2.37)

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Shirotake, 2010 ²¹ Retrospective cohort Medium	Not reported	Not reported, Authors disclosed no COI	
Simone, 2013 ²² Retrospective cohort Medium	Not reported	Not reported, Authors disclosed no COI	No details on how patients were selected for the two procedures

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Zehnder, 2011 ²³ Retrospective cohort High	US and Switzerland Two centers 1985-2005	Radical cystectomy with lymphadenectomy with curative intent for T2-3, clinically N0M0 bladder cancer	Neoadjuvant treatment, positive soft tissue margins, T1 or T4 bladder cancer	<p>A (US cohort): Cystectomy with lymphadenectomy, pure intrapelvic template plus removal of lymphatic tissue along the common iliac vessels, the distal vena cava/aorta to the IMA takeoff and complete dissection of the presacral space from the bifurcation of the aorta into the sacral fossa.</p> <p>B (Switzerland cohort): Cystectomy with lymphadenectomy, pure intrapelvic template ended proximally at the mid-upper third of the common iliac vessels, included the presacral region medial to the internal iliac vessels but left tissue containing the hypogastric nerves located medial to the retracted ureters and inferior to the aortic bifurcation</p> <p>Both groups used pure intrapelvic template for lymphadenectomy, with boundaries of the genitofemoral nerve and the pelvic side wall laterally, the circumflex iliac vein and Cloquet's node distally, the obturator fossa with full exposure of the intrapelvic course of the obturator nerve and the internal iliac vessels posteriorly, and the tissue medial to these vessels.</p>	<p>A: 4-month intervals in year 1, 6-month intervals in year 2, annually thereafter; Median followup: 10.9 years</p> <p>B: 3, 6, 12 months postoperatively, annually thereafter; Median followup: 9.9 years</p>

Author, Year Study Name Study Design Risk of Bias	Number of Subjects Per Group	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Zehnder, 2011 ²³ Retrospective cohort High	A: 554 B: 405	Age, median: 67 vs. 67 years Male: 421/554 vs. 314/405 Race: Not reported Smoking status: Not reported Recurrent bladder cancer: Not reported Stage: T2: 253/554 vs. 169/554; T3: 301/554 vs. 236/405 Tumor grade: G3: 534/554 vs. 390/405 Functional status: Not reported	Pathologically Node-positive: 195/554 vs. 114/405 Recurrence: 38% (210/554) vs. 38% (154/405), RR 1.0 (95% CI 0.85 to 1.17) Recurrence-free survival: ~58% in each group (p=0.75) Overall survival: ~17% in WACH group (p=0.45)

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Zehnder, 2011 ²³ Retrospective cohort High	Not reported	Not reported	

CI, Confidence Intervals; COI, Conflict of interest;; G1, Grade 1; G2, Grade 2; G3, Grade 3; HR, Hazard Ratio; ICU, Intensive Care Unit; IMA, inferior mesenteric artery; M0, Metastasis stage 0; N, Nodes; N-, Node positive; N+, Node negative; N0, Node stage 0; NR, Not reported; Nx, Nodes not removed or unknown; OS, overall survival;pT1, Tumor stage 1 determined by pathology; pT2, Tumor stage 2 determined by pathology; pT3, Tumor stage 3 determined by pathology; pT4, Tumor stage 4 determined by pathology; pTa, Tumor stage a determined by pathology; pTis, Tumor stage *in situ* determined by pathology;RFS, Recurrence free survival; RR, relative risk; SD, Standard deviation; SEER, Surveillance, Epidemiology and End Results program; T0, Tumor stage 0; T1, Tumor stage 1; T2, Tumor stage 2; T3, Tumor stage 3; T3a, Tumor stage 3a; T3b, Tumor stage 3b; T4, Tumor stage 4; T4a, Tumor stage 4a; T4b, Tumor stage 4b; Ta, Tumor stage a; TCC, Transitional cell carcinoma; Tis, carcinoma in situ; USA, United States of America

Table E3. Key Question 3: Included studies

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Bono, 1997 ²⁴ Randomized controlled trial Medium	Italy Nine centers 1984-1987	T2-T4a, and histologically proven muscle-invasive TCC of bladder, at least 3 cm in diameter without clinical evidence of positive LN or distant metastases. Creatinine < 1.6 mg/dL, Normal hepatic and respiratory function.	Other histological subtypes of tumor including SCC; upper tract tumors; other cancers outside of bladder cancer; positive LNs or metastases; "important anemia", uncontrolled diabetes, severe cardiovascular disease, active uncontrolled infections. early death or surgical complications precluding chemotherapy.	A: Radical cystectomy with LN dissection + AC with cisplatinum 70 mg/m ² day 1, and methotrexate 40 mg/m ² days 8 and 15 every 21 days for 4 cycles starting 21- 28 days after surgery (n=35 for pN0 and n= 31 for pN+, total n=66) B: Radical cystectomy with LN dissection (n=48) **pN0 patients were randomized into the groups A or B; pN+ patients were assigned to group A**	Mean: 69.12 months. Method: Every 3 years for 2 years with blood work, chest X-ray, abdominal ultrasound, clinical exam. CT scan of abdomen and bone scan every 6 months for 2 years.

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Bono, 1997 ²⁴ Randomized controlled trial Medium	Screened: Not reported Randomized: 125 Postrandomization exclusions: 5 total Lost to followup: 2 (excluded from analysis) 4 excluded from analysis for "protocol violation" Total 114/125 were analyzed.	Age (mean): 62 vs. 62, 60 in pN+ group Male: 104/114, # in each group Not reported Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Tumor stage: pT2N0: 20% (7/35) vs 27% (13/48), pT2N+: 10% (3/31) pT3aN0: 43% (15/35) vs. 39% (18/48), pT3aN+: 32% (10/31) pT3b-4aN0: 37% (13/35) vs. 35% (17/48), pT3b-4aN+: 58% (18/31) Nodal status: pN+ 22% (31/114)	pN0 A vs. B Progression: 51% (18/35) vs. 56% (27/48) No progression: 49% (17/35) vs. 44% (21/48), RR 0.91 95% CI 0.61-1.37 Survival: 49% (17/35) vs. 38% (18/48) Died of disease: 46% (16/35) vs. 52% (25/48), RR 0.88 95% CI 0.56-1.38 Death, any cause: 51% (18/35) vs. 63% (30/48) pN+ from group A Progression: 58% (18/31) No progression: 42% (13/31) Survival: 32% (10/31) Died of disease: 58% (18/31) Death, any cause: 68% (21/31)

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Bono, 1997 ²⁴ Randomized controlled trial Medium	Chemotherapy toxicity grade 3 or greater: nausea/vomiting: 9/66 mucositis: 13/66 renal toxicity: 11/66 hematologic toxicity (not specified): 1/66 other (not specified): 1/66 Discontinuation of chemotherapy 10.6% (7/66)		chemotherapy discontinued prior to completion of 4 cycles in 4/31 in pN+ group and 3/35 in pN0 group.

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Cognetti, 2012 ²⁵ Randomized controlled trial Medium	Italy 45 centers 2001-2007	pT2G3 (N0-2), pT3-4(N0-2) any G, pN1-2 any T or G Radical cystectomy with no residual tumor Minimum of 10 LNs dissected Eastern Cooperative Oncology Group performance status 0-2 Age <= 75 "Adequate bone marrow reserve" "good renal (Cr <= 1.25 micromole/L, CrCl >= 60 mL/min) and liver function"	Prior neoadjuvant chemotherapy or radiotherapy	A: Cystectomy +/- LN dissection + AC every 28 days for 4 cycles with gemcitabine 1000 mg/m ² days 1,8, and 15 plus cisplatin 70 mg/m ² on day 2 or day 15 (GC) (total n=97; cisplatin day 2 (A1), n=43, cisplatin day 15 (A2), n=46) B: Cystectomy +/- LN dissection + treatment on relapse (n=86)	Median: 35 months Method: Every 3 months for 2 years, then every 6 months for 3 years, then yearly thereafter. CT scan every 6 months for 3 years then yearly thereafter.

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Cognetti, 2012 ²⁵ Randomized controlled trial Medium	Screened: Not reported Randomized: 194 (102 vs. 92) Postrandomization exclusions: Not reported Lost: 11 (5 vs. 6) 8/97 patients randomized to arm A (AC) refused initiation of chemotherapy (unsure whether A1 or A2)	Age (mean): 64 vs. 63 Male: 93% (90/97) vs. 87% (75/86) Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage of disease: pT1: 3% (3/97) vs. 1% (1/86) pT2: 30% (29/97) vs. 22% (19/86) pT3: 47% (46/97) vs. 57% (49/86) pT4: 9% (9/97) vs. 20% (17/86) Grade of tumor: G2: 3% (3/97) vs. 5% (4/86) G3: 93% (90/97) vs. 93% (80/86) Gx or missing: 4% (4/97) vs. 2% (17/86) LN status: pN0: 48% (47/97) vs. 57% (49/86) pN1: 21% (20/97) vs. 22% (19/86) pN2: 31% (30/97) vs. 21% (18/86) Functional status: ECOG PS 0: 81% (79/97) vs. 71% (61/86) ECOG PS 1-2: 17% (16/97) vs. 24% (21/86) ECOG PS missing: 2% (2/97) vs. 5% (4/86) Tumor type: TCC: 98% vs. 99%; other: 2% vs. 1%	A vs. B Overall recurrence: 44% (43/97) vs. 47% (40/86), RR 0.95 95% CI 0.69-1.31 5 year disease-free survival: 42% vs. 37%, p=0.70, HR 1.08, 95% CI 0.73-1.59 5-year disease free survival in node-negative patients: 58% vs. 60%, p=0.97 5 year disease free survival in node-positive patients: 19% vs. 19%, p=0.80 5 year overall survival: 43% vs. 54%, p=0.24 5 year overall survival A1 vs. A2: 47% vs. 40%, p=0.88 5-year overall survival lymph node negative disease: 65% vs. 73%, p=0.65 5-year overall survival lymph node Positive disease: 26% vs. 28% p=0.71 HR for mortality A vs. B: HR = 1.29, CI 0.84-1.99, p=0.24 Independent of treatment arm, mortality hazard was significantly associated with nodal status and T stage: pN1 vs. pN0: HR =2.42, CI 1.38-4.26 pN2 vs. pN0: HR =4.33, CI 2.6-7.2 pT3 vs pT1-2 HR= 2.01, CI 1.14-3.56 pT4 vs. pT1-2 HR =2.57, CI 1.34-4.92

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Cognetti, 2012 ²⁵ Randomized controlled trial Medium	<p>Toxic effect AC (all %/ grade 3/4 %) groups A1 vs. A2</p> <p>Leukopenia: 65%/9% vs. 66%/15%</p> <p>neutropenia: 68%/21% vs. 70%/35%</p> <p>anemia: 63%/5% vs. 55%/6%</p> <p>thrombocytopenia: 49%/26% vs. 45%/4% (p= 0.006 for grade 3/4 A1 vs. A2)</p> <p>Fever: 39% vs. 28%</p> <p>nausea and vomiting: 48%/9% vs. 54% /2%</p> <p>cephalea 7% vs. 4% diarrhea: 19%/2% vs. 17%</p> <p>stomatitis/mucositis: 21% vs. 11%</p> <p>decrease in Creatinine clearance: 14%/2%vs. 9%</p> <p>proteinuria: 14% vs. 4%</p> <p>alopecia: 28% vs. 23%</p> <p>infection 21%/5% vs. 11% asthenia: 65%/5% vs. 46%/2%</p> <p>Dose reduction/ early stop of therapy A1 vs. A2: 67%/39% vs. 72%/26%</p>	Italian Minister of Health	<p>Study underpowered Group B: 23/40 relapses received some kind of chemotherapy, 3/40 received surgery or RT, 5/40 supportive care, 9/40 missing data.</p> <p>Group A: 21/43 relapses received other chemotherapy, 5/43 surgery or RT, 11/43 supportive care, 6/43 missing data.</p> <p>Group A: 92% completed first cycle AC, 78% 2 cycles, 74% 3 cycles, 62% all 4 cycles.</p>

