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Locally Advanced/Metastatic Bladder Cancer

(T4bNxM0, TxN2-3M0, TxNxM1)

Effective Date: October 2024

Cancer Care Alberta

Clinical Practice Guideline GU–014 Version 4
www.ahs.ca/guru

Background

Urinary bladder cancer is the fourth most common cancer among men and accounts for 8% of all new male cancer cases. Urinary bladder cancer is less common among women (ranked 11th) and accounts for less than 3% of all new female cancer cases. Statistics Canada estimates that in 2024 in Canada there will be approximately 12,300 new cases of bladder cancer and 2,600 deaths associated with bladder cancer [link]. Smoking is estimated to account for between 34% and 50% of all bladder cancers.[1, 2]

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.[3] 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.[4] 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 be reviewed in multidisciplinary rounds to determine intent of therapy.
B. Eligible patients with unresectable disease should initially receive systemic therapy.

Enfortumab Vedotin + Pembrolizumab

i. Enfortumab Vedotin + Pembrolizumab was evaluated in the EV302 study with inclusion of locally advanced patients. This demonstrated an improvement in PFS (HR 0.45), OS (HR 0.47) compared to platinum-based chemotherapy in the ITT population.

a. Enfortumab Vedotin + Pembrolizumab: EV 1.25mg/kg Day 1 and Day 8 (max of 125mg), Pembrolizumab 200mg IV Day 1, every 3 weeks. Maximum of 35 cycles of pembrolizumab.

b. EV+P is Health Canada approved (August 2024) and is currently available by patient support program. Funding decisions are pending.

Cisplatin, Gemcitabine, Nivolumab

ii. Cisplatin, Gemcitabine and Nivolumab was evaluated in the Checkmate 901 study with inclusion of patients with unresectable disease who were cisplatin-eligible. . This combination demonstrated an improvement in PFS (HR 0.72) and OS (HR 0.78) compared to cisplatin/gemcitabine alone in the ITT population.

a. Cis/Gem/Nivo: Cis 70mg/m2 on Day 1, Gem 1000mg/m2 Day 1 and Day 8, Nivo 360mg Day 1 every 3 weeks for up to 6 cycles, followed by Nivo 480mg q4weekly (maximum 2 years).

b. Cis/Gem/Nivo is Health Canada approved but not funded. This regimen is not available by patient support program.

Platinum-based chemotherapy

iii. For patients who are ineligible for immunotherapy, 4-6 cycles of systemic platinum-based chemotherapy remain an option.

a. 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:

- Cisplatin-gemcitabine (21-day cycle): cisplatin 70 mg/m^2 day 1, gemcitabine 1250 mg/m^2 days 1 and 8.
- ddMVAC (14-day cycle): methotrexate 30 mg/m^2 day 1, cisplatin 70 mg/m^2 day 2, vinblastine 3 mg/m^2 day 2, doxorubicin 30 mg/m^2 day 2, plus GCSF support.

b. 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/m^2 days 1 and 8

C. For patients who have a favourable response to first-line systemic therapy, 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.

D. 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).

E. 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.

F. Patients who do not receive consolidative local therapy should be managed as per recommendations for metastatic disease (see below).

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 systemic therapy 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. Consideration should be given to send patient samples for FGFR mutation testing, based on test availability and patient status. At time of writing, testing is not publically funded or available. Results will help plan for future lines of therapy.

C. 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 therapy.

D. First-line standard of care treatment options include:

Enfortumab Vedotin + Pembrolizumab

i. Enfortumab Vedotin + Pembrolizumab was compared to standard platinum-based chemotherapy in the EV302 study. Patients were eligible if they were ECOG ≤2, platinum-eligible, eGFR>30 ml/min, and EV and IO eligible. EV+P demonstrated improvements in PFS

(HR 0.45) and OS (HR 0.47) compared to platinum-based chemotherapy. EV+P is Health Canada approved and available by patient support program (Sept 2024).

a. Enfortumab vedotin (1.25 mg/kg body weight IV day 1 and 8) and pembrolizumab (200mg IV day 1) q3 weekly.

b. [Enfortumab Vedotin monograph] [Pembrolizumab monograph]

Cisplatin, Gemcitabine, Nivolumab

ii. In the Checkmate901 study, compared to gemcitabine-cisplatin alone, the addition of nivolumab improved overall survival (HR: 0.78, 95%CI: 0.63-0.96; p=0.02) and improved progression-free survival at 12 months, 21.8% vs 34.2% respectively. The addition of nivolumab to gemcitabine-cisplatin is currently Health Canada approved, but not funded in Alberta.

a. nivolumab 360 mg given every 3 weeks in combination with gemcitabine-cisplatin for up to 6 cycles, followed by nivolumab 480 mg q4 weekly for up to 2 years.

