THE JOURNAL of UROLOGY®
www.auajournals.org/journal/juro

Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer: AUA/ASCO/SUO Guideline (2017; Amended 2020, 2024)

Jeffrey Holzbeierlein,[1] Brooke R. Bixler,[2] David I. Buckley,[3] Sam S. Chang,[4] Rebecca S. Holmes,[3] Andrew C. James,[5] Erin Kirkby,[2] James M. McKiernan,[6] and Anne Schuckman[7]

[1]Department of Urology, University of Kansas Cancer Center, Kansas City, Kansas
[2]American Urological Association, Linthicum, Maryland
[3]Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University, Portland, Oregon
[4]Department of Urology, Vanderbilt University Medical Center, Nashville, Tennessee
[5]Department of Urology, Texas Urology Group, San Antonio, Texas
[6]Department of Urology, Columbia University, New York, New York
[7]Department of Urology, University of Southern California, Los Angeles, California

Purpose: Although representing approximately 25% of patients diagnosed with bladder cancer, muscle-invasive bladder cancer (MIBC) carries a significant risk of death that has not significantly changed in decades. Increasingly, clinicians and patients recognize the importance of multidisciplinary collaborative efforts that take into account survival and quality of life concerns. This guideline provides a risk-stratified, clinical framework for the management of muscle-invasive urothelial bladder cancer.

Methodology/Methods: In 2024, the MIBC guideline was updated through the AUA amendment process in which newly published literature is reviewed and integrated into previously published guidelines in an effort to maintain currency. The amendment allowed for the incorporation of additional literature released since the previous 2020 amendment. The updated search gathered literature from May 2020 to November 2023. This review identified 3739 abstracts, of which 46 met inclusion criteria. When sufficient evidence existed, the body of evidence was assigned a strength rating of A (high), B (moderate), or C (low) for support of Strong, Moderate, or Conditional Recommendations. In the absence of sufficient evidence, additional information is provided as Clinical Principles and Expert Opinions.

Results: Updates were made regarding neoadjuvant/adjuvant chemotherapy, radical cystectomy, pelvic lymphadenectomy, multi-modal bladder preserving therapy, and future directions. Further revisions were made to the methodology and reference sections as appropriate.

Conclusions: This guideline seeks to improve clinicians' ability to evaluate and treat patients with MIBC based on currently available evidence. Future studies will be essential to further support or refine these statements to improve patient care.

Key Words: urinary bladder neoplasms, radiotherapy, cystectomy, drug therapy

Abbreviations and Acronyms

ASCO = American Society of Clinical Oncology
AUA = American Urological Association
CIS = Carcinoma in situ
ctDNA = Circulating tumor cell DNA
DFS = Disease-free survival
EBRT = External beam radiation therapy
MIBC = Muscle-invasive bladder cancer
MRI = Magnetic resonance imaging
NAC = Neoadjuvant chemotherapy
NMIBC = Non-muscle invasive bladder cancer
PET = Positron emission tomography
QOL = Quality of life
RCT = Randomized control trial
SEER = Surveillance, Epidemiology, and End Results
SUO = Society of Urologic Oncology
TURBT = Transurethral resection of bladder tumor
VI-RADS = Vesical imaging-reporting and data system

Submitted April 5, 2024; accepted April 8, 2024; published April 25, 2024.
The complete unabridged version of the guideline is available at https://www.jurology.com.
This document is being printed as submitted, independent of standard editorial or peer review by the editors of *The Journal of Urology®*.
Amendment Panel Disclosures 2024:
Consultant/Advisor: Jeffrey M. Holzbeierlein, Janssen Oncology; Sam S. Chang, GLG, Janssenn, BMS, Pfizer, Urogen, Virtuoso Surgical, mIR, Prokarium, KDx Diagnostics, Tu Therapeutics, Lantheus, Merck, Pacific Edge, Nonagen; James M. McKiernan, mIR Scientific; Anne K. Schuckman, vyriad
Meeting Participant or Lecturer: Anne K. Schuckman, Photocure, Fergene
Scientific Study or Trial: Jeffrey M. Holzbeierlein, MDx Health, Astellas Medivation; Sam S. Chang, NIH, NantBio; Anne K. Schuckman, Urogen
Health Publishing: Sam S. Chang, Uro Today
Corresponding Author: Erin Kirkby, MS, American Urological Association, Linthicum, Maryland (ekirkby@auanet.org)

https://doi.org/10.1097/JU.0000000000003981
Vol. 212, 3-10, July 2024
Printed in U.S.A.

