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Guideline Endorsement 3-21 REQUIRES UPDATING

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Cancer Care Ontario Bladder Cancer Guideline:

An Endorsement of the 2017 American Urological Association Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer: AUA, ASCO, ASTRO, SUO Guideline

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and the Genitourinary Cancer Advisory Committee

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This publication is an endorsement of the 2017 American Urological Association Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer: AUA/ ASCO/ ASTRO/ AUO Guideline. The original publication is available at http://www.auanet.org/guidelines/muscle-invasive-bladder-cancer-new-

An assessment conducted in January 2025 indicated that Guideline Endorsement 3-21 REQUIRES UPDATING. It is still appropriate for this document to be available while this process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

You can access the full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/52171

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GUIDELINE OBJECTIVES

The objectives of this guideline are to provide clinical practice recommendations for the treatment of non-metastatic muscle-invasive bladder cancer (MIBC). Our recommendations are based on the 2017 American Urological Association (AUA) "Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer: AUA/ ASCO/ ASTRO/ SUO Guideline" [1].

TARGET POPULATION

Patients with non-metastatic MIBC.

INTENDED USERS

Primary care providers, urologists, radiation and medical oncologists, and other healthcare providers involved in the management of non-metastatic MIBC.

ENDORSEMENT

The Genitourinary Cancer Advisory Committee (GU CAC) of Cancer Care Ontario (CCO) endorses, in principle, the recommendations of "Treatment of Non-metastatic Muscle-Invasive Bladder Cancer: AUA/ASCO/ASRO/SUO guideline" published by the AUA, available at http://www.auanet.org/guidelines/muscle-invasive-bladder-cancer-new-(2017) (the 2017 AUA Guideline).

BACKGROUND AND JUSTIFICATION FOR GUIDELINE

In 2017, the AUA, the American Society of Clinical Oncology (ASCO), the American Society for Radiation Oncology (ASTRO), and the Society of Urological Oncology (SUO) published a joint guideline. The CCO's GU CAC, the Disease Pathway Management Bladder Cancer Pathway group, and the GU Disease Site Group expressed interest in endorsing the project. With representatives from each of the teams, a MIBC Working Group was established and applied the Program in Evidence-Based Care guideline endorsement process to create this guideline endorsement.

The GU CAC endorses the 2017 AUA Guideline recommendations as outlined in Table 1-1 below. Thirty-one recommendations of the AUA document are endorsed as written and four recommendations are endorsed with modifications (indicated by grey highlighting and italicized text), as described below.

Table 1-1. American Urological Society (AUA) Treatment of Non-Metastatic MIBC Recommendation Assessment Table	
AUA RECOMMENDATIONS[1]	**ASSESSMENT**
Initial Patient Evaluation And Counseling (5 recommendations)	
1. Prior to 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 for a suspected invasive cancer. (Clinical Principle)	**ENDORSE**
2. Prior to 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)	**ENDORSE**
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)	**ENDORSE**
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)	**ENDORSE**
5. Prior to 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)	**ENDORSE**
Treatment - Neoadjuvant/Adjuvant Chemotherapy (4 recommendations)	
6. Utilizing a multidisciplinary approach, clinicians should offer cisplatin-based neoadjuvant chemotherapy to eligible radical cystectomy patients prior to cystectomy. (Strong Recommendation; Evidence Level: Grade B)	**ENDORSE**
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)	**ENDORSE**
8. Clinicians should perform radical cystectomy as soon as possible following a patient's completion of and recovery from neoadjuvant chemotherapy. (Expert Opinion)	**ENDORSE**
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. (Moderate Recommendation; Evidence Level: Grade C)	**ENDORSE**
Treatment - Radical Cystectomy (3 recommendations)	
10. Clinicians should offer radical cystectomy with bilateral pelvic lymphadenectomy for surgically eligible patients with resectable non-metastatic (M0) muscle-invasive bladder cancer. (Strong Recommendation; Evidence Level: Grade B)	**ENDORSE**
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)	**ENDORSE**