Platinum-based chemotherapy

iii. Platinum-based chemotherapy should be considered in patients not eligible for enfortumab vedotin or IO agents.

a. 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:

- Cisplatin-gemcitabine (21-day cycle): cisplatin 70 mg/m^2 day 1, gemcitabine 1250 mg/m^2 days 1 and 8
- ddMVAC (14-day cycle): methotrexate 30 mg/m^2 day 1, cisplatin 70 mg/m^2 day 2, vinblastine 3 mg/m^2 day 2, doxorubicin 30 mg/m^2 day 2, plus GCSF support

b. 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:

- Carboplatin-gemcitabine (21-day cycle): carboplatin AUC5 day 1, gemcitabine 1000 mg/m^2 days 1 and 8

c. 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.

E. Interval restaging should occur every 3-4 cycles.

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

3. Maintenance Therapy – After 1st Line Platinum-Based Chemotherapy

A. For patients who do not progress (ie: have stable disease, a partial response, or complete response) after 4-6 cycles of platinum-based 1st line chemotherapy, maintenance immunotherapy with avelumab is recommended. Standard dosing is provided below:

i. Avelumab (14-day cycle): The recommended dose is 10 mg/kg body weight administered IV over 60 minutes every 2 weeks.
ii. Avelumab is to be started 4-10 weeks after the last dose of chemotherapy.
iii. Avelumab is continued until disease progression or unacceptable toxicity.

4. Second-Line Therapy:

A. For patients who have progressed on enfortumab vedotin + pembrolizumab, subsequent therapy is not well defined. Options may include:
i. Platinum-based chemotherapy.
ii. Erdafitinib for patients with FGFR alterations.
iii. Clinical trials where available.

Erdafitinib

B. is a treatment option in patients with selected FGFR mutations and fusions. The phase III THOR study (Cohort 1) enrolled patients with advanced urothelial carcinoma with prespecified FGFR alterations and demonstrated an improvement in OS with erdafitinib compared to taxane-based chemotherapy in patients with mUC previously treated with platinum-based chemotherapy and immunotherapy. Erdafitinib is currently Health Canada approved and is available via a patient access program, pending provincial approval and funding.
i. This agent has novel toxicities which require monitoring and evaluation. For dosing and toxicity information, please refer to the product monograph. Product monograph link here.

6. Third-Line Therapy and Beyond:

A. Taxane-based chemotherapy can be considered in subsequent lines of therapy. Commonly used agents are single-agent paclitaxel or docetaxel.

7. 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.

8. Follow-up

A. Post-systemic therapy: 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.

9. 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).[7,8] 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.[5] 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.

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 therapy. For patients who are eligible, the recommended regimen is enfortumab vedotin plus pembrolizumab.

The phase 3 open-label EV-302[19] trial randomized (N=886) previously untreated locally advanced or metastatic urothelial carcinoma patients (1:1) to enfortumab vedotin and pembrolizumab or gemcitabine plus cisplatin or carboplatin. After a median follow-up of 17.2 months, PFS was longer in the EV-P group (12.5 months vs 6.3 months) HR: 0.45 (95%CI: 0.38-0.54; p<0.001), as was OS (31.5 months vs. 16.1 months) HR: 0.47 (95%CI: 0.38-0.58; p<0.001). The median number of cycles of EV-P was 12 (range 1-46). Treatment-related grade ≥3 adverse events were lower in the EV-P group (55.9%) compared to the chemotherapy group (69.5%). The combination is Health Canada approved and is available via patient support program (in some locations). Novel toxicities include skin toxicity, neuropathy, hyperglycemia, and ocular toxicity.

The phase 3 open-label CheckMate 901[20] trial randomized (N=608) previously untreated unresectable or metastatic urothelial carcinoma patients (1:1) to gemcitabine-cisplatin ± nivolumab. After a median follow-up of 33.6 months, median OS was longer (21.7 months vs 18.9 months) with nivolumab combination therapy HR: 0.78 (95%CI: 0.63-0.96; p=0.02), as was 12-month PFS (34.2% vs 21.8%) HR 0.72 (95%CI: 0.59-0.88; p=0.001). Treatment-related grade ≥3 adverse events were higher in the nivolumab plus chemotherapy group (61.8%) vs the chemotherapy alone group (51.7%).

This regimen is Health Canada approved but is not currently funded nor available by patient support program.