INTRODUCTION

Epidemiology

There are 83,190 new cases of bladder cancer and 16,840 bladder cancer deaths estimated for 2024 in the U.S.[1] Approximately 25% of newly diagnosed patients have muscle-invasive disease,[2,3] a rate that has not changed significantly over the last 10 years based on data from the Surveillance, Epidemiology, and End Results (SEER) registry.[4] In addition, up to 50% or more patients with high-risk non-muscle invasive bladder cancer (NMIBC) can progress to invasive disease. The male to female ratio is 3:1, and disease incidence increases with age. While rates of bladder cancer are higher in Caucasians than other ethnicities, disease specific survival is worse overall for African-Americans.[3,5]

Prognosis

The overall prognosis of patients with MIBC has not changed significantly. In patients who undergo cystectomy, systemic recurrence rates vary by stage, but range from 20% to 30% for pathologic stage pT2, 40% for pT3, > 50% for pT4 and approximately 70% for node-positive disease.[6,7] Most recurrences will occur within the first two to three years after cystectomy, and at this time, most patients with recurrence after cystectomy are not cured with current systemic therapies.[8]

A pooled analysis of multiple prospective Radiation Therapy Oncology Group protocols evaluating bladder preserving combined-modality therapy for MIBC with a median follow up of 4.3 years found the 5- and 10-year overall survival rates were 57% and 36%, respectively, and the 5- and 10-year disease specific survival rates were 71% and 65%, respectively.[9]

The dominant pathologic predictors for recurrence and survival are tumor stage and nodal status. Other prognostic factors include gender, presence of hydronephrosis, lymphovascular invasion, soft tissue margin status, and molecular subtyping characteristics.[10-15] Variant histology has become better described and recognized, and the treatment for these cancers may vary from conventional urothelial carcinoma. There is also a significant impact of treatment choices on outcome with the type and timing of therapy playing an important role.[16,17]

Scope

The full evidence-based guideline for clinically non-metastatic muscle-invasive urothelial bladder cancer (cT2-T4N0M0) focuses on the evaluation, treatment, and surveillance of MIBC and is guided toward curative intent. The treatment of patients with clinically evident metastatic bladder cancer is outside the context of this guideline and will not be discussed. Optimal initial evaluation of patients with MIBC, including imaging and proper staging, are discussed. The role of radical cystectomy and bilateral pelvic lymphadenectomy is defined. Bladder preserving regimens such as a multi-modal approach that combines maximal transurethral resection of bladder tumor (TURBT), chemotherapy, and radiation therapy as well as partial cystectomy, radiation alone, and maximal TURBT alone, are assessed.

GUIDELINE STATEMENTS

Following review of updated literature, the Panel determined that updates were appropriate for statements related to neoadjuvant/adjuvant chemotherapy, radical cystectomy, pelvic lymphadenectomy, multi-modal bladder preserving therapy, and future directions. Corresponding updates were also made to the associated treatment algorithm (Figure).

Treatment

Neoadjuvant/Adjuvant Chemotherapy.

- **Utilizing a multidisciplinary approach, clinicians should offer cisplatin-based neoadjuvant chemotherapy (NAC) to eligible radical cystectomy patients prior to cystectomy. (Strong Recommendation; Evidence Level: Grade B)**

The Panel continues to advocate for cisplatin-based chemotherapy prior to radical cystectomy based predominantly on two large phase 3 randomized trials that evaluated the effects of NAC vs no NAC on mortality.[18,19] It should be noted that there are no validated predictive factors or clinical characteristics (including age) associated with an increased or decreased probability of response and benefit using cisplatin-based NAC. Further, the best regimen and duration for cisplatin-based NAC remains undefined; however, there are ongoing prospective randomized trials, such as the VESPER trial (gemcitabine and cisplatin versus dose-dense methotrexate + vinblastine + doxorubicin + cisplatin).[20]

The decision regarding eligibility for cisplatin-based NAC should be based on comorbidities and performance status, including cardiac status and presence of peripheral neuropathy, hearing loss, and renal dysfunction.

- **Patients who have not received cisplatin-based NAC and have pT3-4 and/or N+ disease at cystectomy should be offered adjuvant cisplatin-based chemotherapy or adjuvant immunotherapy. Patients who have received cisplatin-based chemotherapy and have pT2-4 and/or N+ at cystectomy should be offered adjuvant immunotherapy. (Moderate Recommendation; Evidence Level: Grade C)**