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Dash, 2008 ²⁶ Retrospective cohort High	United States Single Center 2000-2006	Muscle-invasive bladder cancer, T2-T4a, N0; received NAC with Gemcitabine/Cisplatin or MVAC	Clinical indication of metastatic disease, including adenopathy >2cm, nontransitional cell carcinoma, T4b disease	A: NAC: Gemcitabine + Cisplatin, predominately given as: "Single dose" cisplatin administration consisted of 4 cycles, with 21 day intervals of cisplatin 70 mg/m ² and gemcitabine 1000 mg/m ² on day 1, and gemcitabine 1000 mg/m ² on day 8. "Split-dose" cisplatin administration consisted of 4 cycles, with 21 day intervals of cisplatin 35 mg/m ² and gemcitabine 1000 mg/m ² on days 1 and 8. B: NAC: Methotrexate, vinblastine, doxorubicin and cisplatin given as 4 cycles at 28-day intervals. Doses were not reported.	Overall duration of followup: Not reported Median followup for survivors: Gemcitabine/ Cisplatin: 24.2 months; MVAC: 48.1 months Followup method: Not reported

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Dash, 2008 ²⁶ Retrospective cohort High	Screened: A: >700; B: Not reported Randomized: NA Analyzed: A: 42; B: 54	A vs. B Age (median): 64 vs. 63 Male: 76% (32/42) vs. 8% (43/54) Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage of disease: T2: 45% (19/42) vs. 59% (32/54) T3: 45% (19/42) vs. 28% (15/54) T4: 10% (4/42) vs. 13% (7/54) Tumor grade: Not reported Functional status: Not reported	GC results only. No statistical comparisons of A vs. B. Downstaging tumor at cystectomy: Overall: pT0: 26% (95%CI: 14-42); <pT2: 36% (95%CI: 21-52) <pT2, standard-dose cisplatin: 13/27; <pT2, split-dose cisplatin: 2/15; No statistical comparison, RR 0.60 95% CI 0.40-0.91

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Dash, 2008 ²⁶ Retrospective cohort High	Hospitalized during treatment: 9/42	Not reported	Retrospective cohort, does not report comparisons between MVAC and GC

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Fairey, 2013 ²⁷ Retrospective cohort High	United States Single Center 1985-2011	Underwent cystectomy with super-extended pelvic LN dissection for stage T2- T4N0M0 urothelial cancer of the bladder treated with NAC with GC or MVAC	Received non-GC or non- MVAC NAC, or did not receive NAC Nonurothelial bladder cancer Nonprimary bladder cancer Clinical stage other than T2- T4N0M0	A. NAC, 4 cycles of GC at 21-day intervals over 12 weeks + cystectomy with super-extended pelvic LN dissection (n= 58) B. NAC, 4 cycles of M-VAC at 28-day intervals over 16 weeks + cystectomy with super-extended pelvic LN dissection (n= 58)	Median followup 2.1 years for GC group and 7.4 years for M-VAC group. Method: Every 4 months in year 1, every 6 months in year 2 and annually thereafter. Physical exam and routine blood work was done at each visit. Radiologic evaluation was done at 4 months Postoperatively and annually thereafter unless otherwise clinically indicated.

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Fairey, 2013 ²⁷ Retrospective cohort High	Screened: 2,234 Randomized: NA Postrandomization exclusions: NA Lost to followup: Not reported Analyzed: 116	Age (median): 67 vs. 63 Male: 76% (44/58) vs. 79% (46/58) Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage of disease: T2: 48% (28/58) vs. 48% (28/58) T3: 31% (18/58) vs. 24% (14/58) T4: 20% (12/58) vs. 28% (16/58) Functional status: Not reported	A vs. B Complete response rate (CRR): 27.3% (12/58) vs. 17.1% (6/58), p=0.419 Partial response rate (PRR): 45.5% (20/58) vs. 37.1% (13/58), p=0.498 No statistically significant difference in cumulative incidence of recurrence between the two groups, HR 0.60 (95%CI 0.34-1.03) Cumulative incidence of recurrence in pTany N1-3M0 patients with median time to recurrence: 4 months vs. 7.4 months, p=0.019 Overall mortality: no statistically significant difference, HR 0.90 (95% CI 0.52-1.56) Multivariable analysis showed no independent association between type of NAC and overall mortality or recurrence. HR for OM 1.00 vs. 1.11 (95% CI 0.64-1.91), p=0.721. HR for recurrence 1.00 vs. 1.68 (0.97-2.91), p=0.065. Multivariable analysis showed no independent association between age and overall mortality or recurrence.

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Fairey, 2013 ²⁷ Retrospective cohort High	Not reported	Not reported	Choice of therapy determined by medical oncologist and patient. Time between end of NAC and surgery (days) 54 (GC) vs. 62 (MVAC), p=0.075. Years of treatment: 1985-1999: 7% (4/58) vs. 67% (39/58) 2000-2011: 93% (54/58) vs. 33% (19/58), p< 0.001.

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Freiha, 1996 ²⁸ Randomized controlled trial Medium	USA Single Center 1986- 1993	Stage T3b-4N0/+M0, TCC of bladder who underwent radical cystectomy with LN dissection	Not reported	A: Radical cystectomy with LN dissection + AC, 4 cycles every 21 days with methotrexate 30 mg/m ² , and vinblastine 4 mg/m ² day 1 and 8, 100 mg/m ² cisplatin on day 2 (CMV) (n= 25) B: Radical cystectomy with LN dissection (n=25)	Mean, median: 57 and 62 months Method: Every 3 months for year 1, every 4 months for year 2 and every 6 months thereafter. Physical exam, blood studies, chest X-ray. Urine cytology every 6 months. CT at months 3,6,9,15,24

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Freiha, 1996 ²⁸ Randomized controlled trial Medium	Screened: 56 Randomized: 50 (27 vs. 28) Postrandomization exclusions: 5 (2 vs. 3) Lost to followup: Not reported	Age (mean): 59 vs. 64 Male: 92% (23/25) vs. 88% (22/25) Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage of disease: T3bN0: 16% (4/25) vs. 28% (7/25) T4N0: 12% (3/25) vs. 4% (1/25) pN+, 1 node: 16% (4/25) vs. 40% (10/25) pN+, 2 nodes: 20% (5/25) vs. 12% (3/25) pN+, 3 nodes: 16% (4/25) vs. 8% (2/25) pN+, 4+ nodes: 20% (5/25) vs. 8% (2/25) Grade: G2: 4% (1/25) vs. 0% (0/25) G3: 12% (3/25) vs. 28% (7/25) G4: 84% (21/25) vs. 72% (18/25) Functional status: Not reported	A vs. B Recurrence: 52% (13/25) vs. 76% (19/25), RR 0.68 95% CI 0.44-1.06 with mean / median interval to recurrence: 17.5 / 16.2 months (4-37 months) vs. 11.5 / 10.1 months (2-34 months), p=0.01, log rank test **6/19 recurrences in group B, 6 received CMV therapy** Survival: 52% (13/25) vs 32% (8/25), p=0.32, log rank test, RR 0.71 95% CI 0.42-1.15 Mean and median survival time 56 and 63 months vs. 42 and 36 months Survival according to nodal status N0: 71 % (5/7) vs. 25% (2/8), RR 0.38 95% CI 0.11-1.31 N+: 44% (8/18) vs. 35% (6/17) <= N3: 46% (6/13) vs. 40% (6/15) > N3: 40% (2/5) vs. 0% (0/2)

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Freiha, 1996 ²⁸ Randomized controlled trial Medium	1/25 death from neutropenia and sepsis after cycle 1 of CMV 2/50 deaths from MI after cystectomy (at 40 days and 72 months - not sure from which group) 2/25 in group A episodes of neutropenia and fever requiring hospitalization 8/25 Group A neutropenia that delayed chemotherapy 1/50 Group A heart failure that recovered (? group) 3/25 Group A decrease in GFR requiring modification to chem dosing (2 of 3 recovered fully, 1 had creatinine of 2.6 after last cycle of chemotherapy) 8/25 Group A GI toxicity (2 bleeding, 2 mucositis, 4 nausea and vomiting) 2/25 Group DVT (1 leading to nonfatal PE) (? group)	Not reported	Patients randomized to observation (group B) that showed evidence of recurrence were treated with CMV chemotherapy. One patient received 5-fluorouracil with CMV

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Grossman, 2003 ²⁹ Randomized controlled trial Medium	USA 126 centers 1987-1998	T2-4aN0M0 who were candidates for radical cystectomy, "adequate renal, hepatic, and hematologic function", SWOG performance status 0- 1	Prior pelvic irradiation	A: Neoadjuvant chemotherapy (NAC), three 28-day cycles with methotrexate 30 mg/m ² on days 1, 15 and 22; vinblastine 3 mg/m ² on days 2, 15 and 22; doxorubicin 30 mg/m ² and cisplatin 70 mg/m ² on day 2 (M-VAC) + cystectomy with LN dissection (n=153) B: Cystectomy with LN dissection (n=154)	Median: 8.7 years vs. 8.4 years

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Grossman, 2003 ²⁹ Randomized controlled trial Medium	Screened: Not reported Randomized: 317 (158 vs 159) Postrandomization exclusions: 10 (5 vs. 5) Lost to followup: Not reported	Age (mean): 63 vs. 63 Male: 83% (127/153) vs. 81% (124/154) Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage of disease: T2: 40% (61/153) vs 40% (61/154) T3/T4a: 60% (92/153) vs 60% (93/154) Functional status: Not reported	A vs. B Downstaging tumor (pT0 at time of surgery): 38% (48/126) vs. 12% (15/121), p=<0.001 Deaths: 59% (90/153) vs. 65% (100/154) over followup period with Median survival (months), unstratified: 77 vs. 46, p=0.05 log rank test Survival at 5 years 57% vs. 43%, p=0.06 Median survival (months) stratified for age: age <65: 104 vs. 67, age >= 65: 61 vs 30 p=0.05, log rank test Median survival (months) stratified for tumor stage: T2: 105 vs. 75; T3/T4a: 65 vs 24, p=0.05, log rank test Cystectomy only group had a 33% increased risk of death compared to the MVAC/cystectomy group (stratified analysis) Overall mortality 59% vs. 65%, HR 0.75, 95% CI 0.57 to 1.00 Disease-specific mortality 35% vs. 50%, HR 0.60, 95% CI 0.41 to 0.82, p=0.002

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Grossman, 2003 ²⁹ Randomized controlled trial Medium	Group A: 35/150 and 50/150 had grade 3 and 4 granulocytopenia, respectively. 7/150, grade 3 thrombocytopenia. 9/150 grade 3 anemia 30/150 grade 3 GI toxicity (nausea, vomiting, diarrhea, constipation, stomatitis)	Cooperative Agreements with the National Cancer Institute, Department of Health and Human Services.	Planned cystectomy in 82% (27/153) group A, 81% (30/154) group B. 9 patients (2 vs. 7) had cystectomy outside the study. 3/153 decline chemotherapy in group A. 87% of group A received at least one full cycle of MVAC.

