Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer: AUA/ASCO/ASTRO/SUO Guideline
Introduction

• 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 (QOL) concerns.

• For the first time for any type of malignancy, the American Urological Association (AUA), the American Society of Clinical Oncology (ASCO), the American Society for Radiation Oncology (ASTRO), and the Society of Urologic Oncology (SUO) have formulated a consensus, evidence-based guideline.

• This guideline provides a risk-stratified, clinical framework for the management of muscle-invasive urothelial bladder cancer.
Guideline Development Methodology

The guideline process included:

• a systematic literature review by a research librarian
• an expert panel provides critical review and evidence interpretation to inform guideline recommendations
• final guideline approval by AUA, ASTRO, ASCO, and SUO

The full guideline methodology can be found at:
<table>
<thead>
<tr>
<th>Evidence Strength</th>
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<tbody>
<tr>
<td>A (High Certainty)</td>
<td>B (Moderate Certainty)</td>
<td>C (Low Certainty)</td>
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### Strong Recommendation

(Net benefit or harm substantial)

- **Benefits > Risks/Burdens (or vice versa)**
- Net benefit (or net harm) is substantial
- Applies to most patients in most circumstances and future research is unlikely to change confidence

- **Benefits > Risks/Burdens (or vice versa)**
- Net benefit (or net harm) is substantial
- Applies to most patients in most circumstances but better evidence could change confidence (rarely used to support a Strong Recommendation)

- **Benefits > Risks/Burdens (or vice versa)**
- Net benefit (or net harm) appears substantial
- Applies to most patients in most circumstances but better evidence is likely to change confidence

### Moderate Recommendation

(Net benefit or harm moderate)

- **Benefits > Risks/Burdens (or vice versa)**
- Net benefit (or net harm) is moderate
- Applies to most patients in most circumstances and future research is unlikely to change confidence

- **Benefits > Risks/Burdens (or vice versa)**
- Net benefit (or net harm) is moderate
- Applies to most patients in most circumstances but better evidence could change confidence

- **Benefits > Risks/Burdens (or vice versa)**
- Net benefit (or net harm) appears moderate
- Applies to most patients in most circumstances but better evidence is likely to change confidence

### Conditional Recommendation

(No apparent net benefit or harm)

- **Benefits = Risks/Burdens**
- Best action depends on individual patient circumstances
- Future research unlikely to change confidence

- **Benefits = Risks/Burdens**
- Best action appears to depend on individual patient circumstances
- Better evidence could change confidence

- Balance between Benefits & Risks/Burdens unclear
- Alternative strategies may be equally reasonable
- Better evidence likely to change confidence

### Clinical Principle

A statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature

### Expert Opinion

A statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence

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Summary of Recommendations

INITIAL PATIENT EVALUATION AND COUNSELING

1. Before treatment consideration, a full history and physical exam should be performed, including an exam under anesthesia, at the time of transurethral resection of bladder tumor (TURBT) for a suspected invasive cancer. (Clinical Principle)

2. Before muscle-invasive bladder cancer management, clinicians should perform a complete staging evaluation, including imaging of the chest and cross sectional imaging of the abdomen and pelvis with intravenous contrast if not contraindicated. Laboratory evaluation should include a comprehensive metabolic panel (complete blood count, liver function tests, alkaline phosphatase, and renal function). (Clinical Principle)

3. An experienced genitourinary pathologist should review the pathology of a patient when variant histology is suspected or if muscle invasion is equivocal (e.g., micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid, extensive squamous or glandular differentiation). (Clinical Principle)

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Summary of Recommendations

4. For patients with newly diagnosed muscle-invasive bladder cancer, curative treatment options should be discussed before determining a plan of therapy that is based on both patient comorbidity and tumor characteristics. Patient evaluation should be completed using a multidisciplinary approach. (Clinical Principle)

5. Before treatment, clinicians should counsel patients regarding complications and the implications of treatment on quality of life (e.g., impact on continence, sexual function, fertility, bowel dysfunction, metabolic problems). (Clinical Principle)
Summary of Recommendations