Table 1-1. American Urological Society (AUA) Treatment of Non-Metastatic MIBC Recommendation Assessment Table	
AUA RECOMMENDATIONS[1]	**ASSESSMENT**
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. (Moderate Recommendation; Evidence Level: Grade C)	**ENDORSE**
Treatment - Radical Cystectomy - Urinary Diversion (2 recommendations)	
13. In patients undergoing radical cystectomy, ileal conduit, continent cutaneous, and orthotopic neobladder urinary diversions should all be discussed. (Clinical Principle)	**ENDORSE**
14. In patients receiving an orthotopic urinary diversion, clinicians must verify a negative urethral margin. (Clinical Principle)	**ENDORSE**
Treatment - Radical Cystectomy - Perioperative Surgical Management (4 recommendations)	
15. Clinicians should attempt to optimize patient performance status in the perioperative setting. (Expert Opinion)	**ENDORSE**
GU CAC Addition to this Recommendation The word "extended" has been added to the beginning of the sentence. 16. ***Extended*** perioperative pharmacologic thromboembolic prophylaxis should be given to patients undergoing radical cystectomy. (Strong Recommendation; Evidence Level: Grade B) ***Qualifying Statement:*** Data support the use of extended postoperative thromboprophylaxis in the cystectomy population. There is also evidence to suggest that patients receiving neoadjuvant chemotherapy have a higher risk of thromboembolic events.	**ENDORSED WITH MODIFICATIONS**
17. In patients undergoing radical cystectomy μ -opioid antagonist therapy should be used to accelerate gastrointestinal recovery, unless contraindicated. (Strong Recommendation; Evidence Level: Grade B) ***Qualifying Statement:*** μ -opioid antagonist therapy is not currently available in Ontario/Canada	**ENDORSED WITH MODIFICATIONS**
18. Patients should receive detailed teaching regarding care of urinary diversion prior to discharge from the hospital. (Clinical Principle)	**ENDORSE**
Treatment - Pelvic Lymphadenectomy (2 recommendations)	
19. Clinicians must perform a bilateral pelvic lymphadenectomy at the time of any surgery with curative intent. (Strong Recommendation; Evidence Level: Grade B)	**ENDORSE**
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)	**ENDORSE**
Treatment - Bladder Preserving Approaches - Patient Selection (2 recommendations)	
21. For patients with newly diagnosed non-metastatic 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)	**ENDORSE**
22. In patients under consideration for bladder preserving therapy, maximal debulking transurethral resection of bladder tumor and assessment of multifocal disease/carcinoma in situ should be performed. (Strong Recommendation; Evidence Level: Grade C)	**ENDORSE**

Table 1-1. American Urological Society (AUA) Treatment of Non-Metastatic MIBC Recommendation Assessment Table	
AUA RECOMMENDATIONS[1]	**ASSESSMENT**
Treatment - Bladder Preserving Approaches - Maximal TURBT and Partial Cystectomy (1 recommendation)	
23. Patients with muscle-invasive bladder cancer who are medically fit and consent to radical cystectomy should not undergo partial cystectomy or maximal transurethral resection of bladder tumor as primary curative therapy. (Moderate Recommendation; Evidence Level: Grade C) ***GU CAC Addition to this Recommendation:*** ***Partial cystectomy for tumours found within a bladder diverticulum may be a consideration after careful assessment in selected patients.***	**ENDORSED WITH MODIFICATIONS**
Treatment - Bladder-Preserving Approaches - Primary Radiation Therapy (1 recommendation)	
24. For patients with muscle-invasive bladder cancer, clinicians should not offer radiation therapy alone as a curative treatment. (Strong Recommendation; Evidence Level: Grade C)	**ENDORSE**
Treatment – Bladder-Preserving Approaches - Multi-Modal Bladder-Preserving Therapy (3 recommendations)	
25. For patients with muscle-invasive bladder cancer who have elected multi-modal bladder-preserving therapy, clinicians should offer maximal transurethral resection of bladder tumor, chemotherapy combined with external beam radiation therapy, and planned cystoscopic re-evaluation. (Strong Recommendation; Evidence Level: Grade B)	**ENDORSE**
26. Radiation sensitizing chemotherapy regimens should include cisplatin or 5-fluorouracil and mitomycin C. (Strong Recommendation; Evidence Level: Grade B)	**ENDORSE**
27. Following completion of bladder preserving therapy, clinicians should perform regular surveillance with CT scans, cystoscopy, and urine cytology. (Strong Recommendation; Evidence Level: Grade C)	**ENDORSE**
Treatment – Bladder-Preserving Approaches - Bladder-Preserving Treatment Failure (2 recommendations)	
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. (Strong Recommendation; Evidence Level: Grade C)	**ENDORSE**
29. In patients who have a non-muscle invasive recurrence after bladder-preserving therapy, clinicians may offer either local measures, such as transurethral resection of bladder tumor with intravesical therapy, or radical cystectomy with bilateral pelvic lymphadenectomy. (Moderate Recommendation; Evidence Level: Grade C)	**ENDORSE**
Patient Surveillance and Follow Up – Imaging (1 recommendation)	
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)	**ENDORSE**
Patient Surveillance and Follow-Up - Laboratory Values and Urine Markers (2 recommendations)	
31. Following 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)	**ENDORSE**
32. Following radical cystectomy in patients with a retained urethra, clinicians should monitor the urethral remnant for recurrence. (Expert Opinion)	**ENDORSE**
Patient Surveillance and Follow-Up - Patient Survivorship (2 recommendations)	

Table 1-1. American Urological Society (AUA) Treatment of Non-Metastatic MIBC Recommendation Assessment Table	
AUA RECOMMENDATIONS[1]	**ASSESSMENT**
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)	**ENDORSE**
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)	**ENDORSE**
Patient Surveillance and Follow-Up - Variant Histology (1 recommendation)	
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). ***GU CAC Addition to this Recommendation:*** ***If diverging from a standard treatment plan, the patient's case may require discussion at a multidisciplinary case conference.***	**ENDORSED WITH MODIFICATIONS**

Endorsement of the 2017 American Urological Association Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer: AUA, ASCO, ASTRO, SUO Guideline:

Section 2: Endorsement Methods Overview

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO), supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control. All work produced by the PEBC, and any associated programs, is editorially independent from the OMHLTC.