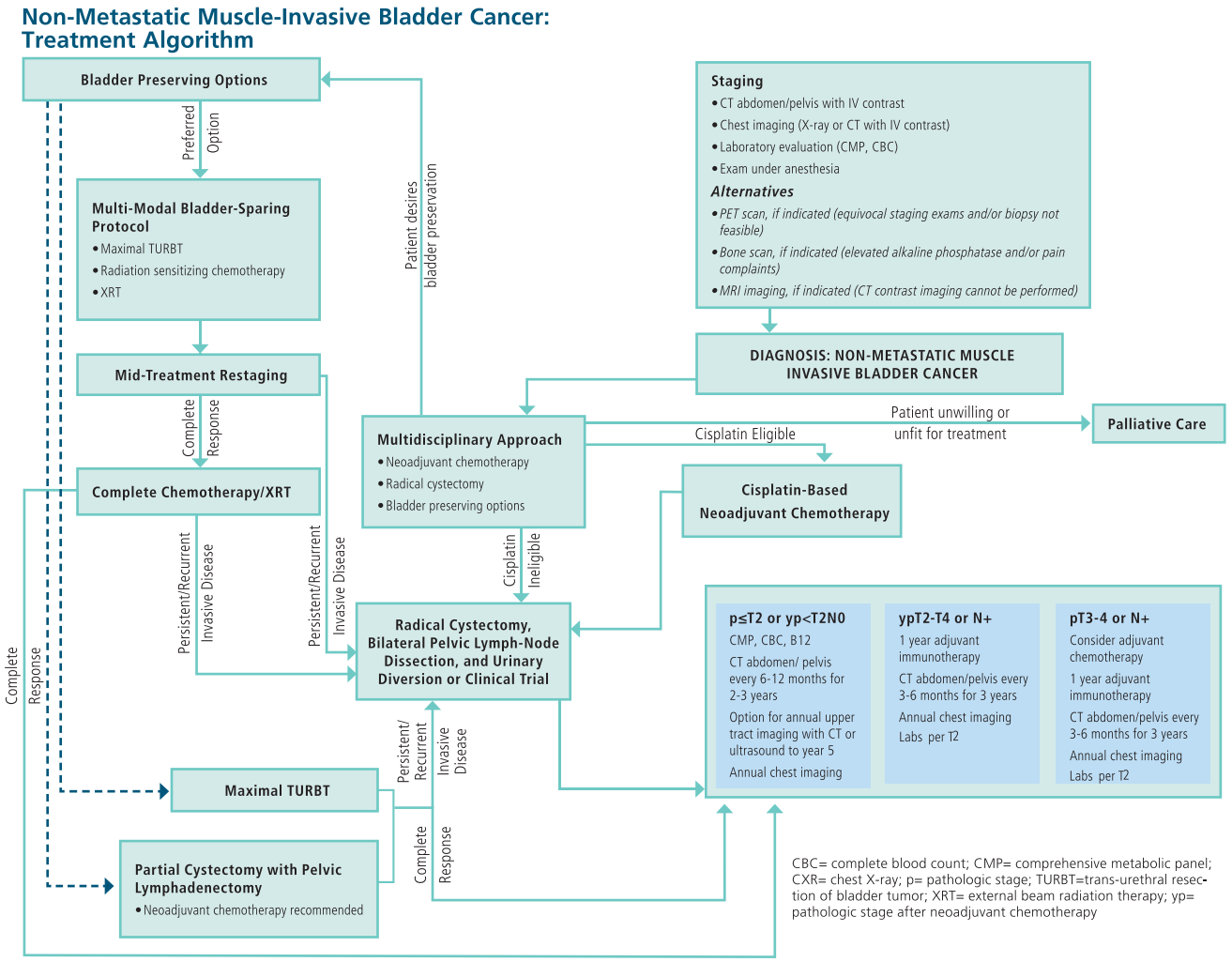

Figure. Non-metastatic muscle-invasive bladder cancer: treatment algorithm.

The CheckMate274 trial, which used adjuvant nivolumab administered to patients with high-risk disease after cystectomy, was published in 2021.[21] This randomized phase 3 trial allowed patients who had received neoadjuvant cisplatin-based chemotherapy and had ypT2-ypT4 or N+ disease or no NAC and had pT3-pT4a or N+ disease to receive nivolumab every 2 weeks for 1 year. The study found that patients who received adjuvant nivolumab had a significantly improved disease-free survival (DFS). Based on this, the recommendation is for patients with high-risk features after cystectomy, with or without NAC, to receive adjuvant nivolumab. Retrospective analysis of the data suggests that the greatest benefit for adjuvant treatment is when it is initiated within 90 days of cystectomy. However, some benefit was still seen even after 90 days post cystectomy.

In contrast, the IMvigor010 trial, which examined the use of adjuvant atezolizumab in a similar population to the CheckMate274 trial, failed to demonstrate a statistically significant improvement in DFS.[22] Therefore, this drug has not been recommended for adjuvant use.

While the AMBASSADOR trial using adjuvant pembrolizumab has reported that it met its endpoint for improvement in DFS, the published results and additional endpoints are still pending at this time.[23]

Radical Cystectomy.