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
International Collaboration of Trialists, 1999 ¹ Randomized controlled trial Medium	20 countries 106 centers 1989-1995	T2G3--T4a TCC of bladder or mixed cell types TCC / squamous or glandular metaplasia. Histologic confirmation of muscle invasion. WBC > 3.5 x10 ⁹ , platelets > 100x10 ⁹	Tumors > 7cm by imaging or bimanual palpation, nodal metastases, GFR < 60 mL/min for first 448 patients, changed to GFR < 50 mL/min thereafter Prior systemic chemotherapy or radiation. Any other prior cancer	A: NAC every 21 days for 3 cycles with methotrexate 30 mg/m ² , vinblastine 4 mg/m ² on day 1 and day 8; cisplatin 100 mg/m ² on day 2 (CMV) + cystectomy +/- LN dissection or radiotherapy (RT) or RT and cystectomy (n=491) B: cystectomy with LN dissection or radiotherapy or RT and cystectomy. (n=485) **Cystectomy as salvage therapy for recurrence in RT group. **local radical treatment chosen before randomization for each patient **radiotherapy protocol permitted a range of radiation dose-schedules. RT prior to cystectomy was 4 Gy x 5 days.	Median: 4 years. Method: Option for group A: cystoscopy, bimanual palpation, TURBT after 3 cycles of chemotherapy before radiotherapy or cystectomy to assess for response.

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
International Collaboration of Trialists, 1999 ¹ Randomized controlled trial Medium	Screened: Not reported Randomized: 976 (491 vs. 485) Postrandomization exclusions: Not reported Lost to followup: 6 (4 vs. 2)	Age (median): 64 vs. 64 Male: 433/491 (88%) vs. 430/485 (89%) Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage of disease: T2: 34% (169/491) vs. 34% (165/485) T3: 58% (285/491) vs. 58% (282/485) T4: 85 (37/491) vs. 8% (38/485) Tumor grade: G1: 1% (6/491) vs. 0.2% (2/485) G2: 11% (52/491) vs. 13% (61/485) G3: 885 (433/491) vs. 87% (421/485) unknown grade: 0% vs 0.2% (1/485) Functional status: WHO 0: 69% (340/491) vs. 69% (337/485) WHO 1: 26% (130/491) vs. 26% (128/485) WHO 2: 4% (20/491) vs. 4% (19/485) WHO 3: 0.2% (1/491) vs. 0.2% (1/485) Nodal status: N0: 67% (327/491) vs. 63% (307/485) NX: 33% (164/491) vs. 37% (178/485) Radical treatment: Radiotherapy: 42% (207/491) vs. 43% (208/485) Cystectomy: 50% (246/401) vs. 49% (239/485) Radiotherapy + cystectomy: 8% (38/491) vs. 8% (38/485)	A vs. B Locoregional disease free survival: 47% vs. 42%, HR 0.87 (0.73-1.02, p=0.087, Mantel-Cox (Mantel-Cox) log rank test) Median locoregional disease free survival (months): 23.5 vs. 20 No evidence of a difference between treatments for locoregional control, HR 0.97 (0.79-1.19, p=0.738 Mantel-Cox log rank) Metastasis free survival: 45% vs. 53%, HR 0.79 (0.66-0.93, p=0.007, Mantel-Cox log rank test) Median metastasis free survival (months): 32 vs. 25 Disease free survival: 46% vs. 39%, HR 0.82 (0.70-0.97, p=0.019, Mantel-Cox log rank test) Median disease free survival (months): 20 vs. 16.5 Deaths: 229/491 vs. 256/485 Survival: HR 0.85 (95% CI 0.71-1.02, p=0.075, Mantel-Cox log rank test) Median survival (months): 44 vs 37.5 Overall 3 year survival: 55.5% vs. 50% (95% CI for difference -0.5-11.0) No significant interaction with age (p=0.38), sex (p=0.39), WHO performance status (p=0.94). Renal function the interaction was significant (p=0.024) with chemotherapy more effective with increased GFR No significant interaction with age (p=0.38), sex (p=0.39), WHO performance status (p=0.94). Renal function the interaction was significant (p=0.024) with chemotherapy more effective with increased GFR **No restriction of salvage therapy which was given to 36% (347/976). 11% (37/347) received CMV, 15% (51/347) received other chemotherapy, total 25%, 88/347 received additional chemotherapy (21 vs 67). 20% (68/347) received radiotherapy, 18% (61/347) had salvage cystectomy; 37 % (130/347) patients underwent other procedures including intravesical chemotherapy.

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
International Collaboration of Trialists, 1999 ¹ Randomized controlled trial Medium	5/491 group A died of toxic effects of chemotherapy (mortality 1%) WHO grade 3-4: leukopenia 16% thrombocytopenia 6.5% neutropenic fever 10% 4 patients did not received planned cystectomy due to chemotherapy toxic effects 18 (6 vs. 12) deaths were attributable to cystectomy (mortality 3.7%) 10.5% Postop wound infections (20 vs. 31)	Not reported	99/491 in group A did not receive all 3 cycles of chemotherapy; 28/99 received no chemotherapy. 76/561 patients did not receive planned cystectomy; 95/415 (23%) did not receive full planned radiotherapy treatment. 159 (32.4%) underwent cystoscopy after chemotherapy; complete response confirmed in 71/159 (44.7%).

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
International Collaboration of Trialists, 2011 ³⁰ Randomized controlled trial Medium	20 countries 106 centers 1989-1995	Histologically proven muscle- invasive urothelial cell carcinoma T2-T4a, GFR > 50 mL/min/1.73 square meters.	Not reported	A: NAC every 21 days for 3 cycles methotrexate 30 mg/m ² and vinblastine 4 mg/m ² on day 1 and 8, cisplatin 100 mg/m ² day 2 (CMV) + radiation therapy (RT), cystectomy or RT and cystectomy (n=491) B: Radiation therapy (RT), cystectomy or RT and cystectomy (n=485) The choice of definitive treatments was based on patient and physician choice, not randomly assigned.	Median: 8 years
Kitamura, 2014 ³¹ Randomized controlled trial Medium	Japan 28 centers 2003-2009	T2-T4aN0M0 bladder cancer within 8 weeks from TURBT, no prior or concomitant urothelial carcinoma, prior chemotherapy or radiation therapy, 25 to 75 years of age, ECOG performance stages 0-1	Hematological, renal, or hepatic test abnormalities	A: NAC, 2 cycles 28 days apart with methotrexate 30 mg/m ² on days 1, 15, and 22, vinblastine 3 mg/m ² on days 2, 15, and 22, doxorubicin 30 mg/m ² on day 2, and cisplatin 70 mg/m ² on day 2 (n=64) + radical cystectomy B: Cystectomy with LN dissection including the external iliac, internal iliac, and obturator nodes (n=66)	Median: 55 months

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
International Collaboration of Trialists, 2011 ³⁰ Randomized controlled trial Medium	Screened: Not reported Randomized: 976 (491 vs. 485) Postrandomization exclusions: Not reported Lost to followup: 6 (4 vs. 2)	No per group numbers listed Age (mean): 64 Male: 863 (88%) Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage: T2: 334 (34%) T3: 567 (58%) T4a: 75 (8%) Functional Status: WHO 0-3 (most 0-1) Local definitive treatment: RT: 415/976, 43% (193 vs. 210) Cystectomy: 485/976, 50% (216 vs. 212) RT + cystectomy: 76/976 (8%)	A vs. B (cystectomy patients only) Locoregional recurrence: 40% (84/212) vs 39% (84/216) Locoregional disease-free survival 55% (119/216) vs. 65% (137/212), HR 0.74 (95% CI 0.58-0.95, p=0.019) Overall survival in patients: HR 0.74 (CI 0.57-0.96) p=0.022 No interaction related to stage of disease (p=0.35) or nodal status (p=0.96). G3 cancers were associated with greater benefit than G1/G2 cancers (p=0.003 for interaction). Interaction for tumor size close to but did not reach statistical significance (p=0.06)
Kitamura, 2014 ³¹ Randomized controlled trial Medium	Screened: Not reported Randomized: 130 (64 vs. 66) Postrandomization exclusions: 6 (5 vs. 1) Lost to followup: Not reported	Age (median): 63 vs. 63 Male: 89% vs. 91% Race: Not reported Smoker: Not reported Recurrent bladder cancer: None Stage: T2: 55% (35/64) vs. 53% (35/66) T3: 42% (27/64) vs. 42% (28/66) T4a: 3.1% (2/64) vs. 4.5% (3/66)	A vs. B Mortality: HR 0.65 (95% CI 0.19-2.18) Overall survival at 5 years: 72% vs. 62% Survival interval (median, months): 102 vs. 82 Disease progression at 5 years: 36% (23/64) vs. 45% (29/64), HR 0.64 (95% CI 0.37-1.11) Progression-free survival at 5 years: 68% vs. 56% Progression-free survival interval (median, months): 99 vs. 78 No differences in estimates based on age, tumor stage, papillary vs. nonpapillary, solitary vs. multiple, tumor size, tumor grade

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
International Collaboration of Trialists, 2011 ³⁰ Randomized controlled trial Medium	5/491 patients who received CMV died from toxic effects during treatment (mortality rate, 1%) In CMV group WHO grade 3-4 leukopenia, thrombocytopenia and neutropenic fever occurred in 16%, 6.5%, and 10% of patients respectively No grade 3 or 4 renal toxic events occurred, but 26% of those in CMV arm required dose decreases or dose delays because impaired renal function	Not reported	**The choice of definitive treatment was based on patient and physician choice, NOT randomly assigned**
Kitamura, 2014 ³¹ Randomized controlled trial Medium	A vs. B Intraoperative hypotension: 39% vs. 29% (p=0.26) Intraoperative venous/arterial injury: 11.9% vs. 9.2% (p=0.77) Anastomotic leak: 12.1% vs. 1.5% (p=0.03) Lymph leakage: 1.7% vs. 12.3% (p=0.04) Renal dysfunction: 69% vs. 72% (p=0.70) Grade 3-4 adverse events in patients undergoing NAC: 1.8% fatigue, 29% appetite loss, 5.4% constipation, 21% nausea, 1.8% stomatitis, 3.6% vomiting, 17.9% febrile neutropenia, 87.3% neutropenia, 5.4% thrombocytopenia, 14.3% anemia, 5.4% hyponatremia	Japanese government funding	Study failed to meet recruitment goal and stopped early due to insufficient power to reach definitive conclusion

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
<p>Malmstrom, 1996³² Randomized controlled trial Medium</p> <p>Rintala, 1993³³</p>	<p>Finland, Norway, Sweden 36 centers 1985-1989</p>	<p>T1G3-T4aNXM0 bladder cancer</p>	<p>Prior radiation therapy or systemic chemotherapy. Prior or current other malignancy</p>	<p>A: NAC, 2 cycles separated by 3 weeks with cisplatin 70 mg/m² and doxorubicin 30 mg/m² + RT + cystectomy with LN dissection (n=151)</p> <p>B: RT and cystectomy with LN dissection (n=160)</p>	<p>Malmstrom: Minimum of 5 years</p> <p>Rintala 1993: Mean 18 months for all (1-74) and 47 months for those still alive (21-75). 4 month intervals x 2 years, then every 6 months x 1 year, then yearly (no mention of what was done at followup).</p>

