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# Guidelines for Muscle Invasive Bladder Cancer *

*Learning Objective:* At the conclusion of this continuing medical education activity, the participant will have a thorough understanding of the recently released AUA/ASCO/ASTRO/SUO guidelines for non-metastatic muscle invasive bladder cancer using a risk stratified clinical framework for management.

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## INTRODUCTION

In 2017, 79,030 new cases of bladder cancer and 16,870 bladder cancer deaths were predicted in the U.S.[1] Approximately 25% of patients will present with muscle invasive disease,[2] and the risk of death from this disease has unfortunately not changed in decades.[3] Furthermore, in up to 50% of patients high risk non-muscle invasive bladder cancer will eventually progress to invasive disease. While surgical advances have been made with the advent of robotic technology, its impact on survival remains unclear.[4] It has also been well established that extirpative surgery alone for MIBC is less effective for advanced disease.[5] Nevertheless, comparative effectiveness data of therapies, including bladder sparing therapies versus radical cystectomy, and the roles of extended lymphadenectomy and adjuvant chemotherapy remain nascent.[6] Additionally, multidisciplinary collaborative efforts have formed to improve survival rates and quality of life concerns, and previous guidelines have been particularly effective in limiting variations in care. In this Update we attempt to assist with understanding the current AUA treatment guidelines for muscle invasive bladder cancer, highlighting areas for reform.

## INITIAL EVALUATION

*History and physical evaluation*. In an era of increasing technology and expanding imaging modalities the history and physical examination have been deemphasized in medical education.[7] Nevertheless, a comprehensive history and physical exam are important for patients with bladder cancer to assess their overall health status, current symptomatology, and social environment and potential fitness for major surgery. Recent data have even suggested that unemployment, physically unhealthy days, air pollution and lack of insurance are associated with increased rates of bladder cancer mortality in addition to the well-known risk factors such as smoking and well water use.[8]

Patients with MIBC often have multiple comorbidities that put them at risk for treatment related complications. The clinical assessment plays a critical role in determining the optimal treatment plan as well as the type of diversion best suited for the patient if he/she is deemed a cystectomy candidate.[9] In addition, the exam provides an opportunity to prepare for any intraoperative challenges from previous surgeries or aberrant anatomy. **An exam under anesthesia should be performed to assess the resectability of the primary tumor at the time of surgery**, and to look for the presence of a large, 3-dimensional residual mass after TURBT (cT3b), invasion of adjacent structures (cT4a) and/or fixation (cT4b) to determine the potential need for neoadjuvant chemotherapy.[10]

In corroboration with the physical exam, preoperative imaging helps to determine the clinical stage and tumor extent. Unfortunately, no imaging modality to date has been proven superior over another, and all lack excellent sensitivity and specificity in determining intra-abdominal and distant metastatic disease. Nevertheless, preoperative imaging can determine the 1) feasibility and safety of removing the bladder, 2) presence of pelvic or retroperitoneal lymph node metastases, 3) presence of hydronephrosis, 4) presence of upper tract disease, 5) local extent of disease and 6) possible visceral/distant metastatic sites.[11] For hydronephrosis, a ureteral stent or nephrostomy tube should be placed to maximize renal function. Improvement in renal function may even allow for a change in the preoperative chemotherapy regimen to maximize the chance of a favorable response. Recent data suggest that patients who receive a Double-J® stent versus percutaneous drainage before radical cystectomy are at higher risk for upper urinary tract recurrence but further research is needed before definitively recommending a change in management.[12]

**The current recommendations for preoperative imaging include cross-sectional CT or MRI of the abdomen and pelvis, and chest x-ray**. Intravenous contrast with a delayed urogram phase should be performed when possible to evaluate the upper tract.[13] In those patients who are not able to receive intravenous contrast MRI with gadolinium and non-contrast imaging with retrograde pyelograms are acceptable alternatives. The proper specific chest imaging is less obvious given possible false-positive findings. Nevertheless, current guidelines recommend at a minimum a chest x-ray with posterior-anterior and lateral images. If the alkaline phosphatase level is normal, a bone scan is not indicated unless there are symptoms of bone pain.[14]

The use of PET for bladder cancer staging remains undefined and, therefore, it is not routinely indicated for initial staging.[15] Although the current panel guidelines acknowledge that there are data to suggest increased sensitivity with regard to identifying abnormal pelvic lymph nodes and chest lesions in cases of MIBC,[11] **currently PET should be reserved for cases with abnormal chest, abdomen or pelvic imaging which require further evaluation**. Finally, a comprehensive metabolic panel should be drawn in all patients as the ultimate choice for urinary diversion depends, in part, on any metabolic abnormalities such as renal acidosis, or hepatic or renal insufficiency. A complete blood count helps infer information regarding anemia and an albumin/prealbumin level helps better elucidate the nutritional status of the patient.