- **When performing a standard radical cystectomy with curative intent, clinicians should remove the bladder, prostate, and seminal vesicles in males; clinicians should remove the bladder in females and should consider removal of adjacent reproductive organs based on individual disease characteristics and need to obtain negative margins. Organ sparing procedures in females should be considered based on disease location and characteristics on an individual basis. (Clinical Principle)**

Radical cystectomy involves removal of the bladder (cystectomy) along with the organs at highest risk of harboring tumors that extend beyond the bladder. In males, this includes the prostate and seminal vesicles. In females this may include the anterior vaginal wall, uterus, cervix, fallopian tubes, and ovaries. Recently, the necessity of removing adjacent reproductive organs in all patients has been re-evaluated. Considering the overall low incidence of urothelial cancer involvement of the uterus, ovaries, and vagina and the absence of conclusive evidence suggesting a measurable outcome difference in removing these organs, this scrutiny is appropriate. When performing ovarian/uterine sparing procedures in women who do not desire fertility, consideration to salpingectomy should be given to reduce the risk of ovarian cancer. In select women with early-stage disease and a desire to preserve fertility and/or sexual function, organ preservation may be considered as long as complete tumor resection can be achieved.

Preoperative counseling should be performed for patients who have invasive cancer at the bladder neck or trigone region in regards to risk of organ sparing surgery.[24,25] If a prostatectomy is performed and there is high-grade cancer at the margin of resection at the apical urethra, a urethrectomy should be performed (immediate or delayed). This can be assessed with a frozen section or final pathology performed at the time of radical cystectomy.[26] A urethrectomy should be performed for women not undergoing reconstruction with a neobladder in order to reduce the likelihood of a positive surgical margin or tumor recurrence.

Pelvic Lymphadenectomy.

- **When performing bilateral pelvic lymphadenectomy, clinicians should remove, at a minimum, the external and internal iliac and obturator lymph nodes (standard lymphadenectomy). (Clinical Principle)**

The quality of the evidence does not currently support a uniform recommendation for the optimal extent of the pelvic lymphadenectomy to maximize therapeutic benefit. However, in order to facilitate adequate staging, a standard lymphadenectomy (bilateral external iliac, internal iliac, and obturator lymph nodes), at a minimum, needs to be completed with $>$ 12 lymph nodes evaluated. The number of lymph nodes identified by the pathologist is a surrogate for the adequacy of the lymphadenectomy. It reflects the quality and completeness of the surgical dissection as well as the quality of the pathologic examination.[27] Submission of separate nodal packets appears to facilitate identification of lymph nodes and is associated with an increased number of reported lymph nodes.

Earlier cohort studies reported more extensive lymphadenectomy (with boundaries extending above the common iliac bifurcation up to or beyond the aortic bifurcation) to be associated with improved all-cause or bladder cancer-specific mortality versus less extensive lymphadenectomy, but these studies had methodological limitations, including variability in the lymphadenectomy techniques evaluated, and inconsistency in results.[28-34] Previous cohort studies found that more extensive lymphadenectomy (above the bifurcation of the common iliac arteries) was associated with a lower risk of bladder cancer recurrence or progression, but again most studies had methodological limitations and inconsistent results.[35,36]

A 2019 randomized trial (n = 401) reported that there was no improvement with an extended lymph node dissection (LND) in recurrence-free survival (primary endpoint of this study), cancer specific survival, or overall survival.[37] More recent observational and cohort studies have varying results with several showing no benefit, but in those that did report an advantage with a more extensive LND, this advantage was noted in patients who had not received NAC.[38-41] The largest observational study (n = 19,020) using SEER data did report statistically significant associations between the extent of pelvic LND and cancer-specific mortality (HR = 0.99; $P < .001$) and rates of lymph node invasion (OR = 1.01; $P = .001$) in a mixed population of patients with MIBC and NMIBC; however, the effect sizes were very small.[41]

Bladder Preserving Approaches

Multi-Modal Bladder Preserving Therapy.

- **For patients with MIBC who have elected tri-modality therapy with organ preservation, clinicians should offer maximal TURBT followed by chemotherapy combined with external beam radiation therapy (EBRT). Planned cystoscopic surveillance per high-risk NMIBC schedule should be performed. (Strong Recommendation; Evidence Level: Grade B)**

An important component of multi-modal therapy is the maximal resection of all visible tumor with TURBT prior to EBRT and chemotherapy. This has been shown in prospective series to improve local control by approximately 20%.[9] Additionally, ideal patients for tri-modality therapy include those in whom complete resection is feasible and who have no hydronephrosis and no CIS.

