Guideline on Muscle-Invasive and Metastatic Bladder Cancer (European Association of Urology Guideline): American Society of Clinical Oncology Clinical Practice Guideline Endorsement
Introduction

• The purpose of this American Society of Clinical Oncology (ASCO) Guideline is to endorse the European Association of Urology (EAU) Guidelines on muscle-invasive and metastatic bladder cancer, published by Witjes JA et al. and published online by the EAU in March 2015.

• This ASCO endorsement reinforces the recommendations offered in the guidelines on muscle-invasive and metastatic bladder cancer and acknowledges the effort put forth by the EAU to produce an evidence-based guideline informing practitioners who care for patients with muscle-invasive and metastatic disease.
ASCO Endorsement Methodology

The ASCO Clinical Practice Guidelines Committee endorsement review process includes:

- a methodological review by ASCO guidelines staff
- a content review by an ad hoc expert panel
- final endorsement approval by ASCO CPGC.

The full ASCO Endorsement methodology supplement can be found at:

www.asco.org/endorsements/MIBC

EAU Guideline Methodology can be found at:

Clinical Questions

The EAU guideline did not disclose specific research questions, but instead presented the recommendations according to the following domains:

• primary assessment of presumably invasive bladder tumors
• classification of muscle-invasive bladder cancer
• treatment failure in non–muscle invasive bladder cancer
• neoadjuvant chemotherapy
• comorbidity scales
• radical cystectomy and urinary diversion
• nonresectable tumors and palliative care
• preoperative radiotherapy
• bladder-sparing treatments for localized disease
• adjuvant chemotherapy
• metastatic disease
• health-related quality of life
• follow-up

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Target Population and Audience

Target Population
Patients with muscle-invasive or metastatic bladder cancer

Target Audience
Primary care providers, urologists, radiation and medical oncologists, and other providers
Summary of Recommendations

Primary assessment of presumably invasive bladder tumors

• Cystoscopy should describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended when feasible.

• Biopsy of the prostatic urethra is recommended when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible. Additionally, prostatic urethral biopsy should be considered for cases of bladder neck tumour or when bladder CIS is present or suspected.

• If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.

• In women undergoing subsequent orthotopic neobladder construction, procedural information is required (including histological evaluation) of the bladder neck and urethral margin, either prior to or at the time of cystectomy.

• The pathological report should specify the grade, histology, depth of tumour invasion, and whether the lamina propria and muscle tissue are present in the specimen.
Summary of Recommendations

Comorbidity scales

- **Any** decision regarding bladder-sparing or radical cystectomy in elderly/geriatric patients with invasive bladder cancer should be based on tumour stage, **bladder function, and the ability to tolerate major surgery, radiotherapy and/or chemotherapy.**

- The ASA score does not address comorbidity and should not be used in this setting.

Treatment failure in non–muscle invasive bladder cancer

- In all T1 tumors at high risk of progression (i.e., high grade, multifocality, CIS, and tumor size, as outlined in the EAU guidelines for non-muscle-invasive bladder cancer*), immediate radical treatment is an option.

- In all T1 patients failing intravesical therapy, radical treatment should be offered.

*Available at: [http://www.uroweb.org/guidelines/online-guidelines](http://www.uroweb.org/guidelines/online-guidelines).
Neoadjuvant chemotherapy

- Neoadjuvant chemotherapy is recommended for T2-T4a, cN0M0 bladder cancer and should always be cisplatin-based combination therapy.
- Neoadjuvant chemotherapy is not recommended in patients who are ineligible for cisplatin-based combination chemotherapy, *unless the goal is downstaging surgically unresectable tumors*.

Pre- and postoperative radiotherapy

- Pre-operative radiotherapy is not recommended to improve survival.
Summary of Recommendations

Radical cystectomy and urinary diversion

• *For patients that are not receiving neoadjuvant chemotherapy*, cystectomy *for MIBC should be performed within* 3 months of *diagnosis to lower* the risk of progression and cancer-specific mortality.

• Before cystectomy, the patient should be fully informed about the benefits and potential risks of all possible alternatives, and the final decision should be based on a balanced discussion between patient and surgeon.

• *In addition to ileal conduit diversion*, an orthotopic bladder substitute should be offered to male and female patients lacking any contraindications and who have no tumor in the urethra or at the level of urethral dissection.

• Preoperative radiotherapy is not recommended *for patients undergoing* cystectomy with urinary diversion.

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Summary of Recommendations

- Pre-operative bowel preparation is not mandatory. “Fast track” measurements may reduce the time of bowel recovery.
- Radical cystectomy is recommended in T2-T4a, N0 M0, and high-risk non-MIBC. *Chemo-radiation based organ preservation treatment may be offered to select patients with MIBC.*
- Lymph node dissection should be an integral part of cystectomy. Extended LND is recommended.
- The urethra can be preserved if margins are negative. If no bladder substitution is attached, the urethra must be surveyed regularly in males.
- Laparoscopic cystectomy and robot-assisted laparoscopic cystectomy are both management options. However, current data have not sufficiently proven the advantages or disadvantages for oncological and functional outcomes.

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Summary of Recommendations

Nonresectable tumors: palliative cystectomy for muscle-invasive bladder carcinoma

- In patients with inoperable locally advanced tumors (T4b), primary radical cystectomy is a palliative option and cannot be offered as curative treatment.
- In patients with symptoms palliative cystectomy may be offered.