The PEBC was asked to develop a guideline on the management of non-metastatic muscle invasive bladder cancer (MIBC). In consultation with the genitourinary cancer advisory committee (GU CAC), a MIBC Working Group was identified. This Working Group consisted of two uro-oncologic surgeons, a radiologist, a medical oncologist, and an anatomic pathologist (See Appendix 1).

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [2,3]. This process includes a systematic review, interpretation of the evidence, and draft recommendations by the members of the MIBC Working Group, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [4] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

CHOICE OF GUIDELINE FOR ENDORSEMENT

The GU CAC reviewed the 2017 American Urological Association (AUA) Guideline [1] and accepted it as useful and relevant to support future revisions to the clinical pathway. The Guideline provides a risk-stratified clinical framework for the management of non-metastatic MIBC, designed to be used in conjunction with an associated treatment algorithm http://www.auanet.org/guidelines/muscle-invasive-bladder-*cancer*-new-(2017). The issues addressed by the 2017 AUA Guideline covered a broad range of options around non-metastatic MIBC.

Details of the AGREE II assessment can be found in Appendix 2.The overall quality of the guideline was rated as “6” by appraisers 1 and 3 and as “5” by appraiser 2 (on a scale from 1 to 7); all three appraisers stated that they would recommend this guideline for use. The AGREE II quality ratings for the individual domains were varied; they were assessed at 94% for scope and purpose, 69% for stakeholder involvement, 77% for rigour of development, 89% for clarity of presentation, 46% for applicability, and 83% for editorial independence.

DESCRIPTION OF AUA GUIDELINE ON NON-METASTATIC MIBC

The original systematic review forming the base of the 2017 AUA Guideline was funded by the Agency for Healthcare Research and Quality; an additional review was funded by the AUA to address additional research questions and to update the literature search.

The guideline addressed 35 recommendations in the following 15 categories related to non-metastatic MIBC: 1) Initial patient evaluation and counselling, 2) Treatment – neoajuvant/adjuvant chemotherapy, 3) Treatment - radical cystectomy, 4) Treatment - radical cystectomy - urinary diversion, 5) Treatment - radical cystectomy - perioperative surgical management, 6) Treatment - pelvic lymphadecectomy, 7) Treatment - bladder-preserving approaches - bladder-preserving treatment failure, 8) Treatment – bladder-preserving approaches – maximal TURBT [transurethral resection of bladder tumour] and partial cystectomy, 9) Treatment – bladder-preserving approaches – primary radiation therapy, 10) Treatment – bladder-preserving approaches – multi-modal bladder-preserving therapy, 11) Treatment – bladder-preserving approaches – bladder-preserving treatment failure, 12) Patient surveillance and follow-up – imaging, 13) Patient surveillance and follow-up - laboratory values and urine markers, 14) Patient surveillance and follow-up - patient survivorship, and 15) Patient surveillance and follow-up - variant histology.

When adequate evidence was present, the evidence for a recommendation was assigned a strength rating of A (high), B (moderate), or C (low) for support of Strong, Moderate, or Conditional Recommendations, as per the AUA methodology. Clinical principles and expert opinion were used in the absence of sufficient evidence by the AUA.

FORMATION OF THE MIBC WORKING GROUP

This project was led by a small working committee of the group, referred to as the MIBC Working Group (AF, TF, GH, SH, MO), whose members were responsible for reviewing the recommendations in the 2017 AUA Guideline on non-metastatic MIBC in detail and making an initial determination as to any necessary changes, drafting the first version of the endorsement document, and leading the response to the Expert Panel (See Appendix 1 for a list of MIBC Working Group members and conflict of interest declarations). Conflict of interest declarations for all Guideline Development Group members were managed in accordance with the *PEBC Conflict of Interest Policy.*

All members of the GU CAC contributed to the endorsement process, refinement of the endorsement document, and approval of the final version of the document. Competing interests in the areas being addressed were declared and individuals with competing interests were not allowed to participate as a member of the MIBC Working Group unless otherwise stated (See Appendix 1 for a list of GU CAC members and conflict of interest declarations).

