Locally Advanced/Metastatic Bladder Cancer
(T4bNxM0, TxN2-3M0, TxNxM1)

Effective Date: May, 2020
Background

Urinary bladder cancer is the fourth most common cancer among men and accounts for 8.1% of all new male cancer cases.\textsuperscript{1} Urinary bladder cancer is less common among women (ranked 11\textsuperscript{th}) and accounts for less than 3% of all new female cancer cases.\textsuperscript{1} Bladder cancer is the fifth leading cause of cancer death among men and 11\textsuperscript{th} leading cause of cancer death among women, accounting for 4% and 2% of all deaths, respectively. Statistics Canada estimates that there were over 8,900 new cases in Canada in 2017, with approximately 10% of those diagnosed in Alberta.\textsuperscript{1} Smoking is estimated to account for between 34% and 50% of all bladder cancers.\textsuperscript{2,3}

There are several histological types of bladder cancer. Urothelial carcinoma (also known as transitional cell carcinoma, henceforth referred to as urothelial) is the most common subtype, accounting for more than 90% of all cases in North America. Other histologic variants include squamous differentiation, glandular differentiation, nested pattern, microcystic, micropapillary, lymphoepithelioma-like, plasmacytoid and lymphoma-like, sarcomatoid/carcinosarcoma, giant cell, trophoblastic differentiation, clear cell, lipid cell, and undifferentiated.\textsuperscript{4} Other important histologic variants include adenocarcinoma (urachal and non-urachal) and small cell carcinoma. Less commonly, urothelial cancers can arise in other parts of the urinary tract including the renal pelvis, ureter and urethra.

Staging of bladder cancer is currently based on the eighth edition (2017) of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual.\textsuperscript{5} One of the major updates from the seventh edition (2010) is that lymph node involvement limited to the true pelvis and/or common iliac lymph nodes (N1-N3) in combination with a T1-T4a primary tumour now constitutes stage III disease (previously stage IV). A detailed description of the staging system can be found in the Appendix.

The objective of this guideline is to provide physicians with the latest, evidence-based management strategies for locally advanced/metastatic bladder cancer in Alberta. Guidelines for non-muscle-invasive bladder cancer, muscle-invasive bladder cancer, and upper tract urothelial cancer are available separately.

Guideline Questions

1. What work-up is required for locally advanced/metastatic bladder cancer?
2. What is the appropriate stage-specific treatment (i.e., surgery, systemic therapy, radiotherapy) for patients with locally advanced/metastatic bladder cancer?
3. Following treatment for locally advanced/metastatic bladder cancer, what is the appropriate follow-up?
Search Strategy

The pubmed database was searched from 1, Jan. 2018 to 1, Mar. 2020 using the following search criteria: ("muscles"[MeSH Terms] OR "muscles"[All Fields] OR "muscle"[All Fields]) AND invasive[All Fields] AND ("urinary bladder neoplasms"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields] AND "neoplasms"[All Fields]) OR "urinary bladder neoplasms"[All Fields] OR ("bladder"[All Fields] AND "cancer"[All Fields]) OR "bladder cancer"[All Fields])) AND (Clinical Trial, Phase III[ptyp] AND ("2018/01/01"[PDAT] : "2020/12/31"[PDAT])).

Target Population

The target population for this guideline is adult patients (18 years of age or older) with a diagnosis of locally advanced/metastatic bladder cancer (i.e. T4bNxM0, TxN2-3M0, TxNxM1).

Recommendations

Management of Locally Advanced Disease (Stages T4bNxM0, TxN2-3M0)

Indications include pre-operatively identified direct pelvic/abdominal wall invasion (cT4b), multiple regional lymph node metastases in the true pelvis (cN2), or lymph node metastases to common iliac lymph nodes (cN3). For post-operatively identified pT4b or pN1-3 disease, please see Muscle-Invasive Bladder Cancer AHS Guidelines for recommendations re: adjuvant therapy.