*Role of pathology rereview.* During the last decade the clinical impact of variant histology has been increasing, and in 2016 the World Health Organization highlighted the importance of histology for the therapeutic management of bladder cancer.[16] Nevertheless, the proper identification of variant bladder cancer histology is difficult with high interobserver variability among even well trained pathologists.[17] If variant histology is suspected, it is important for the TURBT pathology slides to be reviewed by a genitourinary pathologist who can then specify the percentage of cancer involved by this variant histology.

**ABBREVIATIONS**: CT (computerized tomography), MIBC (muscle invasive bladder cancer), MRI (magnetic resonance imaging), MVAC (methotrexate, vinblastine, doxorubicin, cisplatin), NMIBC (non-muscle invasive bladder cancer), NAC (neoadjuvant chemotherapy), PET (positron emission tomography), TURBT (transurethral resection of bladder tumor)

**Experienced genitourinary pathologists can identify variants that may alter treatment in up to 33% of cases.**[18] As opposed to pure urothelial carcinoma, tumors with variant histology may be more locally advanced, affecting decisions about surgery, neoadjuvant chemotherapy and bladder preservation.[19-21]

*Patient counseling.* Informing the patient of treatment options requires shared decision making and a multidisciplinary discussion involving surgery, chemotherapy and radiotherapy. If possible, consultations with multiple providers in the same clinical setting will facilitate and enrich the experience. **At a minimum, the multidisciplinary approach should include discussing the potential risks and benefits of all accepted treatment options. For extirpative surgery, this discussion includes the risks and benefits of NAC as well as radical cystectomy. Patients should also be counseled on all possible forms of urinary diversion as well as any expected lifestyle changes with these diversions. The patient should be referred to a urologist specifically trained in performing continent diversions.**[22] For patients considering bladder preservation, a multidisciplinary consultation with the urologist, radiation oncologist and medical oncologist should determine if the tumor and health status favor this approach. Favorable characteristics for bladder preservation include tumor unifocality, no evidence of carcinoma in situ, no hydronephrosis and a tumor that can be resected entirely endoscopically.

In addition to a thorough discussion of possible treatment complications, expectations for quality of life after treatment must be discussed. While untreated disease can affect urinary continence, cause significant bleeding, produce intractable pain and exacerbate lower urinary tract symptoms, treatments such as radical cystectomy with diversion can significantly impact continence, sexual function, bowel function and acid-base disturbances. Furthermore, chemotherapy and radiation can also impact quality of life due to the aforementioned side effects. Overall, shared decision making should be conducted with the patient's vision in mind and what treatment option best aligns with his/her wishes.[23]

With regard to quality of life, several instruments are currently available that assess patient reported outcomes of MIBC.[24] Patients should have a good understanding of the possible impact of age and gender on the rate of complications, as the elderly and females have higher complication rates.[25] Age has also recently been associated with worse overall and cancer specific survival.[26] Mortality rates are currently less than 3% in most series, although reported as high as 4% to 6% in patients older than 75 years.[25, 26] Readmission rates vary from 10% to 30%, and a recent study revealed a 26% rate of readmission to an intensive care unit.[27] Psychological distress has also been associated with an impaired immune response and poor wound healing.[28] Similar to radical cystectomy, bladder preserving multimodal therapy has been associated with early and late (more than 120 days after therapy) complications.[29] Finally, the low rate of secondary malignancies should be addressed in those treated with radiation.

In addition to these complications, patients must understand the possible complications of diversion. Those with an ileal conduit must know how to use the external appliance or have someone who can assist with changing the device. Preoperative counseling with an enterostomal therapist proves extremely valuable for the patient and is recommended. Meanwhile, patients with continent cutaneous reservoirs will require self-catheterization for life and are subject to complications such as stomal incontinence, stricture, stones, pouchitis, metabolic abnormalities, parastomal hernias and problems with appliance fit. The risk of nocturnal incontinence is high for those treated with an orthotopic neobladder, and bladder neck contractures, voiding dysfunction with retention, fistula formation and metabolic abnormalities may develop as well. Urinary retention with neobladder is reportedly higher in women with catheterization rates up to 10% for men and 30% to 50% for women.[30] Finally, those treated with continent cutaneous diversion may have difficulty catheterizing, leakage and increased need for subsequent revision surgery.