Bladder-sparing treatments for localized disease

- Transurethral resection of bladder tumor (TURB) alone is not a curative treatment option in most patients.
- Radiotherapy alone is not recommended as primary therapy for localised bladder cancer.
- Chemotherapy alone is not recommended as primary therapy for localized bladder cancer.
Summary of Recommendations

• Neoadjuvant chemotherapy followed by radical cystectomy or bladder-preserving chemoradiotherapy treatments are the preferred curative therapeutic approaches as they are more effective than radiotherapy alone.

• Bladder-preserving multimodality treatment could be offered as an alternative to cystectomy in appropriately selected patients, and may be appropriate in some patients for whom cystectomy is not an option.

Adjuvant chemotherapy

• Adjuvant cisplatin based combination chemotherapy may be offered to patients with pT3/4 and/or pN+) disease if no neoadjuvant chemotherapy has been given.

• While neoadjuvant chemotherapy is recommended, adjuvant chemotherapy may be offered to high-risk patients that did not receive neoadjuvant treatment*.

*The word “offered” should be interpreted as having a detailed discussion with the patient about the risks and benefits and limitations of the available data to facilitate shared decision making.
Summary of Recommendations

Metastatic disease
First-line treatment for fit patients:
• First-line treatment for fit patients: Use cisplatin-containing combination chemotherapy with *GC, MVAC, or HD-MVAC with G-CSF*.
• Carboplatin and non-platinum combination chemotherapy is not recommended.

First-line treatment in patients ineligible (unfit) for cisplatin:
• Use carboplatin combination chemotherapy or single agents.
• For cisplatin-ineligible (unfit) patients, with PS2 or impaired renal function, as well as those with 0 or 1 poor Bajorin prognostic factors and impaired renal function, treatment with carboplatin-containing combination chemotherapy, preferably with gemcitabine/carboplatin is indicated.

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Summary of Recommendations

Second-line treatment:

• In patients progressing after platinum-based combination chemotherapy for metastatic disease, **entry into a clinical trial is preferred.** 
  Alternatively, single-agent therapy may be offered (e.g. paclitaxel, docetaxel, or vinflunine where available).

• Zoledronic acid or denosumab **may be offered** for treatment of bone metastases*.

Biomarkers

• Currently, no biomarkers can be recommended in daily clinical practice because they have no impact on predicting outcome, treatment decisions, or monitoring therapy in muscle-invasive bladder cancer.

*The word “offered” should be interpreted as having a detailed discussion with the patient about the risks and benefits and limitations of the available data to facilitate shared decision making.
Summary of Recommendations

Health-related quality of life

• The use of validated questionnaires is recommended to assess HRQoL in patients with MIBC.

• Unless a patient’s comorbidities, tumour variables and coping abilities present clear contraindications, a continent urinary diversion should be offered to patients undergoing cystectomy.

• Pre-operative patient information, patient selection, surgical techniques, and careful post-operative follow-up are the cornerstones for achieving good long-term results.

• Patients should be encouraged to take active part in the decision-making process. Clear and exhaustive information on all potential benefits and side-effects should be provided, allowing them to make informed decisions.

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Follow-up

Local recurrence, poor prognosis: Treatment should be individualized depending on the local extent of tumor.

- Radiotherapy, chemotherapy and possibly surgery are options for treatment, either alone or in combination.

Distant recurrence, poor Prognosis:

- Chemotherapy is the first option, and consider individualized cases for metastatectomy when oligometastatic disease is present.
Summary of Recommendations

Secondary urethral tumor: Staging and treatment should be done as for primary urethral tumor.

- Local conservative treatment is possible for non-invasive tumor.
- In isolated invasive disease, urethrectomy should be performed.
- Urethral washes and cytology *should be considered in high risk patients.*
In particular, the panel:
1) Emphasizes that radiotherapy alone is inferior to chemo-radiation.
2) Maintains that adjuvant cisplatin-based chemotherapy is an option in high-risk patients that did not receive neoadjuvant chemotherapy.
3) Encourages clinical trial participation for those patients with metastatic disease that progress after platinum-based combination chemotherapy.

Given the lethality of muscle invasive and metastatic bladder cancer and its severe impact on patient quality of life, the importance of multidisciplinary care (e.g. the importance of a referral to a medical oncologist for a discussion of neoadjuvant chemotherapy) in the management of this disease cannot be overemphasized. Implementation of these guidelines requires the integration of urology, medical and radiation oncology expertise in order to provide the highest level of care to patients.
This is an endorsement of European Association of Urology (EAU) Guidelines on muscle-invasive and metastatic bladder cancer, by Witjes JA et al, which was published in the journal European Urology in 2014 and then updated online by the EAU in March 2015; reprinted with permission by European Association of Urology.
Endorsement Recommendation

ASCO endorses all but one of the recommendations within the EAU Guidelines on muscle-invasive and metastatic bladder cancer, published by Witjes JA et al., in 2015, with minor qualifying statements.
Additional Resources

More information, including a Data Supplement with a reprint of all EAU recommendations, a Methodology Supplement, slide sets, and clinical tools and resources, is available at

www.asco.org/endorsements/MIBC

Link to original guideline:

Patient information is available at www.cancer.net
# ASCO Endorsement Panel Members

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