1. Staging
   A. CT chest abdomen and pelvis
   B. Alkaline phosphatase
   C. Bone scan if elevated alkaline phosphatase or symptoms.
   D. Brain imaging reserved for patients with clinical suspicion of cerebral metastases.
   E. CBC and diff, electrolytes, creatinine, calcium, magnesium, liver panel within 2 weeks of starting chemotherapy. All patients starting systemic chemotherapy should be considered for HBV screening.

2. Primary Therapy
   A. Patients with pre-operatively identified locally advanced disease should initially receive 4-6 cycles of systemic platinum-based chemotherapy.
   B. In cisplatin-eligible patients, cisplatin containing regimens (e.g. cisplatin-gemcitabine, dose-dense MVAC) are preferred. A standard dosing option for each regimen is provided below:
      i. Cisplatin-gemcitabine (21-day cycle): cisplatin 70 mg/m² day 1, gemcitabine 1250 mg/m² days 1 and 8
      ii. ddMVAC (14-day cycle): methotrexate 30 mg/m² day 1, cisplatin 70 mg/m² day 2, vinblastine 3 mg/m² day 2, doxorubicin 30 mg/m² day 2, plus GCSF support
C. For cisplatin-ineligible patients (CrCl < 60 ml/min, PS ≥ 2, NYHA ≥ 3 heart failure, ≥ Grade 2 peripheral neuropathy, ≥ Grade 2 hearing loss) recommended first-line chemotherapy regimens include: carboplatin-gemcitabine, gemcitabine-paclitaxel, single-agent gemcitabine, single-agent paclitaxel. A standard dosing option for carboplatin-gemcitabine is provided below:

i. Carboplatin-gemcitabine (21-day cycle): carboplatin AUC5 day 1, gemcitabine 1000 mg/m² days 1 and 8

D. For patients who have a favourable response to first-line chemotherapy, consideration of consolidative definitive loco-regional treatment (i.e. cystectomy with pelvic lymphadenectomy or bladder-preserving trimodality therapy) should be considered in the multidisciplinary setting.

E. Patients who do not have a favourable response to first-line chemotherapy and/or are not candidates for local definitive consolidative therapy should be managed as per recommendations for metastatic disease (see below).

F. Patients who are ineligible for aggressive multi-agent chemotherapy may be treated with single modality therapy, i.e. single-agent chemotherapy or radiotherapy for palliation and/or survival prolongation.

3. Palliative local therapies
A. Palliative local therapies (i.e. TURBT, cystectomy, radiation) may be considered for patients experiencing intolerable pain/voiding symptoms or recurrent/refractory hematuria.

4. Follow-up
A. In patients with favourable response to first-line chemotherapy who undergo subsequent consolidative curative-intent locoregional therapy (i.e. surgical resection versus bladder-preserving trimodality therapy), follow up should be performed as outlined in the Muscle-Invasive Bladder Cancer AHS Guidelines.

B. In patients who do not undergo curative intent locoregional therapy, follow up should be performed as outlined for Metastatic Bladder Cancer (see below).

**Management of Metastatic Disease (TxNxM1)**

Indications include the development of recurrent/metastatic disease post radical therapy or presentation with de novo metastatic disease.

1. Staging
   A. CT chest abdomen and pelvis
   B. Alkaline phosphatase
   C. Bone scan if elevated alkaline phosphatase or symptoms.
   D. Brain imaging reserved for patients with clinical suspicion of cerebral metastases.
E. CBC and diff, electrolytes, creatinine, calcium, magnesium, liver panel within 2 weeks of starting chemotherapy. All patients starting systemic chemotherapy should be considered for HBV screening.

2. First-line Therapy

A. Clinical trials should be considered for patients across all lines of therapy.

B. In patients who present with de novo metastatic disease or for those that develop recurrent/metastatic disease after a definitive local therapy, the mainstay of treatment is systemic chemotherapy.