Different metabolic abnormalities may occur depending on the bowel segment and length used for the diversion. Harvesting ileal or colonic segments may create malabsorption of bile salts, although this occurs infrequently with conduits. Using the distal ileum can result in inadequate absorption of vitamin B12 intrinsic factor complex, leading to megaloblastic anemia and neurological symptoms. Electrolyte abnormalities, such as hyperchloremic hypokalemic metabolic acidosis, may also occur when using ileal or colonic segments, although unusual in patients with normal renal function. Nevertheless, there may be renal function decline over time in patients undergoing cystectomy, and the rate of fractures after cystectomy may also be higher secondary to metabolic acidosis.[31, 32]

## INCORPORATION OF SYSTEMIC CHEMOTHERAPY IN THE TREATMENT PLAN

*Patient selection for neoadjuvant chemotherapy.* In the era predating effective combination chemotherapy, relapse rates within 2 years of radical extirpative surgery have been high, likely due to the presence of micrometastatic disease. Since the landmark article by Grossman et al in 2003,[5] the development of effective neoadjuvant chemotherapy has significantly benefited those with MIBC and been linked to improved survival.[33] Currently, the most commonly used neoadjuvant regimens are cisplatin based therapies, including MVAC (typically 4 weeks per cycle), dose-dense or dose escalated MVAC (typically 2 weeks per cycle), gemcitabine and cisplatin, and cisplatin, methotrexate and vinblastine.

It has also been reported that response to NAC varies by molecular subtype. Seiler et al performed whole transcriptome profiling on TURBT specimens with MIBC and classified samples according to 4 molecular subtypes.[34] Altogether, luminal tumors had the best overall survival with and without NAC, whereas basal tumors showed the most improvement in overall survival with NAC compared with surgery alone. Despite being based on a retrospective collection of data, to our knowledge this is the first single sample classifier to subtype MIBC, which may eventually be integrated into routine clinical practice after more extensive validation.

The optimal duration of NAC also remains undefined. Most studies evaluated 3 to 4 cycles of preoperative chemotherapy

during approximately 3 months, with several small studies testing shortened intensified regimens of 6 to 8 weeks of chemotherapy.[35] Nevertheless, there have been no RCTs comparing outcomes between the different regimens. Dose-dense or dose escalated MVAC has become a viable alternative for patients, with the European Organization for Research and Treatment of Cancer data suggesting significantly better complete response rates for the dose-dense regimen of 25% versus only 11% with traditional MVAC (p=0.006).[36]

With all of these NAC options, cisplatin eligibility is a major determinant of candidacy for NAC. Given its nephrotoxicity, diminished cardiac function, potential for hearing loss and neurotoxicity, 30% to 50% of patients with MIBC are ineligible for cisplatin based chemotherapy.[37] Baseline renal dysfunction with an estimated or calculated creatinine clearance <60 ml/minute is generally thought to prohibit patients from cisplatin based chemotherapy, although some patients still receive the medication using split-dosing and aggressive hydration. New York Heart Association Class III-IV heart failure with marked limitation in activity is prohibited, given the volume of intravenous fluid required for safe cisplatin administration. Hearing loss at a decrease of >25 dB in at least 1 ear on 2 separate occasions is also a contraindication, given that cisplatin may lead to an additional 20 dB loss. **For patients who cannot receive cisplatin, current guidelines recommend proceeding to definitive locoregional surgery rather than undergoing non-cisplatin based regimens in either the neoadjuvant or adjuvant setting. There is no high level evidence that carboplatin based regimens lead to increased survival of MIBC**, and they appear inferior in the metastatic setting based on the results of small randomized trials.[38]

Although there are data showing that delay in cystectomy beyond 3 months from diagnosis is associated with worse outcomes in patients treated with primary surgery, there are no substantive data currently regarding the optimal timing of cystectomy after NAC.[39] The guidelines recommend radical cystectomy within 6 to 8 weeks of chemotherapy completion but absolutely no longer than 4 months unless medically incapable of proceeding.[11] Further delay is believed to diminish the therapeutic benefit of systemic therapy, although this has recently been called into question.[40]