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Malmstrom, 1996 ³² Randomized controlled trial Medium Rintala, 1993 ³³	Screened: Not reported Randomized: 325 (157 vs. 168) Postrandomization exclusions: 14 (6 vs. 8) Lost to followup: 2 total	Age (mean): Not reported Male: 82% (124/151) vs. 76% (122/160) Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage of disease: T1G3: 18% (27/151) vs. 19% (31/160) T2: 34% (52/151) vs. 40% (64/160) T3: 46% (69/151) vs. 34% (55/160) T4a: 2% (3/151) vs. 6% (10/160) Functional status: WHO 0: 74% (111/151) vs. 76%(121/160) WHO 1-2: 26% (40/151) vs. 24% (39/160)	Malmstrom: A vs. B Recurrence in those patients with no signs of cancer after cystectomy: total 71/249 (31 vs. 40, RR0.82 (95% CI 0.54-1.24) with median interval to relapse 23 months vs. 14 months, p=0.42) Overall survival at 5 years: 59% vs. 51%, p=0.10, log rank test Cancer specific survival at 5 years: 64% vs. 54%, p=0.07, log rank test Overall survival at 5 years for 266 patients undergoing cystectomy/ resection: 65% vs. 58%, no p value given Cancer specific survival at 5 years for 266 patients undergoing cystectomy/ resection: 71% vs. 62%, no p-value given Relative risk of death, adjusted for tumor stage: RR= 0.69 (95% CI 0.49-0.98) 5 year survival by age Patients < 60 years (N=75): 61% vs. 49%, p=0.21 Patients ≥ 60 years (N=236): 58% vs. 51%, p=0.21 Cancer specific survival at 5 years by tumor grade: T1: 77% vs. 71%, not statistically significant T2 58% vs. 55%, not statistically significant T3-T4a: 52% (n=72) v s. 37% (n=65), p=0.03, log rank test Rintala: Survival, patients with T2-T4a, according to downstaging, p0-1 vs. p2 (n=213), no specific number given but in favor of p0-1, p=0.0005 Downstaging of tumors at time of surgery pT1G3 tumors pretreatment --> pT0, pTis, pT1: 20/27 vs. 22/31 (p= 0.002, chi-squared test) T2-T4a tumors pretreatment--> pTis/pTa/pT1: 41/124 vs. 32/129 (p = 0.42, chi-squared test)

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Malmstrom, 1996 ³² Randomized controlled trial Medium Rintala, 1993 ³³	6 deaths (2 vs. 4) within 1 month after cystectomy 16 wound dehiscence (6 vs. 10) 17 small bowel obstruction (13 vs. 4) 8 pelvic abscess (4 vs. 4) 7 thromboembolic events (3 vs. 4) 6 with sepsis (3 vs. 3) 10 urine leakages (6 vs. 4) 32 "other" (not specified) (13 vs. 19)	Not reported	11% T2-T4a tumors with no histologic proof of muscle invasion; Deviations from scheduled surgery: 21 vs. 26 (2 partial bladder resection, 30 laparotomy only, 15 no laparotomy). No chemotherapy in 10, only 1 cycle in 8 and > 25% reduction cisplatin in 4 and no radiotherapy 8.

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Matsubara, 2012 ³⁴ Retrospective cohort High	Japan Single center 2005-2010	T2-4, N0-2, M0 bladder cancer with confirmed MIBC by TURBT	Clinical stage < T2, distant metastasis, upper tract carcinoma, patients receiving other chemotherapeutic regimens or a partial cystectomy (organ-sparing surgery)	A: NAC, 4 cycles at 4 week intervals with gemcitabine 1000 mg/m ² and cisplatin 70 mg/m ² + cystectomy with LN dissection (n=25) B. Cystectomy with LN dissection + AC, 4 cycles at 4 week intervals with gemcitabine 1000 mg/m ² and cisplatin 70 mg/m ² (n=17)	Median: 28.6 months
Millikan, 2001 ³⁵ RCT Medium	United States Single Center 1986-1998	Invasive "high risk" urothelial cancer with lymphovascular invasion on a transurethral biopsy, clinically extravesical disease as demonstrated by a three-dimensional mass on evaluation under anesthesia, or involvement of adjacent organs; Left ventricular ejection fraction ≥ 40%; CrCl ≥ 40 mL/min; ANC ≥ 2000 cells/μL; Platelets ≥ 100000/μL; Zubrod performance status ≥ 2	Two dimensional mass on evaluation under anesthesia; fixation of bladder (T4b disease); Nodal involvement; Previous systemic chemotherapy	A: Cystectomy + 5 cycles adjuvant chemotherapy with methotrexate 30 mg/m ² , vinblastine 3 mg/m ² , doxorubicin 30 mg/m ² , cisplatin 70 mg/m ² (MVAC) beginning 4 weeks Postoperatively B: 2 cycles NAC with methotrexate 30 mg/m ² , vinblastine 3 mg/m ² , doxorubicin 30 mg/m ² , cisplatin 70 mg/m ² + cystectomy, followed by 3 additional cycles of chemotherapy beginning 6 weeks Postoperatively	Median followup: 6.8 years Followup method: Not reported

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Matsubara, 2012 ³⁴ Retrospective cohort High	Screened: Not reported Randomized: NA Postrandomization exclusions: NA Lost to followup: Not reported Analyzed: 42; A: 25, B: 17	Age (mean): 65 vs. 65 Male: 60% (15/25) vs. 94% (16/17) Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage of disease: ≤ cT2: 36% (9/25) vs. 24% (4/17) > cT2: 64% (16/25) vs. 77% (13/17) Functional status: Not reported	A vs. B Recurrence (metastatic): 9/25 (36%) vs. 3/17 (18%) Recurrence-free survival (at median followup): 66.7% vs. 76%, p=0.124, log-rank Overall HR 0.65 (95% CI 0.36-1.17) trending in favor of NAC Clinical response in group A only: CR: 44% (11/25) PR: 16% (4/25) Stable disease: 28% (7/25) Progressive disease: 12% (3/25)
Millikan, 2001 ³⁵ RCT Medium	Screened: Not reported Eligible: Not reported Randomized: 140 Postrandomization exclusions Not reported Lost to followup: Not reported Analyzed: 70 vs. 70	A vs. B Age (median): 67 vs. 66 years Male: 47/70 (64%) vs. 55/70 (79%) Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage of disease: < T3b: 23/70 (33%) vs. 21/70 (30%) T3b: 39/70 (56%) vs. 42/70 (60%) T4a: 6/70 (9%) vs. 7/70 (10%) Upper tract: 2/70 (3%) vs. 0/70 Tumor grade: Not reported Functional status: Not reported	A vs. B Overall survival: NSD, numbers Not reported Time to progression: NSD, numbers Not reported Cure fraction: NSD, numbers Not reported Disease- free survival: 42/70 (60%) vs. 39/70 (56%), NSD, RR 0.90 95% CI 0.61-1.33

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Matsubara, 2012 ³⁴ Retrospective cohort High	Anemia, G1-2/G3/G4: 17 (68%) / 8 (32%)/ 0 vs. 15 (88%) / 2 (12%) / 0 Thrombocytopenia, G1-2/G3/G4: 14 (56%) / 7 (28%) / 3 (12%) vs. 9 (53%) / 3 (17%) / 2 (12%) Neutropenia, G1-2/G3/G4: 13 (52%) / 7 (28%) / 3 (12%) vs. 8 (47%) / 5 (29%) / 1 (5.8%) Febrile neutropenia, G1-2/G3/G4: - / 1 (4%) / 1 (4%) vs. - / 1 (5.8%)/ 0	Not reported	Patients in this institution would typically received NAC and cystectomy so those in the AC group received that therapy for specific reasons listed as severe hematuria, pollakiuria and muscle-invasion discovered during cystectomy. Nodal status varied between A and B with 64% (16/25) vs. 94% (16/17) cN0 and remainder cN1 or 2. Treatment duration varied 134 vs 150 days
Millikan, 2001 ³⁵ RCT Medium	Patients receiving at least 2 cycles of chemotherapy Postoperatively: 54/70 (77%) vs 68/70 (97%) Adverse Events: Death due to toxicity of therapy: 6/70 (9%) vs. 6/70 (9%) Perioperative deaths: 3/66 (5%) vs. 1/63 (2%) Myocardial infarction: 3/66 (5%) vs. 1/63 (2%) Thromboembolic: 3/66 (5%) vs. 3/63 (5%) Arrhythmia: 1/66 (2%) vs. 4/63 (6%) Ileus, > 10 days to normal diet: 13/66 (20%) vs. 18/63 (29%) Small bowel obstruction: 2/66 (3%) vs. 2/63 (3%) Pancreatitis: 0/66 (0%) vs. 1/63 (2%) Pneumonia: 6/66 vs. 1/63 (2%) Urine leak: 1/66 (2%) vs. 1/63 (2%) Stricture of ureteral anastomosis: 1/66 (2%) vs. 1/63 (2%)	Not reported	

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Pal, 2012 ³⁶ Retrospective Cohort High	United States Single Center 1995-2012	Pathologically verified urothelial carcinoma at time of cystectomy	Not reported	A: NAC with methotrexate, vinblastine, doxorubicin, cisplatin B: NAC with gemcitabine, carboplatin C: NAC with "other" chemotherapeutic regimens Target doses were assumed to be a total of 3 months of NAC	Median followup: 28.7 months Method of followup: Not reported

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Pal, 2012 ³⁶ Retrospective Cohort High	Screened: Not reported Eligible: A: 22; B: 24; C: 15 Randomized: NA Postrandomization exclusions: NA Lost to followup: Not reported	A vs. B vs. C Age (median): 60.1 vs. 68.6 vs. 77.3 Male: 20/22 (90.9%) vs. 19/24 (79.2%) vs. 13/15 (86.7%) Race: Not reported Smoking status: Not reported Recurrent disease: Not reported Tumor stage (clinical stage): ≤ T2: 18/22 (81.8%) vs. 19/24 (91.7%) vs. 7/15 (73.3%) T3: 1/22 (4.5%) vs. 2/24 (8.3%) vs. 3/15 (20.0%) T4: 2/22 (9.1%) vs. 0/24 vs. 1/15 (6.7%) Tumor Grade: II (intermediate): 1/22 vs. 0/24 vs. 1/15 III (high): 21/22 (95.4%) vs. 24/24 (100%) vs. 14/15 (93.3%) Functional Status: Charleston Comorbidity Index: 4.0 vs. 5.0 vs. 6.0; p<0.05	Survival (months): A/B vs. C: 35.3 vs. 16.3; P=0.055 A vs.: 104.3 vs. 21.8; P=0.73 Patients downstaged to <pT2; A vs. B: 11/22 (50%) vs. 14/24 (58%) Patients downstaged to pT0; A vs. B: 4/22 (22.5%) vs. 6/24 (25%)

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Pal, 2012 ³⁶ Retrospective Cohort High	Not reported	Not reported	