Comparing multi-modal bladder preserving surgery with radical cystectomy is difficult. Much of the data, including one RCT and multiple cohort and registry series, have compared EBRT with and without chemotherapy versus radical cystectomy.[42-45] The RCT found no difference in overall survival

between the two approaches, although a higher risk of loco-regional failure was seen in the bladder preservation arm.[42] Unfortunately, none of these studies adequately corrected for age, comorbidities, nodal status, and pathologic versus clinical staging. In the absence of randomized data, Zlotta and colleagues reported on a multi-institutional comparison of patients with MIBC treated with tri-modality therapy vs cystectomy using propensity score matching and weighted analysis.[46] This showed that in well selected patients, similar outcomes in metastasis-free survival, cancer-specific survival, DFS and overall survival could be achieved. Overall survival slightly favored tri-modality therapy; however, 13% of patients in the tri-modality therapy group did undergo radical cystectomy. Mak et al reported a 5-year survival of 57% for all study patients, of whom 80% did have an intact bladder.[9] It is unclear what proportion of patients who, having initially chosen bladder preservation, ultimately require cystectomy in a non-study setting. The reported bladder preservation rates may be dependent upon the degree of initial patient evaluation and selection. Thus, currently the Panel believes that multi-modal bladder preserving therapy is the preferred treatment in those patients who desire bladder preservation and understand the unique risks associated with this approach or those who are medically unfit for surgery.

- **Following completion of bladder preserving therapy, clinicians should perform regular surveillance with computed tomography (CT) scans, cystoscopy, and urine cytology. (Strong Recommendation; Evidence Level: Grade C)**

Following bladder preserving treatment, clinicians should address any bladder and bowel issues that may result from treatment and consider referral of patients to experienced medical professionals to evaluate and treat. Patients should have a follow up cystoscopy with biopsy to identify occult persistent malignancy. Those who are biopsy-proven complete responders to bladder preserving protocols remain at risk for both invasive and non-invasive recurrences as well as new tumors in the upper tracts. Recurrences may be successfully managed by prompt salvage therapy. Although there is no direct evidence to determine optimal frequency of surveillance, most bladder preserving protocols encourage careful follow up. The overall survival rates achieved in bladder preserving series that appear comparable to those obtained with immediate cystectomy are likely in part due to the use of close surveillance with early salvage cystectomy in patients with residual/recurrent disease as well as careful patient selection. Published protocols recommend every 3 month cystoscopy during the first year, every 4 to 6 months in the second, and every 6 to 12 months thereafter.[9,47] In addition, the Panel recommends cross-sectional imaging of the abdomen and pelvis and chest imaging every 6 months for the first 2 years, although, again, there are no published data showing that this improves survival.

FUTURE DIRECTIONS

Several key areas of future research need emphasis to improve clinical care and provide a path to better patient outcomes with invasive bladder cancer.

Detection and Markers

Improved imaging modalities to better locally stage tumors and define extent of disease are needed. This includes cystoscopic and radiographic imaging of local disease and more effective and accurate evaluation techniques of regional lymphatics and distant sites. The role of magnetic resonance imaging (MRI), vesical imaging-reporting and data system (VI-RADS) for local staging and defining the role of positron emission tomography (PET) imaging, the best PET imaging agent, and the investigation/validation of other novel technologies are deemed high-priority.

Urine cytology can be used to monitor for recurrence after TURBT and cystectomy, but difficulties with interpretation after urinary diversion have limited its usefulness after bladder removal. Radiation therapy can alter the appearance of shed cells and oftentimes result in atypical results. Current urinary markers have a limited role in the routine monitoring for recurrence of urothelial carcinoma after radical cystectomy due to false positive rate. Future studies should focus on the development of urinary and serum-based markers that can be used to identify early urothelial based and/or distant recurrences.

Increased knowledge gained from comprehensive genetic studies of invasive bladder cancer should be utilized to identify and validate markers that could be used to guide diagnosis and therapeutic decision-making. This would include the identification of prognostic markers capable of stratifying patients at risk for advanced disease, and predictive markers for the response to chemotherapeutic/immunotherapeutic agents as well as radiation-based therapies. In addition, further studies are needed to evaluate and validate the prognostic and predictive information obtained from novel molecular classifications of bladder cancer.

Therapy

The rapid introduction of novel immunotherapeutic agents for the treatment of bladder cancer has begun to show promise. Phase 2 and 3 studies have now demonstrated significant antitumor activity of

the anti-PD-1 and anti-PDL-1 antibodies in the metastatic setting. Additional studies are needed to further define the role of these agents alone or in combination with other therapies for all stages of bladder cancer.

In addition, further studies are needed to better integrate multi-modal therapy in patients with invasive bladder cancer. Specific examples include the role for adjuvant chemotherapy or immunotherapy in patients who have previously received NAC followed by surgery but still possess high-risk pathology (residual invasive disease or regional lymph node involvement) and the role of immunotherapy in bladder preservation. A phase 1 trial investigating the addition of concurrent immune-checkpoint inhibition to chemoradiation for bladder preservation in patients with muscle-invasive disease found high rates of metastasis-free and overall survival, and a phase 3 trial (NCT03775265) investigating the role of atezolizumab with chemoradiation completed enrollment and will provide further data regarding the role of immunotherapy with bladder preservation.[48] Additionally, the role of radiation in patients undergoing radical cystectomy for T3 and T4 disease, including the use of intraoperative radiation therapy, is yet to be clearly defined.