*Patient selection for adjuvant chemotherapy.* Current guidelines recommend adjuvant cisplatin based chemotherapy for those who have not received NAC and have non-organ confined (pT3/T4 and/or N+) disease at the time of cystectomy (Moderate recommendation; Evidence Level: Grade C).[11] **To date, however, no randomized clinical trial has demonstrated significant improvement in overall survival with adjuvant chemotherapy**. Whereas multiple trials demonstrated an associated decreased risk of mortality versus no adjuvant chemotherapy, no statistically significant benefit was found.[41,42] However, the largest setback of these trials is that they were all terminated early and subsequently underpowered to show a statistically significant benefit of adjuvant chemotherapy. Meta-analyses indicate a possible benefit, although the strength of evidence remains questionable.[43]

The current guidelines suggest that **cisplatin eligible patients with high risk pathological features should be offered adjuvant chemotherapy after a multidisciplinary consultation.[11] For those patients not eligible for cisplatin, referral to a clinical trial should be considered. There are currently multiple clinical trials of adjuvant therapy under way, most of which are focused on the use of new immunotherapy compounds**. Bellmunt et al evaluated cases of advanced urothelial carcinoma that progressed after platinum based chemotherapy in an open-label, international, phase 3 randomized controlled trial.[44] Patients were randomized to receive either pembrolizumab, an antibody against PD-1, or the investigator's choice of chemotherapy. Pembrolizumab was associated with a 3-month longer overall survival and fewer adverse events in patients who had a tumor PD-L1 combined positive score of 10% or more. Currently 5 PD-1 or PD-L1 antibodies are approved by the U.S. Food and Drug Administration for the treatment of metastatic bladder cancer, several of which are currently being tested in the adjuvant setting.

## CYSTECTOMY TECHNICAL PRINCIPLES

*Preoperative preparation*. Perioperative patient optimization is essential to a rapid recovery after radical cystectomy given the significant risk or morbidity and prolonged convalescence. As such, **current guidelines recommend patient optimization in line with enhanced recovery pathway principles.**[45] Because many patients are malnourished before surgery and preoperative malnourishment (albumin <3.5 gm/dL, body mass index <18.5 kg/m$^2$ and preoperative weight loss >5% of body weight ) has been linked to a significant increase in postoperative mortality at 90 days and 3 years, nutritional counseling is recommended to optimize nutritional status before cystectomy (see table).[46,47] In addition to nutrition counseling, all patients should receive counseling on smoking cessation as cessation has been linked to a reduction in postoperative complications and improvement in long-term oncology control.[47,48]

*Perioperative management.* A significant risk of any major pelvic surgery including radical cystectomy is a thromboembolic event potentially leading to a life threatening complication. Patients undergoing cystectomy often have multiple risk factors associated with thrombosis as detailed in the AUA best practice statement on prevention of deep vein thrombosis.[49] As such, the guidelines recommend the use of combined mechanical and pharmacologic prophylaxis in patients undergoing radical cystectomy based on strong data support for reduction in venous thromboembolic events in those undergoing pelvic surgery (Strong Recommendation; Evidence Level: Grade B).[11] Pharmacologic prophylaxis should also be given just before induction of anesthesia. The optimal timing and duration of chemoprophylaxis have not been determined, although increasing evidence suggests a preoperative dose may decrease the risk of venous thromboembolism. Furthermore, continuing pharmacologic prophylaxis for up to 4 weeks postoperatively may be beneficial. Although the guidelines committee did not mandate therapy for a longer duration, the degree of benefit was significant in several randomized trials to warrant continuation of chemoprophylaxis postoperatively.[50,51]

In addition to thromboembolic prophylaxis, ileus is another source of postoperative morbidity and increased hospital stay. Peripherally active μ-opioid receptor antagonists are known to enhance bowel function recovery and decrease hospital stay in patients undergoing

**Table**. Predictors of overall complications following cystectomy for treating bladder cancer with special emphasis on selected nutritional-dependent prognostic factors

| | Adjusted Odds Ratio (95% CI) |
|---|---|
| *Albumin distribution dichotomized at 3.5* | |
| Preop albumin <3.5 (p=0.03):<br>Yes<br>No | <br>1.79 (1.06, 3.03)<br>Reference |
| >10% Body wt loss in last 6 mos (p=0.92):<br>Yes<br>No | <br>1.05 (0.44, 2.52)<br>Reference |
| Body mass index/1 unit increase (p=0.73) | 1.01 (0.98, 1.04) |
| *Continuous albumin distribution* | |
| Preop albumin/0.5 mg/dL decrease (p=0.02) | 1.20 (1.02, 1.40) |
| >10% Body wt loss in last 6 mos (p=0.94):<br>Yes<br>No | <br>1.03 (1.02, 1.40)<br>Reference |
| Body mass index/1 unit increase (p=0.84) | 1.00 (0.97, 1.03) |