C. First-line standard of care treatment is determined based on eligibility to receive cisplatin or carboplatin-based treatments. Patients may be categorized into one of the following three categories: I) cisplatin-eligible, II) cisplatin-ineligible but carboplatin eligible, III) chemotherapy-ineligible. See below for treatment recommendations for each group.

D. Patients receiving platinum-based regimens should be recommended to receive 4-6 cycles of first-line chemotherapy with interval restaging every 2-3 cycles.

E. In cisplatin-eligible patients, cisplatin containing regimens (e.g. cisplatin-gemcitabine, dose-dense MVAC) are preferred. A standard dosing option for each regimen is provided below:

   i. Cisplatin-gemcitabine (21-day cycle): cisplatin 70 mg/m² day 1, gemcitabine 1250 mg/m² days 1 and 8

   ii. ddMVAC (14-day cycle): methotrexate 30 mg/m² day 1, cisplatin 70 mg/m² day 2, vinblastine 3 mg/m² day 2, doxorubicin 30 mg/m² day 2, plus GCSF support

F. For cisplatin-ineligible patients (CrCl < 60 ml/min, PS ≥ 2, NYHA ≥ 3 heart failure, ≥ Grade 2 peripheral neuropathy, ≥ Grade 2 hearing loss) who are eligible for carboplatin-based combination chemotherapy, the recommended first-line chemotherapy is carboplatin-gemcitabine. A standard dosing option is provided below:

   i. Carboplatin-gemcitabine (21-day cycle): carboplatin AUC5 day 1, gemcitabine 1000 mg/m² days 1 and 8

G. For patients who are ineligible for any of the above systemic treatment options, alternative regimens that may be considered include: gemcitabine-paclitaxel, single-agent gemcitabine, single-agent paclitaxel.

H. For patients who are chemotherapy-ineligible, best supportive care is recommended.

3. Second-line therapy:

A. In eligible patients, pembrolizumab should be considered post-progression on a platinum-based combination therapy in the 1st line setting, or in those who have recurred/progressed within 12 months of receiving platinum-based chemotherapy in the (neo)adjuvant setting. This is not currently publicly funded but may be available through patient support programs. Standard dosing of pembrolizumab is as follows:

   i. Pembrolizumab (21-day cycle): 200 mg IV day 1
B. Retreatment with platinum-based regimens can be considered if initial progression-free interval to platinum was > 12 months.
C. For patients who received immunotherapy alone in the first-line setting as part of a clinical trial, platinum-based chemotherapy is recommended as per first-line therapy above if the patient is eligible and has not previously received platinum-based treatment. If prior platinum-based therapy has been received (with <12 month treatment-free interval) and/or the patient is ineligible, second-line options are as per third-line therapy and beyond (see below).

4. Third-line therapy and beyond:
   A. Taxane-based chemotherapy can be considered post-progression on platinum-based chemotherapy and pembrolizumab. Commonly used agents are single-agent paclitaxel or docetaxel.

5. Palliative local therapies
   A. Palliative local therapies (i.e. TURBT, cystectomy, radiation) may be considered for patients experiencing intolerable pain/voiding symptoms or recurrent/refractory hematuria.
   B. RT or surgery should be considered in patients with symptomatic sites of bony metastases and/or with impending fracture/complication.

6. Follow-up
   A. Post-chemotherapy: clinical evaluation and imaging (e.g. CT chest, abdomen, pelvis) to evaluate tumour response and then as indicated (q3months is a reasonable interval for most patients).
   B. Consider early palliative care referral as indicated.

7. Special situations
   A. Non-urothelial histology
      i. All pathology reported to have variant histology should be reviewed by an expert GU pathologist.
      ii. All patients with pure non-urothelial histology should be discussed in a multidisciplinary setting.
      iii. Generally, platinum-based chemotherapy as recommended for metastatic urothelial carcinomas are felt to less effective for pure non-urothelial histologies. However, there are no high-quality data to recommend alternate systemic therapy options for this population.
      iv. For urachal or non-urachal bladder adenocarcinoma, it is reasonable to consider systemic therapy options similar to those used in the management of metastatic colorectal cancer (e.g. FOLFOX). Cisplatin-5FU is another reasonable option.
v. For metastatic squamous cell carcinoma of the bladder, standard urothelial cisplatin-based regimens are appropriate. It is also reasonable to consider 5-FU or taxane-based chemotherapy.

vi. For metastatic small cell carcinoma of the bladder, first-line treatment should consist of platinum-etoposide combination chemotherapy in all eligible patients. Guidelines for management of metastatic small cell carcinoma of the lung should be followed.