Robotic cystectomy has been adopted as a surgical option for the treatment of patients with invasive bladder cancer with the hope that it will improve the morbidity associated with radical cystectomy. RCTs have shown decreased blood loss with robotic cystectomy as compared to open cystectomy with no difference in complications, length of hospitalization, readmission rates, pain, QOL, or postoperative mortality and no difference in short-term progression-free survival.[49,50] Long-term data are needed to demonstrate the oncologic efficacy, potential for improved clinical outcomes, and QOL using this technology compared to standard open techniques.

Tissue regenerative technology continues to advance, stimulating the hope that organ replacement may be available in the future. Support of basic and translational research is needed to move tissue regeneration forward into clinical use for patients who require bladder removal for invasive bladder cancer.

The currently unpublished SWOG S1011 trial compared extended LND with standard LND and found no significant difference in DFS or overall survival.[51] However, presentation of unpublished long-term follow up of the German LEA AUO AB 25/02 trial suggests improvement in survival associated with an extended LND.[37]

In addition, studies emphasizing patient reported outcomes after treatment for invasive bladder cancer are needed. This information is necessary to help further support patient centered outcomes and identify specific areas of treatment that require further attention to improve patient QOL.

Surveillance

Finally, the optimal strategies for surveillance after definitive treatment for invasive bladder cancer to identify pelvic, distant, and urothelial recurrences need to be defined. The role of specific imaging tests and laboratory studies as well as their appropriate interval has yet to be established. Some evidence suggests a potential role for circulating tumor cell DNA (ctDNA) in detecting recurrence and progression following radical cystectomy. Future studies are needed to further define the potential role of ctDNA for surveillance.

REFERENCES

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin.* 2024;74(1):12-49. doi. 10.3322/caac.21820
2. Smith AB, Deal AM, Woods ME, et al. Muscle-invasive bladder cancer: evaluating treatment and survival in the national cancer data base. *BJU Int.* 2014;114(5):719-726. doi. 10.1111/bju.12601
3. Burger M, Catto JW, Dalbagni G, et al. Epidemiology and risk factors of urothelial bladder cancer. *Eur Urol.* 2013;63(2):234-241. doi. 10.1016/j.eururo.2012.07.033
4. Charlton ME, Adamo MP, Sun L, Deorah S. Bladder cancer collaborative stage variables and their data quality, usage, and clinical implications: a review of seer data, 2004-2010. *Cancer.* 2014;120(suppl 23):3815-3825. doi. 10.1002/cncr.29047
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin.* 2017;67(1):7-30. doi: 10.3322/caac.21387
6. Karakiewicz PI, Shariat SF, Palapattu GS, et al. Nomogram for predicting disease recurrence after radical cystectomy for transitional cell carcinoma of the bladder. *J Urol.* 2006;176(4 Pt 1):1354-1362. doi. 10.1016/j.juro.2006.06.025
7. International Bladder Cancer Nomogram Consortium, Bochner BH, Kattan MW, Vora KC. Postoperative nomogram predicting risk of recurrence after radical cystectomy for bladder cancer. *J Clin Oncol.* 2006;24:3967-3972. doi. 10.1200/JCO.2005.05.3884
8. Seisen T, Sun M, Leow JJ, et al. Efficacy of high-intensity local treatment for metastatic urothelial carcinoma of the bladder: a propensity score-weighted analysis from the national cancer data base. *J Clin Oncol.* 2016;34(29):3529-3536. doi. 10.1200/JCO.2016.66.7352
9. Mak RH, Hunt D, Shipley WU, et al. Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined-modality therapy: a pooled analysis of radiation therapy oncology group protocols 8802, 8903, 9506, 9706, 9906, and 0233. *J Clin Oncol.* 2014;32(34):3801-3809. doi. 10.1200/JCO.2014.57.5548
10. Dobruch J, Daneshmand S, Fisch M, et al. Gender and bladder cancer: a collaborative review of etiology, biology, and outcomes. *Eur Urol.* 2016;69(2):300-310. doi. 10.1016/j.eururo.2015.08.037

11. Lotan Y, Gupta A, Shariat SF, et al. Lymphovascular invasion is independently associated with overall survival, cause-specific survival, and local and distant recurrence in patients with negative lymph nodes at radical cystectomy. *J Clin Oncol.* 2005;23(27):6533-6539. doi. 10.1200/JCO.2005.05.516

12. Choi W, Czerniak B, Ochoa A, et al. Intrinsic basal and luminal subtypes of muscle-invasive bladder cancer. *Nat Rev Urol.* 2014;11(7):400-410. doi. 10.1038/nrurol.2014.129