The p values are after adjusting for significant variables on bivariable analysis (body mass index, age, sex, resident present in operating room, year of surgery, smoking history, preoperative pulmonary and cardiac comorbidity, preoperative acute renal failure, prior surgery within 30 days, operative time, ASA® classification and preoperative blood transfusion). Remaining nutritional parameters are included in the multivariable model regardless of bivariable significance.

radical cystectomy.[52] **In a prospective randomized controlled trial of 277 patients use of μ-opioid receptor antagonists correlated with significant improvement in bowel function recovery after radical cystectomy (5.5 vs 6.8 days, p <0.0001) and shortened hospital stay (7.4 vs 10.1 days, p=0.005).[52]**

Recent data do not support use of mechanical bowel preparation before colorectal surgery, and there appears to be no increased risk of perioperative complications in its absence. Furthermore, preoperative carbohydrate loading appears to reduce postoperative insulin resistance and decrease length of stay. It has not been shown to increase the anesthetic risk and may improve the return of bowel function.[53]

*Importance of node dissection.* Current guidelines state that clinicians must perform bilateral pelvic lymphadenectomy at the time of any surgery with curative intent (Strong Recommendation; Evidence Level: Grade B) and when clinicians should remove the external, internal iliac and obturator lymph nodes (standard lymphadenectomy) at a minimum (Clinical Principle).[11] Several mapping studies have indicated that the risk of regional lymph node metastases correlates with the depth of invasion of the primary tumor. Numerous studies have shown pelvic lymphadenectomy to improve disease specific survival and pelvic recurrence risk at the time of radical cystectomy.[54] Furthermore, there has been a documented crossover risk to the contralateral lymphatic chain and as such, all patients should undergo bilateral pelvic lymphadenectomy.

Although the use of extended node dissection has gained significant traction in the last decade, no standardized, uniform recommendation exists for the optimal extent of pelvic lymphadenectomy that should be performed to maximize therapeutic benefit. Nevertheless, **at a minimum lymphadenectomy involving the bilateral external iliac, internal iliac and obturator lymph nodes with >12 lymph nodes evaluated should be performed**.[55] The total lymph node number identified by the pathologist is used as a surrogate for the extent of lymphadenectomy performed, as it reflects the completeness of surgical dissection and quality of the pathological examination. Despite the lack of a uniform recommendation for the extent of lymphadenectomy, cohort studies have found that extending lymphadenectomy above the common iliac bifurcation to the level of the aortic bifurcation is associated with improved all-cause bladder cancer specific mortality. However, these results have been inconsistent with variability in the techniques evaluated, leading to the inability to recommend an extended template for all patients.[56]

*Role of nerve and uterine sparing in radical cystectomy.* Radical cystectomy is well-known to pose a significant risk for sexual dysfunction. Nevertheless, performance of nerve sparing cystectomy is infrequent and even with nerve sparing, erectile dysfunction rate is 40% or greater.[57] Meanwhile, females also report sexual dysfunction, most notably loss of sexual desire (49%), orgasmic disorders (39%), dyspareunia (25%) and vaginal lubrication disorders (9.5%). The sexual dysfunction rates reported for patients undergoing a vaginal sparing technique vs conventional radical cystectomy are 10% vs 59%.[58] **Additionally, preservation of the uterus, anterior vaginal wall, and ovaries may be options for highly select women, and preservation of the ovaries has not been associated with bladder cancer recurrence**. Prostate and seminal vesicle preservation for men desiring continued fertility may be offered only to select men.[59]