Discussion

Management of Locally Advanced Disease (T4b and/or N2-3, M0)

In patients with locally advanced disease (T4b and/or N2-3, M0), recommended first-line therapy is systemic platinum-based chemotherapy for those that are eligible. Subsequent disease management depends on the response to primary systemic chemotherapy.

A retrospective study of 659 patients with node-positive urothelial bladder cancer assessed the effectiveness of induction chemotherapy for downstaging (REF). Amongst patients with cN2-3 disease, the rate of pathologic complete downstaging was 27% in those receiving induction treatment. Patients who exhibit substantial downstaging should be considered for consolidation definitive loco-regional therapy. 3-year OS rates for patients receiving induction chemotherapy followed by radical cystectomy have been reported to be 43% in patients with cN2-3 disease, with 3-year OS rates >80% in those achieving pathologic complete downstaging prior to surgery (REF).

Patients who do not have a favourable response to first-line chemotherapy and/or are not candidates for loco-regional definitive consolidative therapy should be managed as per recommendations for metastatic disease (see below).

Management of Recurrent or Metastatic Disease (Tx, Nx, M1)

Recurrent or metastatic disease should be treated primarily with systemic chemotherapy. A cisplatin-based regimen is the preferred initial therapy for patients with metastatic urothelial cancer for patients who are eligible. Eligible patients are defined as those who do not have one of the following criteria: CrCl <60 ml/min, PS ≥ 2, NYHA ≥ 3 heart failure, ≥ Grade 2 peripheral neuropathy, ≥ Grade 2 hearing loss. All patients with impaired renal function with a potential reversible cause (e.g. obstructive uropathy due to tumour), should be considered for treatment measures to improve renal function prior to initiation of platinum-based therapy.

Recommended cisplatin-based first-line therapies include cisplatin-gemcitabine and dose-dense MVAC. A randomized, phase III RCT compared cisplatin-gemcitabine to conventionally dosed MVAC in 405 patients and demonstrated no significant differences in response rate (49% vs 46%) or overall survival (HR 1.04, p=0.75). However, cisplatin-gemcitabine was better tolerated with lower rates of
side effects including neutropenia, febrile neutropenia, and mucositis. Dose-dense MVAC was also shown to have similar efficacy as conventionally dosed MVAC, with a reduction in toxicity (N=263). Given the data from these 2 landmark trials, conventionally dosed MVAC is no longer recommended.

In general, triplet combination chemotherapy with paclitaxel, gemcitabine and cisplatin is not recommended due to an increase in toxicity with no significant differences in PFS or OS.

For patients who are not candidates for cisplatin, carboplatin may be substituted in the recurrent/metastatic setting.

For platinum-ineligible patients, first-line immunotherapy with pembrolizumab is Health Canada approved. This is based on the KEYNOTE-052 single-arm phase II study that demonstrated a response rate of 29% (7% CR, 22% PR) with pembrolizumab as first-line therapy in platinum-ineligible patients. Patients may be able to access pembrolizumab for this indication through patient support programs.