ENDORSEMENT PROCESS

The MIBC Working Group reviewed the 2017 AUA Guideline in detail and reviewed each recommendation of the guideline to determine whether it could be endorsed, endorsed with modifications, or rejected. The MIBC Working Group considered the following issues for each of the 35 recommendations:

1) Does the Working Group agree with the interpretation of the evidence and the justification of the original recommendation?
2) Are modifications required to align with the Ontario context?
3) Is it likely there is new, unidentified evidence that would call it into question the recommendation?
4) Are statements of qualification/clarification to the recommendation required?

The modifications made to the recommendations were as follows (see Table 1-1 in Section 1 of this report):

- Recommendation #16: We endorse the recommendation in principle but the word "extended" has been added to the beginning of the recommendation with a qualifying statement that "Data support the use of extended postoperative thromboprophylaxis in the cystectomy population. There is also evidence to suggest that patients receiving neoadjuvant chemotherapy have a higher risk of thromboembolic events."
- Recommendation #17: We endorse the recommendation in principle but have added the qualifying statement that "μ-opioid antagonist therapy is not currently available in Ontario/Canada."
- Recommendation #23: We endorse the recommendation in principle but have added a sentence to the end of the recommendation that states "Partial cystectomy for tumours found within a bladder diverticulum may be a consideration after careful assessment in selected patients."
- Recommendation #35: We endorse the recommendation in principle but have added a sentence to the end of the recommendation that states "If diverging from a standard treatment plan, the patient's case may require discussion at a multidisciplinary case conference."

INTERNAL REVIEW

MIBC Expert Panel Review and Approval

Following the formulation of the first draft, the recommendation endorsement was reviewed by the Director and Assistant Director of the PEBC and the MIBC Working Group was responsible for ensuring the necessary changes were made. An Expert Panel of clinical content experts reviewed the draft endorsement document, provided feedback, and approved the final version (See Appendix 1 for a list of MIBC Expert Panel members and conflict of interest declarations).

In November 2017, 13 of the 14 Expert Panel members (excluding the Working Group) cast votes for a 93% response rate. Of those that cast votes, 13 (100%) approved the document. The main comments from the Expert Panel and the Working Group's responses are summarized in Table 2-1.

Table 2-1: Expert Panel Comments[1] and Working Group Responses		
Recommendations	**Expert Panel Comments**	**Working Group Responses**
Comment Set #1 (Urology)		
#17 In patients undergoing radical cystectomy, μ-opioid antagonist therapy should be used to accelerate gastrointestinal recovery, unless contraindicated. (Strong Recommendation; Evidence Level: Grade B) ***Qualifying Statement:*** μ-opioid antagonist therapy is not currently available in Ontario/Canada	"I do worry though with several caveats to the well laid out guideline with the CCO recommendations that the message may get lost. The only (in my mind) "Canadian/Ontario" modification that is relevant is number 17...mu receptor antagonist availability. That's relevant for our group to comment on. The other three where we make modifications are much less relevant and to be honest may take away from CCO endeavour to "accept". To make my argument against the modifications....."	We agree and have previously acknowledged that μ –opioid is not available for use in Ontario/Canada.
#16 Extended perioperative pharmacologic thromboembolic prophylaxis should be given to patients undergoing radical cystectomy. (Strong Recommendation; Evidence Level: Grade B)	"Number 16 is wrong. Though I agree that a month of anti-coagulation is correct the guidelines as written already state that in the document. If we add the word "extended" it assumes the rest of the statement is still Grade B evidence. It is not! Case series and our observational population data is not Grade B. In fact our data suggests NACT is NOT associated with higher risk despite Pinthus case series. I would not include the word Extended. It's fine as it is."	We appreciate the feedback from the expert panel member and edited the sentence accordingly. We do wish to capture the sentiment that VTE prophylaxis should continue after discharge from hospital.
#23 Patients with muscle-invasive bladder cancer who are medically fit and consent to radical cystectomy should not undergo partial cystectomy or maximal transurethral resection of bladder tumor as primary curative therapy. (Moderate Recommendation; Evidence Level: Grade C)	"Similarly recommendation 23 on partial cystectomy. This statement isn't too helpful. The guidelines do a good job describing the occasional time we should consider it. RARELY do we find MIBC in a diverticulum. They often don't have muscularis propria. This statement shouldn't be added...not sure what the point is. Leave it as is? It's more a comment for a NMIBC guideline."	Although it is discussed in the document, there are certain statements that are made to highlight important points that may not be as widely accepted as one may believe.
#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).	"Finally, recommendation 35 is fine but throughout it is stated that all decisions should be made at MCC. Over and over again. This addition is not helpful. I worry that the more we "modify" without good strong Canadian rationale it distracts from the message."	We appreciate the feedback but believe that the importance of variant histology should be highlighted.
Comment Set #2 (Medical Oncology)		
#30 Clinicians should obtain chest imaging and cross-sectional imaging of the abdomen and pelvis with CT or	"Regarding imaging of the chest, although stated well in the body of the document, it would be good to recommend cross-sectional (CT) imaging	The goal of the document is to endorse the AUA guidelines as written. Addressing