## BLADDER PRESERVATION

*Patient selection and role of maximal transurethral resection and*

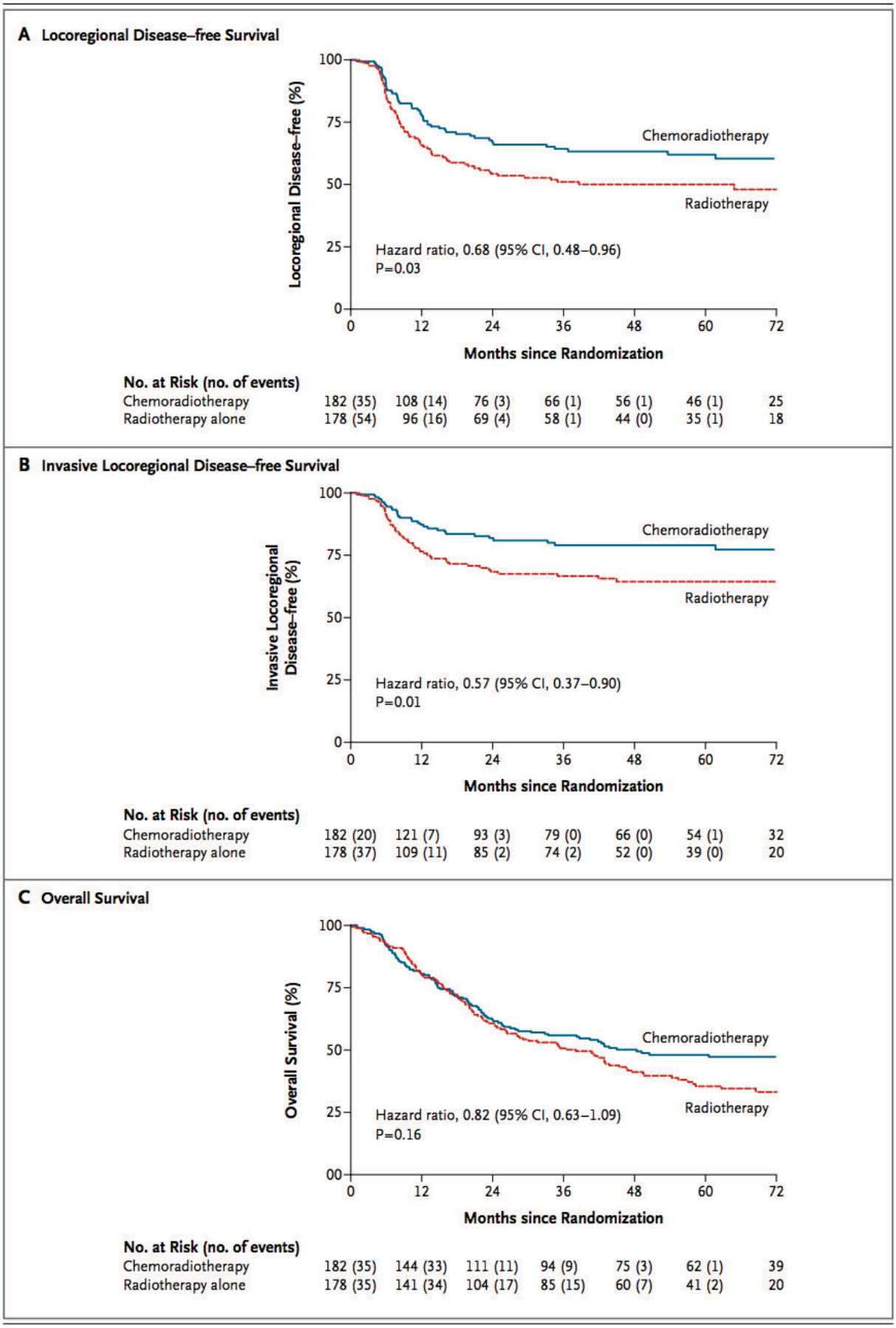


**Figure**. Effect of chemotherapy and radiation vs radiation alone on locoregional disease-free survival according to subgroup.

*concomitant chemotherapy.* Although it is not the current standard of care and clinicians should offer radical cystectomy to patients with localized disease who are fit for surgery, bladder preserving treatments are being performed at most U.S. institutions for patients who refuse or are not considered surgical candidates for radical cystectomy. Randomized data indicate that chemotherapy is superior to radiation alone for localized disease treated via a bladder preserving approach (see figure).[60] An essential component is maximal resection of all visible tumor with TURBT before chemotherapy and external beam radiotherapy, which improves local control.[61]

For medically fit patients receiving staged multimodal therapy, providers may offer a mid course evaluation to detect non-responders before giving consolidation radiotherapy. Radical cystectomy may be more difficult with the potential for increased complications after prior full dose external beam radiation therapy and the choice of urinary diversion and/or the ability to perform nerve sparing surgery may be limited.[60] Furthermore, all bladder preserving therapies mandate close and continued follow-up of the bladder.[62]

*Supporting the role of bladder preservation as a viable alternative to radical cystectomy.* The current guidelines state that multimodal bladder preserving therapy is the preferred treatment for patients medically unfit for surgery, and for those who desire bladder preservation and understand its associated risks. Nevertheless, few studies have compared the effects of various bladder preserving therapies to radical cystectomy, and to date there have been 1 randomized clinical trial,[63] 7 retrospective studies[64] and 1 non-randomized clinical trial.[65] Sample sizes varied from 145 to 2455 patients, and none reported the percentage of patients with clinically localized disease found to have nodal metastases on pathological staging or whether these patients were excluded from analyses. Furthermore, the randomized controlled trial had a high risk of bias due to baseline differences between treatment groups and questionable reporting of attrition, and the treatment arm involved antiquated radiotherapy regimens and surgical techniques.