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Sengelov, 2002 ³⁷ Randomized controlled trial, based on two associated trials DAVECA 8901 and 8902 Medium	Based on 2 prior studies, 1989-1993	Histologically proven TCC of the bladder, T2-T4b, NX-3, M0 Normal blood count values, normal renal function	Distant metastases, including LN metastases proximal to the bifurcation of the common iliac vessels Prior radiotherapy or systemic chemotherapy	A: NAC, 3 cycles at 3 week intervals with cisplatin 100 mg/m ² , methotrexate 250 mg/m ² + cystectomy with LN dissection or XRT 3 weeks after chemotherapy (n=79; 17 underwent cystectomy) B: Cystectomy with LN dissection or XRT (n=74; 16 underwent cystectomy)	Minimum 42 months

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Sengelov, 2002 ³⁷ Randomized controlled trial, based on two associated trials DAVECA 8901 and 8902 Medium	Screened: 157 Randomized: 153 Postrandomization exclusions: Not reported Lost to followup: Not reported Analyzed: 153	Below comparisons are cystectomy (n=33) vs. XRT (n=120), no comparisons done within cystectomy only group in this paper Age: 66 vs. 63 Male: 79% (26/33) vs. 82% (98/120) Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Stage of disease: T1: 6% (2/33) vs. 0 T2: 21% (7/33) vs. 13% (16/120) T3A: 39% (13/33) vs. 28% (33/120) T3B: 18% (6/33) vs. 28% (33/120) T4A: 12% (4/33) vs. 16% (19/120) T4B: 0 vs. 15% (18/120) Functional/Performance status: 0: 55% (17/33) vs. 37% (44/120) 1: 42% (13/33) vs. 58% (69/120) 2: 3% (1/33) vs. 5% (6/120)	For cystectomy patients only (n=33, 17 vs. 16) Median survival: 82.5 months vs. 45.8 months, p = 0.76 5-year survival rates: 64% vs. 46% Progression-free survival rate at 5 years: 41% vs. 36%

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Sengelov, 2002 ³⁷ Randomized controlled trial, based on two associated trials DAVECA 8901 and 8902 Medium	2 patients declined further chemotherapy after 1 cycle due to side effects	Danish Cancer Society	Urologists decided on local therapies based on tumor and nodal stage. The study included 2 patients with T1 disease. 2 of 33 patients did not undergo cystectomy because of disease progression during chemotherapy One of 33 was given XRT in accordance with patient preference. 3 patients in cystectomy only group received cisplatin-based chemotherapy at recurrence.

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Sherif, 2002 ³⁸ Randomized controlled trial Medium	Sweden, Finland, Norway Multi-center, number not reported 1991-1997	T2-4aNXM0 urothelial bladder cancer, "normal - moderately reduced kidney function" (by predefined nomogram), "acceptable bone marrow function" (WBC > 3 x 10 ⁹ /l, platelet >= 100 x 10 ⁹ /l and WHO performance status <= 2	SCC or adenocarcinoma of bladder, previous RT or chemotherapy, previous history of/or concomitant other malignancy (except in situ cancer cervix or BCC skin)	A: NAC, 3 cycles at 3 week intervals with cisplatin 100 mg/m ² , methotrexate 250 mg/m ² + cystectomy with LN dissection (n=155) B: Cystectomy with LN dissection (n=154)	Median: 5.3 years. Method: Every 4 months for 2 years, then every 6 months for 2 years, then yearly for 1 year. (physical exam, creatinine, chest X-ray, Intravenous pyelography at 4, 16 and 36 months).

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Sherif, 2002 ³⁸ Randomized controlled trial Medium	Screened: Not reported Randomized: 317 (158 vs. 159) Postrandomization exclusions: 8 (3 vs. 5) Lost to followup: Not reported	Age (mean): 64.6 vs. 65.1 Male: 75% (116/155) vs. 86% (133/154) Race: Not reported Smoker: Not reported Recurrent bladder cancer: Not reported Tumor stage: T2: 41% (64/155) vs. 42% (65/154) T3: 52% (80/155) vs. 49% (76/154) T4a: 7% (10/155) vs. 8% (13/154) Tx: 1% (1/155) vs. 0% Functional status: Not reported	A vs. B Recurrence locoregional and distant mets: 6% (9/155) vs.8% (12/154) Recurrence locoregional only: 10% (15/155) vs. 9% (14/154), RR 1.06, 95% CI 0.53-2.13 Recurrence distant mets only: 13% (20/155) vs. 16% (24/154) None of recurrence statistically significant Overall 5-year survival: 53% vs. 46% (p=0.2375, log rank test) Overall survival HR, HR= 0.8 (0.6-1.1) 5 year survival in T2 group, p=0.5356, log rank test Overall survival HR T2 group, HR = 0.8 (0.5-1.5) 5 year survival in T3-T4a group, p=0.2740, log rank test Overall survival HR T3-T4a group, HR =0.8 (0.6-1.2) Downstaging tumors (defined as pT0 disease compared to other pT-stages): 26.4% (37/140) vs. 11.5% (16/139)

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Sherif, 2002 ³⁸ Randomized controlled trial Medium	Not reported	Swedish Cancer Society, Swedish Society of Medicine, Johanna Hagstrands and Sigfrid Linnars Foundation, Finnish Cancer Society	Deviations from protocol: In experimental arm, A, 14 patients received no NAC, 9 received 1 cycle, 14 received 2 cycles and 3 with missing data. In control arm, B, 1 patient received 3 cycles of chemotherapy. 132/155 vs. 139/154 underwent cystectomy

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Skinner, 1991 ³⁹ Randomized controlled trial Medium	USA Single center 1980-1988	Surgically confirmed invasive carcinoma of the bladder (TCC or TCC associated with squamous or glandular differentiation with or without carcinoma in situ), stage p3, p4, or N+ and M0, no involved LNs above the aortic bifurcation, age 9-75 years	Prior noncutaneous malignancy within 10 years, prior chemotherapy or pelvic RT, bilirubin > 1.5, serum glutamic oxaloacetic transaminase more than 2 times normal, elevated alkaline phosphatase, WBC < 3.5, platelets < 150,000, Serum Creatinine > 1.0, Karnofsky performance status less than 50, medical/social/ psychological factors that would make patient poor risk for completion of chemotherapy.	A: Cystectomy with LN dissection + AC, 4 cycles at 28-day intervals starting 6 weeks after surgery with cisplatin 100 mg/m ² , doxorubicin 60 mg/m ² and cyclophosphamide 600 mg/m ² (n=44) B: Cystectomy with LN dissection (n=47)	Median: 32 months, with all but 6 patients followed beyond 1 year. Method: Every 4 months for 1 year, then every 6 months for 3 years, then yearly thereafter. (Chest X-ray, urogram, laboratory tests, physical exam. CT, MRI or bone scans based on symptoms/ abnormal lab values).

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Skinner, 1991 ³⁹ Randomized controlled trial Medium	Screened: 498 Eligible: 160 (59 declined) Consented: 101 (10 had pure SCC or adenocarcinoma) Randomized: 91 Postrandomization exclusions: Not reported Lost to followup: Not reported	Age (median): 61 vs. 62 Male: 77% (34/44) vs. 74% (35/47) Race: Not reported Smoker: Not reported Recurrent bladder cancer (prior bladder resections): 7% vs. 19% Tumor stage: T1 or 2: 7% (3/44) vs. 11% (5/47) T3a: 23% (10/44) vs. 15% (7/47) T3b: 45% (20/44) vs. 51% (24/47) T4: 25% (11/44) vs. 23% (11/47) Tumor grade: G2 5% (2/44) vs. 9% (4/47) G3 50% (22/44) vs. 50% (23/47) G4 45% (20/44) vs. 41% (19/47) missing: 0/44 vs 1/47 Lymph node status: 0 nodes 61% (27/44) vs. 66% (31/47) 1 +LN 16% (7/44) vs. 21% (10/47) 2+ +LN 23% (10/44) vs. 13% (6/47) Functional status: Not reported	A vs. B Probability of disease recurrence at 3 years: 0.30 (SE=0.08) vs. 0.54 (SE=0.08), p=0.011, unstratified Wilcoxon test Time to recurrence for node negative patients only is significant with p=0.043 Probability of dying from bladder cancer within 3 years: 0.29 (SE=0.08) vs. 0.50 (SE=0.08) Probability of dying of any cause within 3 years: 0.34 (SE=0.08) vs. 0.50 (SE=0.08) No survival benefit of chemotherapy for all patients, p=0.099 For node negative patients only there was not overall survival benefit to chemotherapy, p=0.14 Chemotherapy benefit seen for LN negative and 1 LN positive cases protection from recurrence and the survival advantage were seen in first 3 years, less evident by 5 years. Benefit of chemotherapy was significant for time to recurrence, (p=0.0010, stratified Wilcoxon) and for survival, (p=0.0062 stratified Wilcoxon) after stratifying for the 3 nodal groups (N0, N1, N2+)

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Skinner, 1991 ³⁹ Randomized controlled trial Medium	10 total admissions for chemotherapy complications in 7 patients. Cause of hospitalization: neutropenic fever in 5, dehydration in 1, dehydration + neutropenic fever in 4 No chemotherapy related drug toxicity deaths or long term sequelae.	Not reported	17 patients in group A received individualized chemotherapy regimens, thereafter all received the same regimen. 11/44 patients in group A did not receive chemotherapy; of 33 patients who did receive chemotherapy 1/33 received 6 cycles, 20/33 4 cycles, 2/33 3 cycles, 6/33 2 cycles, 4/33 1 cycle; 32/33 received cisplatin and 25/33 received either doxorubicin or cyclophosphamide.

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Wosnitzer, 2012 ⁴⁰ Retrospective Cohort Medium	United States Single Center 1988-2009	T2-T4a, N0-N2, M0	Metastatic disease at initiation of induction or salvage chemotherapy	A: Neoadjuvant chemotherapy, cisplatin or carboplatin based B: Adjuvant chemotherapy, cisplatin or carboplatin based Dosing/Duration: Not reported	Median followup: A vs. B: 12.8 vs. 14 months

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Wosnitzer, 2012 ⁴⁰ Retrospective Cohort Medium	Screened: 687 Randomized: NA Postrandomization exclusions: NA Lost to followup: Not reported Analyzed: 146; A: 73, B: 73	A vs. B: Age (mean): 64 vs. 66 years Male: 52/73 (71%) vs. 53/73 (73%) Race: Caucasian: 60/73 (82%) vs. 56/73 (77%); African American: 3/73 (4%) vs. 2/73 (3%); Latin: 8/73 (11%) vs. 1/73 (1%); Other: 6/73 (8%) vs. 10/73 (14%) Smoker: 20/73 (27%) vs. 19/73 (26%) Recurrent disease: Not reported Stage of disease >T2: 18/73 (25%) vs. 40/73 (55%); Node status >N0: 5/73 (7%) vs. 29/73 (40%) Tumor grade: Not reported Functional status: Not reported	A vs. B Disease specific survival: Univariate HR=1.28 (95%CI: 0.76-2.16), p=0.36; multivariate HR=1.24 (95%CI: 0.70-2.18), p=0.46 Overall survival: Univariate HR=1.12 (95% CI: 0.73-1.73), p=0.60; multivariate HR=1.08 (95% CI: 0.67-1.73), p=0.76 Cisplatin based treatment: median survival: 11 vs. 12.5 months Disease specific survival: NSD, data Not reported Overall survival: NSD, data Not reported MVAC treatment: median survival: 16 vs. 22 months Disease specific survival: NSD, p=0.555 Overall survival: NSD, p=0.573 Gemcitabine/cisplatin treatment: median survival: 11 vs. 10.5 months Disease specific survival: HR=10.06 (95%CI: 1.01-112.2), p=0.049 Overall survival: NSD, p=0.607 Carboplatin based treatments: median survival: 8.9 vs. 10 months Disease specific survival: NSD, p=0.764 Overall survival: NSD, p=0.388

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Wosnitzer, 2012 ⁴⁰ Retrospective Cohort Medium	Not reported	Not reported	Stage of disease reported as clinical stage in group A, but pathologic stage in group B.