Table 2-1: Expert Panel Comments[1] and Working Group Responses		
Recommendations	**Expert Panel Comments**	**Working Group Responses**
MRI at 6-12-month intervals for 2-3 years and then may continue annually. (Expert Opinion)	of the chest. Also would be good to indicate ideal timing for cystectomy after neoadjuvant- or adjuvant chemotherapy after cystectomy."	additional imaging modalities is outside the scope of this endorsement.
Comment Set #3 (Urology)		
# 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)	"This is not an expert opinion- there is strong evidence to suggest that carbo doesn't work here- this should be Grade C or clinical principle."	Assigning level of evidence as determined by the original guideline authors is beyond the scope of this endorsement.
# 8 Clinicians should perform radical cystectomy as soon as possible following a patient's completion of and recovery from neoadjuvant chemotherapy. (Expert Opinion)	"We could reflect Canadian data here and include a tighter timeline; perhaps the notion of completing chemo and RC within 6 months is reasonable."	Addressing new entities such as timelines are outside the scope of this endorsement.
# 16 Perioperative pharmacologic thromboembolic prophylaxis should be given to patients undergoing radical cystectomy. (Strong Recommendation; Evidence Level: Grade B)	"Need to reflect new guidelines that prophylaxis be extended with LMWH for a period not less than 4 weeks after cystectomy, especially mandatory in patients with neadjuvant chemotherapy. One may consider starting prophylaxis before cystectomy, or perhaps even doing preoperative dopplers (this would be expert opinion)."	We appreciate the feedback and have edited the sentence accordingly. We do wish to capture the sentiment that VTE prophylaxis should continue after discharge from hospital.
# 17 In patients undergoing radical cystectomy μ - opioid antagonist therapy should be used to accelerate gastrointestinal recovery, unless contraindicated. (Strong Recommendation; Evidence Level: Grade B)	"Unless I am missing something here - this iOS not available in Canada for widespread use."	We agree and have previously acknowledged that μ –opioid is not available for use in Ontario/Canada.
# 18. Patients should receive detailed teaching regarding care of urinary diversion prior to discharge from the hospital. (Clinical Principle)	"This should have the option of home care involvement, stoma therapy as indicated for conduit."	Assessing additional therapies and institutional involvement is beyond the scope of the project.
# 21 For patients with newly diagnosed non-metastatic 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.	"There should be something here to suggest that a referral to a tertiary care institution where bladder sparing expertise is available should be considered if such an option is being presented to patients. This reflects better the Canadian landscape."	Assessing specific referral patterns is beyond the scope of the project.
Comment Set #4 (Pathology)		
#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,	"Ad 3) (e.g. micropapillary, (large) nested, plasmacytoid, neuroendocrine, sarcomatoid, extensive / pure squamous or glandular	The value of using frozen sections at time of cystectomy seem very dependent on both the surgeon and the case.

Table 2-1: Expert Panel Comments[1] and Working Group Responses		
Recommendations	**Expert Panel Comments**	**Working Group Responses**
neuroendocrine, sarcomatoid, extensive squamous or glandular differentiation). (Clinical Principle)	differentiation) to be inserted after "variant histology" instead of at the end of the sentence."	
#10 to #18	"Ad Treatment – Radical Cystectomy I wonder if any statement on the performance of frozen section assessment of the ureter resection margins should be made (as a "Clinical Principle")?"	The Working Group cannot extrapolate beyond the AUA guidelines.
Comment Set #5 (Radiology)		
# 2 Prior to 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).	• "The recommended preoperative imaging evaluation consists of cross-sectional imaging of the abdomen and pelvis in addition to chest imaging. The most common forms of imaging include CT or MRI of the abdomen and pelvis. Ideally, the patient should have intravenous contrast with delayed imaging that allows for evaluation of the renal pelvis and ureters for upper tract carcinomas. In patients who are not able to receive intravenous contrast, cross-sectional imaging with MRI (with gadolinium, if possible) or non-contrast imaging combined with retrograde pyelograms are acceptable alternatives. • In addition to abdominal and pelvic imaging, patients should have chest imaging. While realizing the possibility of false positive findings, there is a strong association of bladder cancer with smoking, therefore, prior smokers may benefit from a chest CT while non-smokers should have a minimum of a chest x-ray (with posterior-anterior and lateral images). Non-smokers also may benefit from CT imaging to evaluate for metastatic cancer. In the absence of an elevated alkaline phosphatase, a bone scan need not be performed, but should be performed with bone pain symptoms. • The role of PET imaging is currently undefined in the staging of bladder cancer and is not routinely indicated for all initial staging evaluations. Although some studies have demonstrated increased sensitivity to identify abnormal pelvic lymph nodes and chest lesions in	Although the comments from the Expert Panel are reasonable, we do not think it is absolutely necessary to make changes to the recommendations.