The majority of these studies concluded that bladder preserving therapies were associated with worse outcomes than radical cystectomy. Nevertheless, the comparative arms were heterogeneous, and the randomized trial showed no difference in median survival duration between bladder preserving external beam radiotherapy and radical cystectomy plus external beam radiotherapy, despite an increased risk of local or regional disease recurrence. The majority of the non-randomized studies concluded that bladder preserving therapies correlated with higher mortality or risk of disease recurrence.[64]

## SURVEILLANCE

*After cystectomy.* Imaging: **Current guidelines recommend chest and cross-sectional imaging with intravenous contrast as well as delayed images to evaluate the collecting system and other areas for sites of possible metastatic disease.** Imaging the abdomen and pelvis also allows for thorough evaluation of the urinary diversion to rule out hydronephrosis. With regard to upper tract recurrence, a meta-analysis of 13,185 participants from 27 studies revealed an overall prevalence of upper tract urothelial cell carcinoma after cystectomy of 0.75% to 6.4%.[66] Of the patients 62% were diagnosed based on symptoms such as hematuria, whereas the other 38% were diagnosed based on follow-up investigation. Of 5537 patients who underwent upper urinary tract imaging renal pelvic and/or ureteral cancer was detected in 7.6/1,000. Symptoms again were the precipitating sign for diagnosis of upper tract disease despite surveillance, and these malignancies often presented later than the first 2 years after definitive treatment.[67]

While PET/CT is believed to help resolve equivocal abnormal findings, it is not recommended for routine surveillance imaging. Imaging after 5 years is deemed to be a decision between the patient and provider after shared decision making, as upper urinary tract disease can occur many years after cystectomy, especially in those who continue to smoke. Longer surveillance imaging may also help detect strictures resulting from the diversion, allowing for an intervention(s) before upper tract deterioration occurs.

Laboratory Values: In addition to imaging, all patients should undergo renal function studies and assessment of electrolytes after radical cystectomy and diversion. A significant number experience renal function decline after cystectomy and, depending on the type and length of bowel used, hypokalemia, hyponatremia and/or hypokalemic hyperchloremic metabolic acidosis can occur.[68] Vitamin B12 levels should also be checked, especially when >60 cm of ileum or the terminal ileum has been resected, as there is an increased risk of deficiency and resultant neurological damage.[69] Routine performance of complete blood cell count and liver function tests as a metric for tumor recurrence has not been validated at this time.

**Current guidelines do not recommend routine urine cytology for patients after radical cystectomy.** While it is non-invasive and easy to collect, its overall usefulness is limited as the yield is low and it may prove confusing. In addition, patients with a positive cytology may not manifest tumors for several years.[70] The previously mentioned meta-analysis estimated it would require 2000 urinary cytology examinations to find a single invasive upper tract malignancy.[66] Urine collected from intestinal urinary diversion or a previously irradiated bladder often contains desquamated intestinal epithelial cells or atypia, which likely lowers the diagnostic specificity as well. The rate of primary detection with upper tract imaging was 29.6% vs 7% for urine cytology.[66] Thus, data to recommend the routine use of urine cytology or other urinary markers for detection of upper tract urothelial cell carcinoma are insufficient. Recently, several new protein and cell based urine biomarkers have shown promise for detecting urothelial cell carcinoma recurrence in the bladder and upper tract,[71] but they have neither been evaluated extensively for NMIBC nor validated in patients treated with cystectomy and diversion or radiation.[72]

Retained Urethra: It is important to monitor the urethral remnant for recurrence after cystectomy as the risk ranges from 4% to 17%, with the greatest risk factors being tumor multiplicity, papillary pattern, carcinoma in situ, bladder neck involvement, prostatic urethral mucosal involvement and prostatic stromal invasion.[73] Symptomatic patients at the time of urethral recurrence tend to present with a higher stage of disease vs those who are asymptomatic. Urethral wash cytology is recommended for detecting carcinoma in situ and urethral

cancer in asymptomatic patients. The overall survival benefit of a urethral wash is uncertain, but current guidelines consider it possibly valuable in high risk patients.[74] As such**, a urethral wash should be considered at follow-up as should a discussion of urethral symptoms including discharge and spotting.**