Author, Year Study Name Study Design Risk of Bias	Setting and Study Years	Inclusion Criteria	Exclusion Criteria	Type of Intervention (experimental and control groups, dose, duration of treatment)	Duration of Followup and Followup Method
Yeshchina, 2012 ⁴¹ Retrospective Cohort High	United States Single Center 1988-2010	T2-T4a; N0-N2;M0 bladder cancer, platinum based treatment	carboplatin based treatment	A: Methotrexate, vinblastine, doxorubicin, cisplatin B: Gemcitabine, cisplatin Dosing/Duration: Not reported	Median followup: A vs. B: 30 vs. 25 months Followup method Not reported

Author, Year Study Name Study Design Risk of Bias	Number of Treatment and Control Subjects	Population Characteristics by Treatment Group (age, sex, race, smoking status, recurrent bladder cancer, stage of disease, tumor grade, functional status)	Results
Yeshchina, 2012 ⁴¹ Retrospective Cohort High	Screened: 213 Randomized: NA Post randomization exclusions: NA Lost to followup: Not reported Analyzed: 114, A vs. B: 77 (45 neoadjuvant, 32 adjuvant) vs. 37 (16 neoadjuvant, 21 adjuvant)	A vs. B Age (mean): 62.86 vs. 66.03 years Male: 51/77 (66%) vs. 26/37 (70%) Race: White: 65/77 (84%) vs. 29/37 (78%) Smoking status: Not reported Recurrent disease: Not reported Stage: T2: 63/77 (82%) vs. 28/37 (76%); >T2: 14/77 (18%) vs. 9/37 (24%) Tumor grade: Not reported Functional status: Not reported	Neoadjuvant vs. Adjuvant: Overall survival: HR=0.61 (95% CI: 0.37-1.00), p=0.51 Cancer specific survival: HR=0.69 (95%CI: 0.37-1.29), p=0.247 A vs. B: 5-year overall survival: 47% vs. 35%, p=0.346 5-year disease specific survival: 61% vs. 50%, p=0.482

Author, Year Study Name Study Design Risk of Bias	Adverse Events and Withdrawals due to Adverse Events	Sponsor	Comments
Yeshchina, 2012 ⁴¹ Retrospective Cohort High	Not reported	Not reported	

AC, adjuvant chemotherapy; ANC, Absolute neutrophil count; BCC, basal cell cancer; CI, Confidence Interval; cm, centimeter; CMV, cisplatin, methotrexate, vinblastine ; cN0, clinically determined stage N0 ; cN1, clinically determined stage N1; Cr, serum creatinine level ; CrCl, creatinine clearance; CRR, complete response rate; CT, computerized tomography; dL, deciliter; DVT, Deep venous thrombosis; ECOG , Eastern Cooperative Oncology Group; G, Grade; G1, Grade 1; G2, Grade 2; G3, Grade 3; G4, Grade 4; GC, Gemcitabine plus cisplatin; GFR, glomerular filtration rate; GI, Gastrointestinal ; Gy, Gray; HR, Hazard ratio; L, Liter; LN , Lymph Node; M0, without evidence of metastasis; M2, Metastasis stage 2;; micromol/L, micromole per liter; mg, milligram; mg/m², milligrams per meter squared; MI, Myocardial infarction; mL, milliliter; MRI, Magnetic resonance imaging; MVAC, Methotrexate, Vinblastine, Doxorubicin, Cisplatin; µL, microliter; N+, without regional lymph node involvement; N0, without regional lymph node involvement; N1, Node stage 1; N2, Node stage 2; N3, Node stage 3; NA, Not applicable; NAC, neoadjuvant cisplatin; NR, Not reported; NSD, No significant difference; Nx, Nodes not removed or unknown; p3, pathological stage 3; p4, pathological stage 4; PE, Pulmonary embolus; pN+, pathologically node-positive; pN0, Node stage 0 determined by pathology; pN1, Node stage 1 determined by pathology; pN2, Node stage 2 determined by pathology; PRR, partial response rate; PS, performance status; pT2, Tumor stage 2 determined by pathology; pT3, Tumor stage 3 determined by pathology; pTO, (complete remission) at time of cystectomy; RCT, Randomized Controlled Trial; RR, Relative risk; RT, radiotherapy; SCC, squamous cell carcinoma; SE, standard error; SWOG, Southwest Oncology Group; T, Tumor; T1, Tumor stage 1; T2, Tumor stage 2; T3, Tumor stage 3; T3a, Tumor stage 3a; T3b, Tumor stage 3b; T4, Tumor stage 4; T4a, Tumor stage 4a; T4b, Tumor stage 4b; TCC, Transitional cell carcinoma; TURBT, Trans-urethral resection of bladder tumor; USA, United States of America; WBC, White blood cells; WHO, World Health Organization; XRT, radiation therapy.

Appendix F. Risk of Bias Ratings

Table F1. Key Question 1: Randomized controlled trials risk of bias

Author, Year	Randomization Adequate?	Allocation Concealment adequate?	Groups Similar at Baseline?	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?	Patient Masked?
James, 2012 ⁵	Yes	Yes	Yes	Yes	Unclear	No	No
Sell, 1991 ¹⁰	Yes	No	No	Yes	No	No	No

Author, Year	Attrition Reported?	Overall Loss to Followup <20%? Differential Attrition <10%?	Intention-to-Treat Analysis?	Postrandomization Exclusions	Outcomes Prespecified?	Risk of Bias	Comments
James, 2012 ⁵	Yes	Yes	Yes	Yes (4 patients randomized to chemotherapy)	Yes	Medium	
Sell, 1991 ¹⁰	Yes	Unclear	Yes	Yes (11 patients in EBRT switched to cystoscopy)	Yes	High	Antiquated treatment regimens not used in contemporary practice

EBRT = external beam radiation therapy

Table F2. Key Question 1: Cohort studies risk of bias

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria?	Were the groups comparable at baseline on key prognostic factors (age, sex, race, smoking status-if available, bladder cancer stage; e.g., by restriction or matching)?	Did the study maintain comparable groups through the study period?	Did the study use accurate methods for ascertaining exposures and potential confounders?
Bekelman, 2013 ²	Yes	No (but similar in propensity adjusted analysis)	Unclear	Yes
Goosens-Laan, 2014 ³	Yes	No	No	Yes
Holmang, 1997 ⁴	Yes	Unclear	Unclear	Yes
Kalogeras, 2008 ⁶	Unclear	No	Unclear	Unclear
Kotwal, 2008 ⁷	Unclear	No	Unclear	No
Nieuwenhuijzen, 2005 ⁸	Unclear	No	Unclear	Unclear
Rincon Mayans, 2010 ⁹	Unclear	Unclear	Unclear	Unclear
Solsona, 2009 ¹¹	Unclear	Yes	Unclear	Yes

Author, Year	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Overall loss to followup <20%? Differential attrition <10%?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Risk of Bias
Bekelman, 2013 ²	Unclear	Yes (censoring)	Yes	Unclear	Yes	Medium
Goosens-Laan, 2014 ³	Unclear	No	Yes	No	Yes	High
Holmang, 1997 ⁴	Unclear	No	No	Unclear	Yes	High
Kalogerias, 2008 ⁶	Unclear	Yes (censoring)	No	Unclear	Yes	High
Kotwal, 2008 ⁷	NR	Yes (censoring)	Unclear (reported in text)	Yes, Yes	Yes	High
Nieuwenhuijzen, 2005 ⁸	Unclear	Yes (censoring)	Yes	Unclear	Yes	Medium
Rincon Mayans, 2010 ⁹	Unclear	No	No	Unclear	Yes	High
Solsona, 2009 ¹¹	Unclear	Yes	No	Unclear	Yes	High

Table F3. Key Question 2: Cohort studies risk of bias

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria?	Were the groups comparable at baseline on key prognostic factors (age, sex, race, smoking status-if available, bladder cancer stage; e.g., by restriction or matching)?	Did the study maintain comparable groups through the study period?	Did the study use accurate methods for ascertaining exposures and potential confounders?
Abdollah, 2012 ¹²	Yes	No, differed on age, sex, tumor stage, tumor grade and year of surgery	Unclear	Yes
Brossner, 2004 ¹³	Yes	Yes	Unclear	Unclear
Brunocilla, 2013 ¹⁴	Yes	No, differed on age	Unclear	Yes
Dhar, 2008 ¹⁵	Unclear	Unclear	Unclear	Unclear
Herr, 2002 ¹⁶	No, single group	NA	NA	No
Herr, 2004 ¹⁷	Yes, derived from SWOG RCT	Unclear	Unclear	Yes
Konety, 2003 ¹⁸	Yes	Unclear	Unclear	Yes
Leissner, 2000 ¹⁹	No, single group	NA	NA	Yes
Poulsen, 1998 ²⁰	Yes	Unclear	Unclear	Yes
Shirotake, 2010 ²¹	Yes	Unclear	Unclear	Yes
Simone, 2013 ²²	Unclear	Yes	Unclear	Unclear
Zehnder, 2011 ²³	Yes	Yes	Unclear	Unclear

Author, Year	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Overall loss to followup <20%? Differential attrition <10%?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Risk of Bias
Abdollah, 2012 ¹²	Unclear	No	Yes	Unclear	Yes	Medium
Brossner, 2004 ¹³	Unclear	No	No	Unclear	Unclear	High
Brunocilla, 2013 ¹⁴	Unclear	No	No	Unclear	Yes	Medium
Dhar, 2008 ¹⁵	Unclear	No	No	Unclear	Yes	High
Herr, 2002 ¹⁶	Unclear	Yes	No	Yes, Yes	Yes	High
Herr, 2004 ¹⁷	Unclear	NA	Yes	Yes, Yes	Yes	Medium
Konety, 2003 ¹⁸	Unclear	No	Yes	Unclear	Yes	Medium
Leissner, 2000 ¹⁹	Unclear	Yes	Yes	Yes, Yes	Yes	High
Poulsen, 1998 ²⁰	Unclear	No	No	Unclear	Unclear	High
Shirotake, 2010 ²¹	Unclear	No	Yes	Unclear	Yes	Medium
Simone, 2013 ²²	Unclear	No	Yes	Unclear	Yes	Medium
Zehnder, 2011 ²³	Unclear	No	No	Unclear	Yes	High