Table 2-1: Expert Panel Comments[1] and Working Group Responses		
Recommendations	**Expert Panel Comments**	**Working Group Responses**
	invasive bladder cancer patients, the Panel recommends that PET imaging should be reserved for patients with abnormal chest, abdominal, or pelvic imaging that require further evaluation, or if biopsy of a suspicious lymph node is not feasible. • Additional points ○ The delayed CT imaging described specifically should be CT urography to evaluate the upper tracts. CT Chest at the time of abdominal CT is reasonable alternative to CXR in patient is at high risk (or a smoker as stated) and can be performed at the time of CT abdomen. ○ MRI with MRU urography is an alternative in those centres with expertise in performing and interpreting body MRI in patients who cannot receive CT contrast due to contrast reaction history. ○ As of 2017 FDG PET is not covered by OHIP in Ontario for bladder cancer without application to the PET Scans Ontario program. If the indication is for evaluation of a solitary pulmonary nodule for which a diagnosis could not be established by a needle biopsy due to unsuccessful attempted needle biopsy; the SPN is inaccessible to needle biopsy; or the existence of a contra-indication to the use of needle biopsy this is covered by OHIP. For these reasons, the AUA recommendations for PET imaging except for SPN would require application to PET scan Ontario. The AUA recommendations are reasonable for FDG-PET should the results of FDG-PET result in an alteration of management."	
# 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)	"I agree with these recommendations. The same comments regarding baseline imaging apply to the follow-up scenario."	We agree and the recommendation remains as is.

Table 2-1: Expert Panel Comments[1] and Working Group Responses		
Recommendations	**Expert Panel Comments**	**Working Group Responses**
Comment Set #6 (Radiology)		
# 27 Following completion of bladder preserving therapy, clinicians should perform regular surveillance with CT scans, cystoscopy, and urine cytology. (Strong Recommendation; Evidence Level: Grade C)	For Table 1-1. 27. Include MRI as option.	We would leave as is; If there is a contraindication to intravenous contrast for CT, a non-contrast CT would suffice since there will be baseline imaging for comparison.
Comment Set #7 (Radiation Oncology)		
# 21 For patients with newly diagnosed non-metastatic 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)	"Would suggest modifying to something like: all patients who are clinically appropriate candidates for ..... ."	Although the comments from the Expert Panel are reasonable, we do not think it is absolutely necessary to make changes to the recommendations.
# 24 For patients with muscle-invasive bladder cancer, clinicians should not offer radiation therapy alone as a curative treatment. (Strong Recommendation; Evidence Level: Grade C)	"The principle is sound but as it reads, it would suggest that patients who are not suitable for chemosensitization and radical surgery would not be offered ANY form of curative therapy and RT alone may potentially be curative in that setting, and I do not believe that is true."	We agree and the recommendation remains as is.
# 26 Radiation sensitizing chemotherapy regimens should include cisplatin or 5- fluorouracil and mitomycin C. (Strong Recommendation; Evidence Level: Grade B)	"would reword to cisplatin mito/5FU and gemcitabine (grade C) as that is in clinical practice."	Although the comments from the Expert Panel are reasonable, we do not think it is absolutely necessary to make changes to the recommendations.
Comment Set #8 (Radiation Oncology)		
# 2 Prior to 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).	"I think it is more pragmatic and sensitive to include cross sectional imaging of chest, abdomen and pelvis (as opposed to imaging of the chest and cross sectional imaging of abdomen and pelvis)."	Although the comments from the Expert Panel are reasonable, we do not think it is absolutely necessary to make changes to the recommendations.
# 16 Extended perioperative pharmacologic thromboembolic prophylaxis should be given to patients	"I agree with the 'extended' addition, but suggest this should have also some quantification (e.g. 4	We agree and the recommendation remains as is.

Table 2-1: Expert Panel Comments[1] and Working Group Responses		
Recommendations	**Expert Panel Comments**	**Working Group Responses**
undergoing radical cystectomy. (Strong Recommendation; Evidence Level: Grade B)	weeks or more; or a different timeframe that the panel finds most appropriate)."	
# 21 For patients with newly diagnosed non-metastatic 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)	"I believe that in our Canadian and Provincial setting, it is not overly ambitious to modify and suggest "all patients should be presented with the alternative of bladder preserving approach". In fact, the current statement of "patients who want to retain their bladder" is very general (most if not all will do), and unlikely to identify specific candidates for bladder preservation."	We agree and the recommendation remains as is.
# 24. For patients with muscle-invasive bladder cancer, clinicians should not offer radiation therapy alone as a curative treatment. (Strong Recommendation; Evidence Level: Grade C)	"I totally agree with this principle, but would add '..... should not offer RT alone as a curative treatment, *unless chemosensitization is clinically contraindicated*' "	Although the comments from the Expert Panel are reasonable, we do not think it is absolutely necessary to make changes to the recommendations.
# 26. Radiation sensitizing chemotherapy regimens should include cisplatin or 5- fluorouracil and mitomycin C. (Strong Recommendation; Evidence Level: Grade B)	"I would consider adding Gemcitabine as alternative as per some centre's practices/experiences."	Although the comments from the Expert Panel are reasonable, we do not think it is absolutely necessary to make changes to the recommendations.
# 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)	"Same as comment to #2 above, would suggest having cross sectional imaging of chest, abdomen and pelvis."	Although the comments from the Expert Panel are reasonable, we do not think it is absolutely necessary to make changes to the recommendations.
[1]8 of the 14 Expert Panel members had comments in addition to their approval vote.		