*After chemoradiation*. In patients who have undergone bladder preserving protocols surveillance is still required as they remain at risk for invasive and non-invasive recurrences and tumor formation in the upper tracts. Currently, there are no data to determine the optimal frequency of surveillance, but most protocols encourage frequent follow-up. **The AUA guidelines recommend cystoscopy every 3 months for the first year, every 4 to 6 months in year 2 and every 6 to 12 months thereafter.[11] The guidelines also recommend abdominal and pelvic cross-sectional imaging, and chest imaging every 6 months for the first 2 years,** although the survival benefit is unclear. Salvage cystectomy should be considered in patients with localized muscle invasive recurrence. Local measures may be offered to patients with non-muscle invasive recurrence after bladder preserving therapy, with reports suggesting that NMIBC recurrences may still be managed similarly to *de novo* NMIBC.[72]

## CONCLUSIONS

Despite numerous recent advances in bladder cancer care, key areas of future research are essential to improving outcomes for patients with MIBC. With regard to surgery, radical cystectomy is being performed via a robotic approach more frequently with the hope of decreasing morbidity. Long-term data on improved perioperative morbidity, oncologic benefit and/or improved quality of life remain to be seen, although randomized controlled trials are currently under way. Organ sparing operations, including vaginal and nerve sparing cystectomy, are likely to continue to gain traction as well but the oncologic efficacy must continue to be carefully assessed. Meanwhile, the rapid increase in immunotherapeutic agents for bladder cancer should continue as these agents have shown promise in phase II and phase III clinical trials. These trials have shown significant antitumor activity of the anti-PD-1 and anti-PDL-1 antibodies in the metastatic setting. Their exact role and whether they will be used alone or in combination with other agents for all stages of bladder cancer remain to be seen.

Additional studies are also needed to better incorporate multimodal therapy for MIBC, including specifying the exact roles of adjuvant chemotherapy and immunotherapy in this setting, especially for positive margins or lymph node involvement after cystectomy. Furthermore, research on the therapeutic benefit of an extended lymph node dissection and overall usefulness of adjuvant therapy will help better guide management going forward. Most importantly, we must not forget how each of these modalities affects quality of life. The physical and psychosocial impairments related to therapy are essential to understand, and patient education, bladder cancer survivorship planning and focus on quality of life must play a pivotal role going forward.

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# Study Questions Volume 37 Lesson 29

1. An 85-year-old man with bilateral below the knee amputations from uncontrolled diabetes mellitus and chronic kidney disease (creatinine 2.3 mg/dL) is diagnosed with muscle invasive bladder cancer. In seeking bladder sparing curative therapy, the patient should be advised to undergo
   a. radiation alone
   b. pelvic lymph node dissection only
   c. partial cystectomy
   d. initial complete resection of all visible tumor prior to chemotherapy or radiation

2. A 70-year-old woman with newly diagnosed muscle invasive bladder cancer is debating whether to receive neoadjuvant chemotherapy. It is critical she knows that
   a. there is no known survival benefit of neoadjuvant chemotherapy
   b. cisplatin based neoadjuvant chemotherapy is associated with a decreased risk of cancer-specific mortality for muscle invasive bladder cancer
   c. carboplatin based regimens lead to increased survival for muscle invasive bladder cancer
   d. dose-dense MVAC appears to have worse activity and increased toxicity compared to the traditional MVAC regimen

3. A 68-year-old healthy female underwent TURBT for muscle invasive bladder cancer with no palpable mass on bimanual exam. Preoperatively, renal ultrasound showed no hydronephrosis. Glomerular filtration rate is >62 ml/minute/1.73m$^2$. The next step is
   a. CT or MRI of the abdomen/pelvis with intravenous contrast and chest x-ray or CT
   b. PET/CT
   c. CT or MRI of the abdomen/pelvis without contrast and chest x-ray
   d. proceed with cystectomy

4. A 62-year-old female with high grade muscle invasive urothelial cell carcinoma is taken to the operating room for an open radical cystectomy with continent catheterizable stoma. With regard to the pelvic lymphadenectomy
   a. only obturator nodes need to be removed
   b. a unilateral template lymphadenectomy is acceptable for a small, lateral tumor
   c. a standard lymphadenectomy needs >12 nodes evaluated
   d. an extended node dissection is mandatory in all patients undergoing radical cystectomy

5. A 74-year-old man is preparing to undergo a radical cystectomy with ileal conduit. With regard to perioperative patient optimization, the agent correlated with a decreased hospital stay is
   a. enoxaparin
   b. magnesium citrate
   c. carbohydrate-rich beverage
   d. μ-opioid antagonist therapy

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