NA = not applicable, RCT = randomized controlled trial

Table F4. Key Question 3: Randomized controlled trials risk of bias

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline? (age, sex, race, smoking status-if available, bladder cancer stage)	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?	Patient Masked?
Bono, 1997 ²⁴	Yes	Yes	Yes	Yes	Unclear	No	No
Cognetti, 2012 ²⁵	Yes	Yes	Yes	Yes	Unclear	No	No
Freiha, 1996 ²⁸	Unclear	No	Age: No (59 vs. 64) Sex: Yes smoking status: Unclear Bladder cancer stage: No	Yes	Unclear	No	No
Grossman, 2003 ²⁹	Yes	Yes	Age: Yes Sex: Yes Smoking status: Unclear Bladder cancer stage: Yes	Yes	Unclear	No	No
International Collaboration of Trialists, 1999 ¹	Unclear	Yes	Age: Yes Sex: Yes Smoking status: Unclear Bladder cancer stage: Yes	Yes	Unclear	No	No
International Collaboration of Trialists, 2011 ³⁰	Unclear. "minimization method for randomly assigning patients was used". Patients stratified by institution, choice of definitive treatment and tumor stage. Each institution selected its preferred definitive local treatment option (cystectomy vs. radiation therapy)	Yes	Unclear	Yes	Unclear	No	No

Author, Year	Attrition Reported?	Overall Loss to Followup <20%? Differential Attrition <10%?	Intention-to- Treat Analysis?	Postrandomization Exclusions?	Outcomes Prespecified?	Risk of Bias
Bono, 1997 ²⁴	Yes	Yes Unclear	Unclear	Unclear	Yes	Medium
Cognetti, 2012 ²⁵	Yes	Yes Yes	Yes	Yes, 5.6% lost and not	Yes	Medium
Freiha, 1996 ²⁸	No	Unclear	Unclear	Yes total (5/55 = 9%)	Yes	Medium
Grossman, 2003 ²⁹	No	Unclear Unclear	Yes	No (total 10/317, 5 vs. 5)	Yes	Medium
International Collaboration of Trialists, 1999 ¹	No	Overall: Yes (6/976 total lost to follow) Differential: Yes (4 vs. 2)	Yes	Unclear	Yes	Medium
International Collaboration of Trialists, 2011 ³⁰	No Refusal to continue CMV therapy noted at 14/491 but no reports of study withdrawal for either group	Overall: Yes (6/976 total lost to follow) Differential: Unclear	Unclear	Unclear	Yes	Medium

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline? (age, sex, race, smoking status-if available, bladder cancer stage)	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?	Patient Masked?
Kitamura, 2014 ³¹	Yes (minimization method)	Yes	Age: Yes Sex: Yes Smoking status: Unclear Bladder cancer stage: Yes	Yes	Unclear	No	No
Malmstrom, 1996 ³² Rintala, 1993 ³³	Unclear	No	Age: Yes Sex: Yes Smoking status: Unclear Bladder cancer stage: No (T1G3 27 vs. 31, T2 52 vs. 64, T3 69 vs. 55, T4 3 vs. 10)	Yes	Unclear	No	No
Millikan, 2001 ³⁵	Unclear	No	Yes	Yes	Unclear	No	No
Sengelov, 2002 ³⁷	Yes	No	Unclear	Yes	Unclear	Unclear	Unclear
Sherif, 2002 ³⁸	Unclear	No	Age: Yes Sex: No (male 116 (75%) vs. 133 (86%)) smoking status: Unclear Bladder cancer stage: Yes	Yes	Unclear	No	No
Skinner, 1991 ³⁹	Yes	Unclear	Age: Yes Sex: Yes Smoking status: Unclear Bladder cancer stage: Yes	Yes	Unclear	No	No

Author, Year	Attrition Reported?	Overall Loss to Followup <20%? Differential Attrition <10%?	Intention-to-Treat Analysis?	Postrandomization Exclusions?	Outcomes Prespecified?	Risk of Bias
Kitamura, 2014 ³¹	Yes	Overall: Yes Differential: Yes	Yes	Yes (6/130)	Yes	Medium
Malmstrom, 1996 ³² Rintala, 1993 ³³	Yes	Overall: Yes (total 2/311) Differential: unclear	Yes	No (total 14/325)	Yes	Medium
Millikan, 2001 ³⁵	No	Overall: Unclear Differential: Unclear	Unclear	Unclear	Yes	Medium
Sengelov, 2002 ³⁷	No	Unclear Unclear	Yes	Unclear	Yes	Medium
Sherif, 2002 ³⁸	No	Unclear Unclear	Yes, for survival No, for tumor downstaging	No (total 8/317)	Yes	Medium
Skinner, 1991 ³⁹	No	Unclear Unclear	Unclear	Unclear	Yes	Medium

CMV, cisplatin, methotrexate, vinblastine; G3, Grade 3; T1, Tumor stage 1; T2, Tumor stage 2; T3, Tumor stage 3; T4, Tumor stage 4.

Table F5. Key Question 3: Cohort studies risk of bias

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (age, sex, race, smoking status-if available, bladder cancer stage; e.g., by restriction or matching)?	Did the study maintain comparable groups through the study period?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?
Dash, 2008 ²⁶	Yes	Yes	Unclear	Unclear	Unclear
Fairey, 2013 ²⁷	Yes	No.	Yes	Yes	Unclear
Matsubara, 2013 ³⁴	Yes	No	Yes	Unclear	Unclear
Pal, 2012 ³⁶	Unclear	Yes	Unclear	Yes	Unclear
Wosnitzer, 2012 ⁴⁰	Yes	No	Unclear	Yes	Unclear
Yeshchina, 2012 ⁴¹	Yes	Yes	Unclear	Unclear	Unclear

Author, Year	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Overall loss to followup <20%? Differential attrition <10%?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Risk of Bias
Dash, 2008 ²⁶	No	No	Unclear	Yes	High
Fairey, 2013 ²⁷	No	Yes	Unclear	Yes	High
Matsubara, 2013 ³⁴	No	No	Unclear	Yes	High
Pal, 2012 ³⁶	No	Unclear	Unclear	Yes	High
Wosnitzer, 2012 ⁴⁰	No	Yes	Unclear	Yes	Medium
Yeshchina, 2012 ⁴¹	No	No	Unclear	Yes	High

Appendix G. Strength of Evidence

Table G1. Strength of evidence

Key Question Outcome	Study Design Number of Studies	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
1. For patients with non-metastatic 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?							
<i>Bladder preserving external beam radiation therapy (60 Gray) versus radical cystectomy plus radiation therapy (40 Gray): Median survival duration, local recurrence, regional recurrence</i>	1 RCT ¹⁰	High	Cannot determine	Direct	Imprecise	Undetected	Insufficient
<i>Bladder-preserving therapies versus radical cystectomy: Overall survival, bladder-specific mortality</i>	7 cohort studies 2, 3, 4, 6, 7, 8, 9	High	Inconsistent	Direct	Imprecise	Undetected	Insufficient
<i>Bladder-preserving therapies versus radical cystectomy: Local recurrence, regional recurrence</i>	3 cohort studies 6, 7, 10	High	Inconsistent	Direct	Imprecise	Undetected	Insufficient
<i>Bladder-sparing therapy versus radical cystectomy: Quality of life</i>	No studies	-	-	-	-	-	Insufficient
1a. Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?							
<i>Bladder-sparing therapy versus radical cystectomy: Effectiveness</i>	No studies	-	-	-	-	-	Insufficient
1b. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, ethnicity, performance status, or medical comorbidities such as chronic kidney disease?							
<i>Bladder-sparing therapy versus radical cystectomy: Effectiveness</i>	No studies	-	-	-	-	-	Insufficient

Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
1c . What is the comparative effectiveness of various combinations of agents and/or radiation therapy used for bladder-preserving chemotherapy?							
<i>Different combinations of chemotherapeutic agents and/or radiation treatment: Effectiveness</i>	No studies	-	-	-	-	-	Insufficient
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?							
<i>One type of bladder-preserving treatment versus another: Mortality and recurrence</i>	1 RCT ⁵	High	Cannot determine	Direct	Imprecise	Undetected	Low
2. For patients with clinically non-metastatic muscle-invasive bladder cancer that is treated with cystectomy, does regional lymph node dissection improve outcomes compared with cystectomy alone?							
<i>Regional lymph node dissection: Mortality</i>	3 cohort studies 12,16, 18	Moderate	Consistent	Direct	Precise	Undetected	Low
2a. Does the comparative effectiveness differ according to tumor characteristics, such as histology, stage, grade, size, or molecular/genetic markers?							
<i>Radical cystectomy with versus without regional lymph node dissection: Mortality</i>	1 cohort study ¹²	Moderate	Cannot determine	Direct	Precise	Undetected	Low

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)?							
<i>More extensive lymph node dissection versus less extensive or standard lymph node dissection: All-cause mortality, bladder cancer-specific mortality</i>	11 cohort studies 12,14,15,16,17,18,19,20, 21,22,23	Moderate	Inconsistent	Direct	Precise	Undetected	Low
Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
<i>Extent of lymph node dissection: Bladder cancer recurrence or progression</i>	6 cohort studies 15,16,17,19,20,23	Moderate	Inconsistent	Direct	Imprecise	Undetected	Low
3. For patients with non-metastatic muscle-invasive bladder cancer that is treated with cystectomy, does neoadjuvant or adjuvant chemotherapy improve outcomes compared with cystectomy alone?							
<i>Neoadjuvant chemotherapy vs. no neoadjuvant chemotherapy: Mortality</i>	6 RCTs 1,31,37,29,32,33,38	Moderate	Consistent	Direct	Precise	Undetected	Moderate
<i>Neoadjuvant CMV vs. no neoadjuvant chemotherapy: Likelihood of metastasis, likelihood of death</i>	3 RCTs 1,31,37	Moderate	Consistent	Direct	Imprecise	Undetected	Low
<i>Neoadjuvant chemotherapy vs. no neoadjuvant chemotherapy: Locoregional bladder cancer recurrence</i>	3 RCTs 1,30,32,38	Moderate	Consistent	Direct	Precise	Undetected	Moderate
<i>Adjuvant chemotherapy vs. no adjuvant chemotherapy: Mortality</i>	4 RCTs 24,25,28,39	Moderate	Inconsistent	Direct	Precise	Undetected	Low
<i>Adjuvant chemotherapy vs. no adjuvant chemotherapy: Bladder cancer progression</i>	1 RCT ²⁴	Moderate	Cannot determine	Direct	Imprecise	Undetected	Insufficient
<i>Adjuvant chemotherapy vs. no adjuvant chemotherapy: Locoregional recurrence</i>	3 RCTs 25,28,39	Moderate	Consistent	Direct	Imprecise	Undetected	Insufficient
3a. What is the comparative effectiveness of various combinations of agents used for neoadjuvant or adjuvant chemotherapy?							
<i>Adjuvant MVAC versus cisplatin and gemcitabine: Comparative effectiveness</i>	3 cohort studies 27,36,41	High	Consistent	Direct	Imprecise	Undetected	Insufficient