13. Xylinas E, Rink M, Novara G, et al. Predictors of survival in patients with soft tissue surgical margin involvement at radical cystectomy. *Ann Surg Oncol.* 2013;20(3):1027-1034. doi. 10.1245/s10434-012-2708-5

14. Comprehensive molecular characterization of urothelial bladder carcinoma. *Nature.* 2014;507:315.

15. Sjödahl G, Lauss M, Lövgren K, et al. A molecular taxonomy for urothelial carcinoma. *Clin Cancer Res.* 2012;18(12):3377-3386. doi. 10.1158/1078-0432.CCR-12-0077-T

16. 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):152-165. doi. 10.1016/j.ccr.2014.01.009

17. 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):3110-3115. doi. 10.1073/pnas.1318376111

18. International Collaboration of Trialists, Medical Research Council Advanced Bladder Cancer Working Party now the National Cancer Research Institute Bladder Cancer Clinical Studies Group, European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group, Australian Bladder Cancer Study Group, National Cancer Institute of Canada Clinical Trials Group, Finnbladder, Norwegian Bladder Cancer Study Group, Club Urologico Espanol de Tratamiento Oncologico Group, , , , , , , Griffiths G, Hall R, Sylvester R, Raghavan D, Parmar MKB. 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):2171-2177. doi. 10.1200/JCO.2010.32.3139

19. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med.* 2003;349(9):859-866. doi. 10.1056/NEJMoa022148

20. Pfister C, Gravis G, Flechon A, et al; VESPER Trial Investigators. Perioperative dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin in muscle-invasive bladder cancer (vesper): survival endpoints at 5 years in an open-label, randomised, phase 3 study. *Lancet Oncol.* 2024;25(2):255-264. doi. 10.1016/S1470-2045(23)00587-9

21. Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. *N Engl J Med.* 2021;384(22):2102-2114. doi. 10.1056/NEJMoa2034442

22. Bellmunt J, Hussain M, Gschwend JE, et al; IMvigor010 Study Group. Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (imvigor010): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2021;22(4):525-537. doi. 10.1016/S1470-2045(21)00004-8

23. Apolo AB, Ballman KV, Sonpavde GP, et al. Ambassador alliance a031501: phase III randomized adjuvant study of pembrolizumab in muscle-invasive and locally advanced urothelial carcinoma (MIUC) vs observation. *J Clin Oncol.* 2024;42(4_suppl I):LBA531. doi. 10.1200/jco.2024.42.4_suppl.lba531

24. Kassouf W, Spiess PE, Brown GA, et al. Prostatic urethral biopsy has limited usefulness in counseling patients regarding final urethral margin status during orthotopic neobladder reconstruction. *J Urol.* 2008;180(1):164-167. doi. 10.1016/j.juro.2008.03.037

25. Gaya JM, Matulay J, Badalato GM, Holder DD, Hruby G, McKiernan J. The role of preoperative prostatic urethral biopsy in clinical decision-making at the time of radical cystectomy. *Can J Urol.* 2014;21(2):7228-7233.

26. Kates M, Ball MW, Chappidi MR, et al. Accuracy of urethral frozen section during radical cystectomy for bladder cancer. *Urol Oncol.* 2016;34(12):532.e1-532.e6. doi. 10.1016/j.urolonc.2016.06.014

27. Bochner BH, Cho D, Herr HW, Donat M, Kattan MW, Dalbagni G. Prospectively packaged lymph node dissections with radical cystectomy: evaluation of node count variability and node mapping. *J Urol.* 2004;172(4 Pt 1):1286-1290. doi. 10.1097/01.ju.0000137817.56888.d1

28. Herr HW, Bochner BH, Dalbagni G, Donat SM, Reuter VE, Bajorin DF. Impact of the number of lymph nodes retrieved on outcome in patients with muscle invasive bladder cancer. *J Urol.* 2002;167(3):1295-1298. doi. 10.1016/s0022-5347(05)65284-6

29. 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):946-950. doi. 10.1097/01.ju.0000052721.61645.a3

30. 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):247-251. doi. 10.1093/jjco/hyp147

31. Brunocilla E, Pernetti 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):711-719. doi. 10.1007/s11255-013-0461-8

32. Dhar NB, Klein EA, Reuther AM, Thalmann GN, Madersbacher S, Studer UE. Outcome after radical cystectomy with limited or extended pelvic lymph node dissection. *J Urol.* 2008;179(3):873-878. doi. 10.1016/j.juro.2007.10.076

33. 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):1261-1268. doi. 10.1016/j.juro.2011.06.004

34. 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):390-397. doi. 10.1111/j.1442-2042.2012.03148.x

35. Siemens DR, Mackillop WJ, Peng Y, Wei X, Berman D, Booth CM. Lymph node counts are valid indicators of the quality of surgical care in bladder cancer: a population-based study. *Urol Oncol.* 2015;33(10):425.e15-425.e23. doi. 10.1016/j.urolonc.2015.06.005