TREATMENT

NEOADJUVANT AND ADJUVANT CHEMOTHERAPY

6. Using a multidisciplinary approach, clinicians should offer cisplatin-based neoadjuvant chemotherapy to eligible radical cystectomy patients prior to cystectomy. (Type of recommendation: evidence based; Evidence quality: grade B; Strength of recommendation: strong)

7. Clinicians should not prescribe carboplatin-based neoadjuvant chemotherapy for clinically resectable stage cT2-T4aN0 bladder cancer. Patients ineligible for cisplatin-based neoadjuvant chemotherapy should proceed to definitive locoregional therapy. (Expert Opinion)

8. Clinicians should perform radical cystectomy as soon as possible following a patient’s completion of and recovery from neoadjuvant chemotherapy. (Expert Opinion)

9. Eligible patients who have not received cisplatin-based neoadjuvant chemotherapy and have non-organ confined (pT3/T4and/or N+) disease at cystectomy should be offered adjuvant cisplatin-based chemotherapy. (Type of recommendation: evidence based; Evidence quality: grade C; Strength of recommendation: moderate)
Summary of Recommendations

RADICAL CYSTECTOMY

10. Clinicians should offer radical cystectomy with bilateral pelvic lymphadenectomy for surgically eligible patients with resectable non-metastatic (M0) muscle-invasive bladder cancer. (Type of recommendation: evidence based; Evidence quality: grade B; Strength of recommendation: strong)

11. When performing a standard radical cystectomy, clinicians should remove the bladder, prostate, and seminal vesicles in males and should remove the bladder, uterus, fallopian tubes, ovaries, and anterior vaginal wall in females. (Clinical Principle)

12. Clinicians should discuss and consider sexual function-preserving procedures for patients with organ-confined disease and absence of bladder neck, urethra, and prostate (male) involvement. (Type of recommendation: evidence based; Evidence quality: grade C; Strength of recommendation: moderate)
Summary of Recommendations

**URINARY DIVERSION**

13. In patients undergoing radical cystectomy, ileal conduit, continent cutaneous, and orthotopic neobladder urinary diversions should all be discussed. (Clinical Principle)

14. In patients receiving an orthotopic urinary diversion, clinicians must verify a negative urethral margin. (Clinical Principle)
15. Clinicians should attempt to optimize patient performance status in the perioperative setting. (Expert Opinion)

16. Perioperative pharmacologic thromboembolic prophylaxis should be given to patients undergoing radical cystectomy. (Type of recommendation: evidence based; Evidence quality: grade B; Strength of recommendation: strong)

17. In patients undergoing radical cystectomy, $\mu$-opioid antagonist therapy should be used to accelerate gastrointestinal recovery, unless contraindicated. (Type of recommendation: evidence based; Evidence quality: grade B; Strength of recommendation: strong)

18. Patients should receive detailed teaching regarding care of urinary diversion before discharge from the hospital. (Clinical Principle)
Summary of Recommendations

PELVIC LYMPHADENECTOMY

19. Clinicians must perform a bilateral pelvic lymphadenectomy at the time of any surgery with curative intent. (Type of recommendation: evidence based; Evidence quality: grade B; Strength of recommendation: strong)

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

BLADDER PRESERVING APPROACHES

PATIENT SELECTION

21. For patients with newly diagnosed nonmetastatic muscle-invasive bladder cancer who desire to retain their bladder, and for those with significant comorbidities for whom radical cystectomy is not a treatment option, clinicians should offer bladder-preserving therapy when clinically appropriate. (Clinical principle)

22. In patients under consideration for bladder-preserving therapy, maximal debulking TURBT and assessment of multifocal disease/carcinoma in situ should be performed. (Type of recommendation: evidence based; Evidence quality: grade C; Strength of recommendation: strong)