Recommended second-line therapy for patients progressing on first-line platinum-based chemotherapy is pembrolizumab. This is based on the KEYNOTE-045 phase III RCT which demonstrated higher response rates (21% vs 11%) and improved OS (10.1 vs 7.3 months, HR 0.70, p=0.002) with pembrolizumab versus chemotherapy in the second-line.
References

Appendix A: Cancer Staging Manual (American Joint Committee on Cancer, 2017)

TNM staging of Bladder Cancer (AJCC/UICC TNM classification of malignant tumours, 8th edition)

<table>
<thead>
<tr>
<th>PRIMARY TUMOUR (T)</th>
<th>And N is...</th>
<th>And M is...</th>
<th>Then the stage group is...</th>
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<tbody>
<tr>
<td>TX</td>
<td>N0</td>
<td>M0</td>
<td>0a</td>
</tr>
<tr>
<td>T0</td>
<td>N0</td>
<td>M0</td>
<td>0is</td>
</tr>
<tr>
<td>TA</td>
<td>N0</td>
<td>M0</td>
<td>I</td>
</tr>
<tr>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>II</td>
</tr>
<tr>
<td>T2A-T2B</td>
<td>N0</td>
<td>M0</td>
<td>II</td>
</tr>
<tr>
<td>T3A, T3B, T4A</td>
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<td>M0</td>
<td>IIIA</td>
</tr>
<tr>
<td>T1-T4A</td>
<td>N1</td>
<td>M0</td>
<td>IIIA</td>
</tr>
<tr>
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<td>M0</td>
<td>IVA</td>
</tr>
<tr>
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<td>Any N</td>
<td>M1a</td>
<td>IVA</td>
</tr>
<tr>
<td>ANY T</td>
<td>Any N</td>
<td>M1b</td>
<td>IVB</td>
</tr>
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<th>REGIONAL LYMPH NODES (N)</th>
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<td>M0</td>
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<tr>
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<tr>
<td>TA</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>II</td>
</tr>
<tr>
<td>PT2A</td>
<td>Tumour invades superficial muscularis propria (inner half)</td>
<td>Microscopically</td>
<td></td>
</tr>
<tr>
<td>PT2B</td>
<td>Tumour invades deep muscularis propria (outer half)</td>
<td>Macroscopically (extravesical mass)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Tumour invades perivesical soft tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT3A</td>
<td>Microscopically</td>
<td></td>
<td></td>
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<tr>
<td>PT3B</td>
<td>Macroscopically (extravesical mass)</td>
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<td></td>
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<tr>
<td>T4</td>
<td>Extravesical tumour directly invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall</td>
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<tr>
<td>T4A</td>
<td>Extravesical tumour invades directly into prostatic stroma, seminal vesicles, uterus, vagina</td>
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<tr>
<td>T4B</td>
<td>Extravesical tumour invades pelvic wall, abdominal wall</td>
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<th>DISTANT METASTASIS (M)</th>
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<td>M0</td>
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<td>Distant metastasis limited to lymph nodes beyond the common iliacs</td>
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<tr>
<td>M1B</td>
<td>Non-lymph node distant metastases</td>
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Development and Revision History

This guideline was reviewed and endorsed by the Alberta GU Tumour Team. Members include surgical oncologists, radiation oncologists, medical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Tumour Teams, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2020.

Levels of Evidence

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<th>Level</th>
<th>Description</th>
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<td>I</td>
<td>Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity</td>
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<td>II</td>
<td>Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity</td>
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<tr>
<td>III</td>
<td>Prospective cohort studies</td>
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<tr>
<td>IV</td>
<td>Retrospective cohort studies or case-control studies</td>
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<tr>
<td>V</td>
<td>Studies without control group, case reports, expert opinion</td>
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Strength of Recommendations

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<th>Description</th>
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<td>A</td>
<td>Strong evidence for efficacy with a substantial clinical benefit; strongly recommended</td>
</tr>
<tr>
<td>B</td>
<td>Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended</td>
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<tr>
<td>C</td>
<td>Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional</td>
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<tr>
<td>D</td>
<td>Moderate evidence against efficacy or for adverse outcome; generally not recommended</td>
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<td>E</td>
<td>Strong evidence against efficacy or for adverse outcome; never recommended</td>
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Maintenance

A formal review of the guideline will be conducted in 2021. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

AHS, Alberta Health Services; CCA, CancerControl Alberta

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial GU Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.