36. Froehner M, Novotny V, Heberling U, et al. Relationship of the number of removed lymph nodes to bladder cancer and competing mortality after radical cystectomy. *Eur Urol.* 2014;66(6):987-990. doi. 10.1016/j.eururo.2014.07.046

37. Gschwend JE, Heck MM, Lehmann J, et al. Extended versus limited lymph node dissection in bladder cancer patients undergoing radical cystectomy: survival results from a prospective, randomized trial. *Eur Urol.* 2019;75(4):604-611. doi. 10.1016/j.eururo.2018.09.047

38. Kaczmarek K, Maøkiewicz B, Lemiński A. Adequate pelvic lymph node dissection in radical cystectomy in the era of neoadjuvant chemotherapy: a meta-analysis and systematic review. *Cancers (Basel).* 2023;15(16):4040. doi. 10.3390/cancers15164040

39. Tochigi K, Nagayama J, Bando S, et al. Relationship between the number of lymph nodes dissected and prognosis in muscle-invasive bladder cancer in the era of neoadjuvant chemotherapy. *Int J Urol.* 2022;29(11):1264-1270. doi. 10.1111/iju.14974

40. Lemiński A, Kaczmarek K, Michalski W, Maøkiewicz B, Kotfis K, Søojewski M. The influence of lymph node count on oncological outcome of radical cystectomy in chemotherapy pretreated and chemotherapy-naöve patients with muscle invasive bladder cancer. *J Clin Med.* 2021;10(21):4923. doi. 10.3390/jcm10214923

41. Kosiba M, Stolzenbach LF, Collà Ruvolo C, et al. Contemporary trends and efficacy of pelvic lymph node dissection at radical cystectomy for

urothelial and variant histology carcinoma of the urinary bladder. *Clin Genitourin Cancer.* 2022;20(2):195.e1-195.e8. doi. 10.1016/j.clgc.2021.10.010

42. Sell A, Jakobsen A, Nerstrøm B, Sørensen BL, Steven K, Barlebo H. 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 Supplementum.* 1991;138:193-201.

43. Bekelman JE, Handorf EA, Guzzo T, et al. Radical cystectomy versus bladder-preserving therapy for muscle-invasive urothelial carcinoma: examining confounding and misclassification Biasin cancer observational comparative effectiveness research. *Value Health.* 2013;16(4):610-618. doi. 10.1016/j.jval.2013.01.005

44. Goossens-Laan CA, Leliveld AM, Verhoeven RH, et al. Effects of age and comorbidity on treatment and survival of patients with muscle-invasive bladder cancer. *Int J Cancer.* 2014;135(4):905-912. doi. 10.1002/ijc.28716

45. Kotwal S, Choudhury A, Johnston C, Paul AB, Whelan P, Kiltie AE. 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):456-463. doi. 10.1016/j.ijrobp.2007.06.030

46. Zlotta AR, Ballas LK, Niemierko A, et al. Radical cystectomy versus trimodality therapy for muscle-invasive bladder cancer: a multi-institutional propensity score matched and weighted analysis. *Lancet Oncol.* 2023;24(6):669-681. doi. 10.1016/S1470-2045(23)00170-5

47. Efstathiou JA, Spiegel DY, Shipley WU, et al. Long-term outcomes of selective bladder preservation by combined-modality therapy for invasive bladder cancer: the mgh experience. *Eur Urol.* 2012;61(4):705-711. doi. 10.1016/j.eururo.2011.11.010

48. de Ruiter BM, van Hattum JW, Lipman D, et al. Phase 1 study of chemoradiotherapy combined with Nivolumab ± Ipilimumab for the curative treatment of muscle-invasive bladder cancer. *Eur Urol.* 2022;82(5):518-526. doi. 10.1016/j.eururo.2022.07.009

49. Maibom SL, Røder MA, Aasvang EK, et al. Open vs robot-assisted radical cystectomy (BORARC): a double-blinded, randomised feasibility study. *BJU Int.* 2022;130(1):102-113. doi. 10.1111/bju.15619

50. Vejlgaard M, Maibom SL, Joensen UN, et al. Quality of life and secondary outcomes for open versus robot-assisted radical cystectomy: a double-blinded, randomised feasibility trial. *World J Urol.* 2022;40(7):1669-1677. doi. 10.1007/s00345-022-04029-9

51. Lerner SP, Tangen C, Svatek RS, et al. SWOG S1011: a phase III surgical trial to evaluate the benefit of a standard versus an extended lymphadenectomy performed at time of radical cystectomy for muscle invasive urothelial cancer. *J Clin Oncol.* 2023;41(16_suppl I):4508. doi. 10.1200/jco.2023.41.16_suppl.4508