UPDATING THE ENDORSEMENT

The PEBC will review the endorsement on an annual basis to ensure that it remains relevant and appropriate for use in Ontario.

ACKNOWLEDGEMENTS

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- The Expert Panel for providing feedback and final approval of the endorsement.
- Melissa Brouwers and Sheila McNair for providing feedback on draft versions.
- Judy Brown, Duvaraga Sivajohanathan and Kristy Yiu for their AGREE II assessments.
- Sara Miller for copy editing.

References

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2. Browman GP, Levine MN, Mohide EA, Hayward RS, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13(2):502-12.
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4. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. Can Med Assoc J. 2010;182(18):E839-E42.

Appendix 1: Affiliations and Conflict of Interest Declarations

Name	Specialty	Location	COI declared
MIBC Working Group			
Antonio Finelli	Uro-oncologic Surgery	Department of Surgical Oncology, University Health Network Urology/ Minimally Invasive Surgery/ Robotic Surgery University of Toronto, ON	None
Trevor Flood	Anatomic Pathology	501 Smyth Road The Ottawa Hospital, Department of Anatomic Pathology Ottawa, ON	None
Girsh Kulkarni	Uro-oncologic Surgery	Division of Urology, University Health Network University of Toronto, ON	See note[1]
Sebastien Hotte	Medical Oncology	Department of Oncology - Division of Medical Oncology Juravinski Cancer Centre 3rd floor 699 Concession Street Hamilton ON	None
Martin O'Malley	Radiologist	Princess Margaret Hospital Dept. of Medical Imaging 610 University Ave., Toronto, ON	None
Judy Brown	Health Research Methodologist	Program in Evidence-based Care Cancer Care Ontario	None
MIBC Expert Panel			
Alejandro Berlin	Radiation Oncology	Princess Margaret Cancer Centre 610 University Avenue Toronto, ON	None
David Berman	Pathology & Molecular Medicine	Queen's Cancer Research Institute, 3rd Floor, Queen's Cancer Research Institute, Kingston, ON	See note[2]
Rodney Breau	Urology	The Ottawa Hospital – General Campus 501 Smyth Road, Box 222 Ottawa, ON	None
Peter Chung	Radiation Oncology	Princess Margaret Cancer Centre, 610 University Avenue, Toronto, ON,	None
Andrew Feifer	Urologist	Credit Valley Hospital	See note [3]
Arthur Grabowski	Community/Urology	95 Bayly Street West, #300, Ajax, ON	None

Name	Specialty	Location	COI declared
Masoom Haider	Radiologist/Senior Scientist	Sunnybrook Health Sciences Centre, 2075 Bayview Ave., Room AG 57,Toronto, ON	See note [4]
Kartik Jhaveri (JDMI)	Radiologist	Abdominal MRI (JDMI), Princess Margaret Hospital, Dept of Medical Imaging, 610 University Ave., Toronto, ON	See note [5]
Sandeep Sehdev	Medical Oncology	The Ottawa Hospital Cancer Centre, Ottawa, ON	See note [6]
Robert Siemens	Urology	Division of Cancer Care & Epidemiology, Department of Urology, Queen's University, Kingston, ON	See note [7]
Srikala Sridhar	Medical Oncology	Cancer Clinical Research Unit (CCRU), Princess Margaret Cancer Centre	See note [8]
George Yousef	Pathology	Keenan Research Centre for Biomedical Science, St Michael's Hospital, Toronto, ON	None
Theo van Der Kwast	Pathology	Toronto General Hospital 200 Elizabeth St. Rm 11E-220, Toronto, ON	None
Phillip Williams	Pathology	Juravinski Hospital and Cancer Centre, Hamilton Health Sciences, 711 Concession Street, Hamilton, ON L8V 1C3	None