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Summary of Recommendations

MAXIMAL TURBT AND PARTIAL CYSTECTOMY

23. Patients with muscle-invasive bladder cancer who are medically fit and consent to radical cystectomy should not undergo partial cystectomy or maximal TURBT as primary curative therapy. (Type of recommendation: evidence based; Evidence quality: grade C; Strength of recommendation: moderate)

PRIMARY RADIATION THERAPY

24. For patients with muscle-invasive bladder cancer, clinicians should not offer radiation therapy alone as a curative treatment. (Type of recommendation: evidence based; Evidence quality: grade C; Strength of recommendation: strong)
Summary of Recommendations

MULTI-MODAL BLADDER PRESERVING THERAPY

25. For patients with muscle-invasive bladder cancer who have elected multi-modal bladder preserving therapy, clinicians should offer maximal TURBT, chemotherapy combined with external beam radiation therapy, and planned cystoscopistic re-evaluation. (Type of recommendation: evidence based; Evidence quality: grade B; Strength of recommendation: strong)

26. Radiation sensitizing chemotherapy regimens should include cisplatin or 5-fluorouracil and mitomycin C. Type of recommendation: evidence based; Evidence quality: grade B; Strength of recommendation: strong)

27. After completion of bladder preserving therapy, clinicians should perform regular surveillance with CT scans, cystoscopy, and urine cytology. (Type of recommendation: evidence based; Evidence quality: grade C; Strength of recommendation: strong)
Summary of Recommendations

BLADDER PRESERVING TREATMENT FAILURE

28. In patients who are medically fit and have residual or recurrent muscle-invasive disease following bladder preserving therapy, clinicians should offer radical cystectomy with bilateral pelvic lymphadenectomy. (Type of recommendation: evidence based; Evidence quality: grade C; Strength of recommendation: strong)

29. In patients who have a non-muscle invasive recurrence after bladder preserving therapy, clinicians may offer either local measures, such as TURBT with intravesical therapy, or radical cystectomy with bilateral pelvic lymphadenectomy. (Type of recommendation: evidence based; Evidence quality: grade C; Strength of recommendation: moderate)
Summary of Recommendations

PATIENT SURVEILLANCE AND FOLLOW UP

IMAGING

30. Clinicians should obtain chest imaging and cross-sectional imaging of the abdomen and pelvis with CT or MRI at 6-12 month intervals for 2-3 years and then may continue annually. (Expert Opinion)

LABORATORY VALUES AND URINE MARKERS

31. After therapy for muscle-invasive bladder cancer, patients should undergo laboratory assessment at three to six month intervals for two to three years and then annually thereafter. (Expert Opinion)

32. After radical cystectomy in patients with a retained urethra, clinicians should monitor the urethral remnant for recurrence. (Expert Opinion)
Summary of Recommendations

**PATIENT SURVIVORSHIP**

33. Clinicians should discuss with patients how they are coping with their bladder cancer diagnosis and treatment and should recommend that patients consider participating in cancer support groups or consider receiving individual counseling. (Expert Opinion)

34. Clinicians should encourage bladder cancer patients to adopt healthy lifestyle habits, including smoking cessation, exercise, and a healthy diet, to improve long-term health and quality of life. (Expert Opinion)

**VARIANT HISTOLOGY**

35. In patients diagnosed with variant histology, clinicians should consider unique clinical characteristics that may require divergence from standard evaluation and management for urothelial carcinoma. (Expert Opinion)
Future Research

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**
  - Enhanced detection of bladder cancer cells via imaging technology or other means
  - Urinary and serum based markers that can be used to identify early urothelial based and/or distant recurrences
  - Prognostic and predictive genetic markers to guide diagnosis and decision making

- **Therapy**
  - Role of antibodies alone or in combination with other therapies
  - Integration of multi-modal therapies
  - Studies emphasizing PROs after treatment

- **Surveillance**
  - The role of specific imaging tests and laboratory studies and their appropriate interval
Additional Resources

More information, including a Data Supplement, a Methodology Supplement, slide sets, and clinical tools and resources, is available at

www.asco.org/genitourinary-cancer-guidelines

Patient information is available at www.cancer.net
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