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,							
<i>Neoadjuvant chemotherapy vs. no neoadjuvant chemotherapy: Effectiveness</i>	4 RCTs 30-31-32-38	Moderate	Consistent	Direct	Imprecise	Undetected	Low
<i>Adjuvant chemotherapy vs. no adjuvant chemotherapy: Effectiveness</i>	2 RCTs 25-28	Moderate	Consistent	Direct	Imprecise	Undetected	Low
Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
3c. Does the comparative effectiveness differ according to patient characteristics, such as age, sex, ethnicity, performance status, or medical comorbidities such as chronic kidney disease?							
<i>Neoadjuvant chemotherapy vs. no neoadjuvant chemotherapy in subgroups based on patient age: Effectiveness</i>	5 RCTs 1-31-37-29-3 2	Moderate	Consistent	Direct	Imprecise	Undetected	Low
<i>Neoadjuvant chemotherapy vs. no neoadjuvant chemotherapy in subgroups of sex, performance status, renal function: Effectiveness</i>	1 RCT ¹	Moderate	Cannot determine	Direct	Imprecise	Undetected	Low
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?							
<i>Adjuvant vs. neoadjuvant MVAC: Overall survival, bladder-cancer specific survival</i>	1 RCT ³⁵ 2 cohort studies ⁴⁰⁻⁴¹	Moderate	Consistent	Direct	Imprecise	Undetected	Low
<i>Adjuvant vs. neoadjuvant gemcitabine plus cisplatin: Recurrence</i>	1 cohort study ³⁴	High	Cannot determine	Direct	Imprecise	Undetected	Insufficient
<i>Adjuvant cisplatin plus gemcitabine on day 2 vs. day 15: 5-year survival</i>	1 RCT ²⁵	Moderate	Cannot determine	Direct	Imprecise	Undetected	Low
4. What are the comparative adverse effects of treatments for non-metastatic muscle-invasive bladder cancer?							
<i>Bladder-sparing therapies versus radical cystectomy: Adverse events</i>	4 cohort studies 4, 6,10,11	High	Cannot determine (harms reported inconsistently)	Direct	Imprecise	Undetected	Insufficient

<i>Extended lymph node dissection vs. standard lymph node dissection: Operative time</i>	1 cohort study ¹³	High	Cannot determine	Direct	Imprecise	Undetected	Insufficient
<i>Neoadjuvant chemotherapy vs. no neoadjuvant chemotherapy: Surgical complications, perioperative deaths</i>	3 RCTs ^{1,29,32}	Moderate	Consistent	Direct	Precise	Undetected	Moderate
<i>Neoadjuvant chemotherapy: Grade 3 or 4 hematological adverse events</i>	2 RCTs ^{1,29}	Moderate	Consistent	Direct	Imprecise	Undetected	Low
<i>Adjuvant chemotherapy vs. no adjuvant chemotherapy: Adverse events</i>	3 RCTs ^{24,28,39}	High	Consistent	Direct	Imprecise	Undetected	Insufficient
Key Question Outcome	Study Design Number of Studies (N)	Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
<i>Neoadjuvant vs. adjuvant MVAC: Mortality related to chemotherapy toxicity</i>	1 RCT ³⁵	Moderate	Cannot determine	Direct	Imprecise	Undetected	Low
4a. 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?							
<i>Adverse effects</i>	No studies	-	-	-	-	-	Insufficient

CMV = cisplatin, methotrexate, vinblastine; MVAC, Methotrexate, Vinblastine, Doxorubicin, Cisplatin; RCT = randomized controlled trial.

References for Appendix G

1. 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.
2. Bekelman JE, Handorf EA, Guzzo T, et al. Radical cystectomy versus bladder-preserving therapy for muscle-invasive urothelial carcinoma: examining confounding and misclassification bias in cancer observational comparative effectiveness research. Value in Health. 2013 Jun;16(4):610-8. PMID: 23796296.
3. Goossens-Laan CA, Leliveld AM, Verhoeven RHA, et al. Effects of age and comorbidity on treatment and survival of patients with muscle-invasive bladder cancer. International Journal of Cancer. 2014 Aug 15;135(4):905-12. PMID: 24420527.
4. 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. Journal of Urology. 1997 Aug;158(2):389-92. PMID: 9224309.
5. James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. New England Journal of Medicine. 2012 Apr 19;366(16):1477-88. PMID: 22512481.
6. Kalogeras D, Lampri E, Goussia A, et al. Radical therapy for muscle-infiltrating bladder cancer (cystectomy or radiotherapy): does age affect the final therapeutic benefit for the patient? Journal of B.U.ON. 2008 Jul-Sep;13(3):353-8. PMID: 18979549.
7. Kotwal S, Choudhury A, Johnston C, et al. Similar treatment outcomes for radical cystectomy and radical radiotherapy in invasive bladder cancer treated at a United Kingdom specialist treatment center. International Journal of Radiation Oncology, Biology, Physics. 2008 Feb 1;70(2):456-63. PMID: 17904301.
8. Nieuwenhuijzen JA, Pos F, Moonen LMF, et al. Survival after bladder-preservation with brachytherapy versus radical cystectomy; a single institution experience. European Urology. 2005 Aug;48(2):239-45. PMID: 16005375.
9. Rincon Mayans A, Rosell Costa D, Zudaire Bergera JJ, et al. Response and progression-free survival in T2 to T4 bladder tumors treated with trimodality therapy with bladder preservation. Actas Urologicas Espanolas. 2010 Oct;34(9):775-80. PMID: 20843454.
10. 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. Scandinavian Journal of Urology & Nephrology Supplementum. 1991;138:193-201. PMID: 1785004.
11. Solsona E, Climent MA, Iborra I, et al. Bladder preservation in selected patients with muscle-invasive bladder cancer by complete transurethral resection of the bladder plus systemic chemotherapy: long-term follow-up of a phase 2 nonrandomized comparative trial with radical cystectomy. European Urology. 2009 Apr;55(4):911-9. PMID: 18722046.
12. Abdollah F, Sun M, Schmitges J, et al. Stage-specific impact of pelvic lymph node dissection on survival in patients with non-metastatic bladder cancer treated with radical cystectomy. BJU International. 2012 Apr;109(8):1147-54. PMID: 21883849.
13. Brossner C, Pycha A, Toth A, et al. Does extended lymphadenectomy increase the morbidity of radical cystectomy? BJU International. 2004 Jan;93(1):64-6. PMID: 14678370.
14. Brunocilla E, Perneti R, Schiavina R, et al. The number of nodes removed as well as the template of the dissection is independently correlated to cancer-specific survival after radical cystectomy for muscle-invasive bladder cancer. International Urology & Nephrology. 2013 Jun;45(3):711-9. PMID: 23666588.

15. Dhar NB, Klein EA, Reuther AM, et al. Outcome after radical cystectomy with limited or extended pelvic lymph node dissection. *Journal of Urology*. 2008 Mar;179(3):873-8; discussion 8. PMID: 18221953.
16. Herr HW, Bochner BH, Dalbagni G, et al. Impact of the number of lymph nodes retrieved on outcome in patients with muscle invasive bladder cancer. *Journal of Urology*. 2002 Mar;167(3):1295-8. PMID: 11832716.
17. Herr HW, Faulkner JR, Grossman HB, et al. Surgical factors influence bladder cancer outcomes: a cooperative group report. *Journal of Clinical Oncology*. 2004 Jul 15;22(14):2781-9. PMID: 15199091.
18. 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. *Journal of Urology*. 2003 Mar;169(3):946-50. PMID: 12576819.
19. Leissner J, Hohenfellner R, Thuroff JW, et al. Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder; significance for staging and prognosis. *BJU International*. 2000 May;85(7):817-23. PMID: 10792159.
20. Poulsen AL, Horn T, Steven K. Radical cystectomy: extending the limits of pelvic lymph node dissection improves survival for patients with bladder cancer confined to the bladder wall. *Journal of Urology*. 1998 Dec;160(6 Pt 1):2015-9; discussion 20. PMID: 9817313.
21. Shirotake S, Kikuchi E, Matsumoto K, et al. Role of pelvic lymph node dissection in lymph node-negative patients with invasive bladder cancer. *Japanese Journal of Clinical Oncology*. 2010 Mar;40(3):247-51. PMID: 19887521.
22. Simone G, Papalia R, Ferriero M, et al. Stage-specific impact of extended versus standard pelvic lymph node dissection in radical cystectomy. *International Journal of Urology*. 2013 Apr;20(4):390-7. PMID: 22970939.
23. 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. *Journal of Urology*. 2011 Oct;186(4):1261-8. PMID: 21849183.
24. Bono AV, Benvenuti C, Gibba A, et al. Adjuvant chemotherapy in locally advanced bladder cancer. Final analysis of a controlled multicentre study. *Acta Urologica Italica*. 1997;11(1):5-8. PMID: No PMID.
25. Cognetti F, Ruggeri EM, Felici A, et al. Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial. *Annals of Oncology*. 2012 Mar;23(3):695-700. PMID: 21859900.
26. Dash A, Pettus JAt, Herr HW, et al. A role for neoadjuvant gemcitabine plus cisplatin in muscle-invasive urothelial carcinoma of the bladder: a retrospective experience. *Cancer*. 2008 Nov 1;113(9):2471-7. PMID: 18823036.
27. 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.
28. Freiha F, Reese J, Torti FM. A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. *Journal of Urology*. 1996 Feb;155(2):495-9; discussion 9-500. PMID: 8558644.
29. 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]. *New England Journal of Medicine*. 2003 Aug 28;349(9):859-66. PMID: 12944571.

30. International Collaboration of Trialists, Medical Research Council Advanced Bladder Cancer Working P, European Organisation for R, et al. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. *Journal of Clinical Oncology*. 2011 Jun 1;29(16):2171-7. PMID: 21502557.
31. 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. *Annals of Oncology*. 2014 Jun;25(6):1192-8. PMID: 24669010.
32. Malmstrom PU, Rintala E, Wahlqvist R, et al. Five-year followup of a prospective trial of radical cystectomy and neoadjuvant chemotherapy: Nordic Cystectomy Trial I. The Nordic Cooperative Bladder Cancer Study Group. *Journal of Urology*. 1996 Jun;155(6):1903-6. PMID: 8618283.
33. Rintala E, Hannisdahl E, Fossa SD, et al. Neoadjuvant chemotherapy in bladder cancer: a randomized study. *Nordic Cystectomy Trial I. Scandinavian Journal of Urology & Nephrology*. 1993;27(3):355-62. PMID: 8290916.
34. Matsubara N, Mukai H, Naito Y, et al. Comparison between neoadjuvant and adjuvant gemcitabine plus cisplatin chemotherapy for muscle-invasive bladder cancer. *Asia-Pacific Journal of Clinical Oncology*. 2013 Dec;9(4):310-7. PMID: 23127231.
35. 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. *Journal of Clinical Oncology*. 2001 Oct 15;19(20):4005-13. PMID: 11600601.
36. Pal SK, Ruel NH, Wilson TG, et al. Retrospective analysis of clinical outcomes with neoadjuvant cisplatin-based regimens for muscle-invasive bladder cancer. *Clinical Genitourinary Cancer*. 2012 Dec;10(4):246-50. PMID: 22981208.
37. Sengelov L, von der Maase H, Lundbeck F, et al. Neoadjuvant chemotherapy with cisplatin and methotrexate in patients with muscle-invasive bladder tumours. *Acta Oncologica*. 2002;41(5):447-56. PMID: 12442921.
38. Sherif A, Rintala E, Mestad O, et al. Neoadjuvant cisplatin-methotrexate chemotherapy for invasive bladder cancer -- Nordic cystectomy trial 2. *Scandinavian Journal of Urology & Nephrology*. 2002;36(6):419-25. PMID: 12623505.
39. Skinner DG, Daniels JR, Russell CA, et al. The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. *Journal of Urology*. 1991 Mar;145(3):459-64; discussion 64-7. PMID: 1997689.
40. 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.
41. 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](#).