1. Sanofi to fund travel to the European Association of Urology meeting. BioSyent provided research funding to perform a cost-effectiveness study of blue light versus white light cystoscopy in the Canadian context. Trimodal Therapy is Inferior to Radical Cystectomy for Muscle-invasive Bladder Cancer using Population-level Data: Is There Evidence in the (Lack of) Details? Kulkarni GS, Klaassen Z. Eur Urol. 2017 Oct;72(4):488-489. doi: 10.1016/j.eururo.2017.04.028. Epub 2017 May 6. No abstract available. PMID: 28483329
2. I am the Correlative Science Committee Chair for the Canadian Cancer Trials Group, which receives funding for clinical trials and operates trials in bladder cancer. I do not receive payment for this role and my income is unaffected by these trials.
3. I published in peer-reviewed publications on the use of multidisciplinary care in MIBC cancer.
4. Research support (non-financial) from Siemens for MRI pulse sequence development.
5. Non-financial Research Collaborations – Siemens.
6. Travel support, Astellas; Discussed the roles of chemotherapy and oral targeted drugs at Prostate Cancer Canada workshops.
7. So many. Mo12.W. Kassouf, A. Aprikian, P. Black, G. Kulkarni, J. Izawa, L. Eapen, A. Fairey, A. So, S. North, R. Rendon, S.S. Sridhar, T. Alam, F. Brimo, N. Blais, C. Booth, J. Chin, P. Chung, D. Drachenberg, Y. Fradet, M. Jewett, R. Moore, C. Morash, B. Shayegan, G. Gotto, N. Fleshner, F. Saad, D.R. Siemens. Recommendations for the improvement of bladder cancer quality of care in Canada: A consensus document reviewed and endorsed by Bladder Cancer Canada (BCC), Canadian Urologic Oncology Group (CUOG), and Canadian Urological Association (CUA), December 201 financial Research Collaborations – Siemens
8. I have acted as a consultant for Roche, Astra Zeneca, Merck, BMS; Sridhar, SS. Journal of Oncology Practice, 2017.

Appendix 2: Agree II Score Sheet

Domain	Item	AGREE II Appraiser Ratings[1]		
		1	2	3
1) Scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described.	7	6	7
	2. The health question(s) covered by the guideline is (are) specifically described.	7	7	6
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	7	7	6
Domain score[2] - (60-9/63-9)*100 = 51/54 *100 = .9444 *100 = **94%**		Obtained score		60
2) Stakeholder involvement	4. The guideline development group includes individuals from all the relevant professional groups.	7	6	6
	5. The views and preferences of the target population (patients, public, etc.) have been sought.	4	1	1
	6. The target users of the guideline are clearly defined.	7	7	7
Domain score[2] - (46-9/63-9)*100 = 37/54 *100 = .6851 *100 = **69%**		Obtained score		46
3) Rigor of development	7. Systematic methods were used to search for evidence.	7	7	7
	8. The criteria for selecting the evidence are clearly described.	7	7	6
	9. The strengths and limitations of the body of evidence are clearly described.	7	6	5
	10. The methods for formulating the recommendations are clearly described.	7	5	6
	11. The health benefits, side effects and risks have been considered in formulating the recommendations.	7	6	6
	12. There is an explicit link between the recommendations and the supporting evidence.	7	6	7
	13. The guideline has been externally reviewed by experts prior to its publication.	6	6	2
	14. A procedure for updating the guideline is provided.	3	1	1
Domain score[2] - (135-24/168-24)*100 = 111/144 *100 = .7708 *100 = **77%**		Obtained score		135
4) Clarity of presentation	15. The recommendations are specific and unambiguous.	7	7	4
	16. The different options for management of the condition or health issue are clearly presented.	7	7	4
	17. Key recommendations are easily identifiable.	7	7	7
Domain score[2] - (57-9/63-9)*100 = 48/54 *100 = .08889 *100 = **89%**		Obtained score		57
5) Applicability	18. The guideline describes facilitators and barriers to its application.	7	6	4
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	7	6	2
	20. The potential resource implications of applying the recommendations have been considered.	4	1	2
	21. The guideline presents monitoring and/ or auditing criteria.	4	1	1

Domain	Item	AGREE II Appraiser Ratings[1]		
		1	**2**	**3**
Domain Score[2] - (45-12/84-12)*100 = 33/72 *100 = .4583 *100 = **46%**		Obtained score		45
6) **Editorial independence**	22. The views of the funding body have not influenced the content of the guideline. 23. Competing interests of guideline development group members have been recorded and addressed.	7 7	7 6	4 5
Domain Score[2] - (36-6/42-6)*100 = 30/36 *100 = .8333 *100 = **83%**		Obtained score		36
Overall Guideline Assessment	1. Rate the overall quality of this guideline.	**6**	**5**	**6**
Overall Guideline Assessment	2. I would recommend this guideline for use.	**Yes**	**Yes**	**Yes**

[1] rated on a scale from 1 to 7, [2] Domain score = (Obtained score – Minimum possible score) /(Maximum possible score – Minimum possible score)