There is currently no data to guide subsequent therapy in patients who have progressed on 1st line enfortumab vedotin plus pembrolizumab. Platinum-based chemotherapy is one option with regimens as noted above. Subsequent therapy may also include erdafitinib for patients with prespecified FGFR alterations. Erdaftinib was compared to chemotherapy (docetaxel, paclitaxel, or vinflunine) in the phase 3 THOR clinical trial cohort 1 in patients whose disease progressed after one or two previous treatments that included anti-PD-1 or anti-PD-L1 therapy. The median overall survival was significantly longer with erdafitinib than with chemotherapy (12.1 months vs 7.8 months, HR 0.64, p=0.005). Median progression free survival was also longer with erdaftinib than chemotherapy (5.6 months vs 2.7 months, HR 0.58, p=<0.001). Testing for FGFR alterations is not currently funded but may be accessed through clinical trials. Erdafitinib is Health Canada approved and available for patients with prespecified alterations via a patient support program.

For patients who are not eligible for enfortumab vedotin plus pembrolizumab in the first-line setting, or for those where is not available, a cisplatin-based regimen is the preferred initial therapy 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.[6] 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.[7] Dose-dense MVAC was also shown to have similar efficacy as conventionally dosed MVAC, with a reduction in toxicity (N=263).[8] Given the data from these 2 landmark trials, conventionally dosed MVAC is no longer recommended.
For patients who are not candidates for cisplatin, carboplatin may be substituted in the recurrent/metastatic setting.[10-13]
Maintenance avelumab is recommended for patients who have stable disease or a response to 1st-line platinum-based chemotherapy. In a randomized phase III trial (JAVELIN Bladder 100),[15] 700 patients with locally advanced unresectable or metastatic urothelial bladder cancer who experienced either an objective response (complete or partial response) or stable disease after four to six cycles of gemcitabine plus platinum-based chemotherapy were randomly assigned to either maintenance avelumab and best supportive care (BSC) or BSC alone. At median follow-up of approximately 19 months, the addition of avelumab to BSC improved OS in the entire study population (median 21 versus 14 months, HR 0.69, 95% CI 0.56-0.86) and in those with PD-L1 positive tumors (median not reached versus 17 months, HR 0.56, 95% CI 0.40-0.79). Avelumab also improved median PFS over BSC in both groups (3.7 versus 2.0 months, HR 0.62, 95% CI 0.52-0.75

in the entire study population; 5.7 versus 2.1 months, HR 0.56, 95% CI 0.43-0.73 in those with PD-L1 positive tumors). Objective response rates to maintenance avelumab in the overall population and those with PD-L1 positive tumors were 10 and 14 percent, respectively.

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.[16]

For patients who have not received 1st line enfortumab vedotin and pembrolizumab, monotherapy with enfortumab vedotin may be considered after platinum-based chemotherapy and PD-1/PD-l1 inhibitor. Enfortumab vedotin was evaluated in a phase III clinical trial (EV-301)[18] of 608 patients with locally advanced unresectable or metastatic urothelial carcinoma (including those with squamous differentiation or mixed cell types) previously treated with platinum-based chemotherapy and PD-1/PD-L1 inhibitor. Patients were randomly assigned to either enfortumab vedotin or investigator's choice of chemotherapy (docetaxel, paclitaxel, or vinflunine). At median follow-up of approximately 11 months, compared with chemotherapy, enfortumab vedotin improved OS (median 13 versus 9 months, HR 0.70, 95% CI 0.56-0.89), PFS (median 6 versus 4 months, HR 0.62, 95% CI 0.51-0.75) and overall response rates (41 versus 18 percent).Grade ≥3 toxicity rates for any adverse event were similar between the two treatment arms (51 versus 50 percent). Grade ≥3 toxicities specifically associated with enfortumab vedotin included rash (15 percent), peripheral neuropathy (5 percent), and hyperglycemia (4 percent). Ocular toxicities, pneumonitis (eg, interstitial lung disease), and severe cutaneous adverse reactions, including cases of Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have also been reported with this agent.

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Appendix A: Cancer Staging

Table 1. TNM staging of Bladder Cancer (AJCC/UICC TNM classification of malignant tumours, 8th edition)

PRIMARY TUMOUR (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
TA	Non-invasive papillary carcinoma
TIS	Urothelial carcinoma *in situ*: "Flat tumor"
T1	Tumour invades lamina propria (subepithelial connective tissue)
T2	Tumour invades muscularis propria
PT2A	Tumour invades superficial muscularis propria (inner half)
PT2B	Tumour invades deep muscularis propria (outer half)
T3	Tumour invades perivesical soft tissue
PT3A	Microscopically
PT3B	Macroscopically (extravesical mass)
T4	Extravesical tumour directly invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4A	Extravesical tumour invades directly into prostatic stroma, seminal vesicles, uterus, vagina
T4B	Extravesical tumour invades pelvic wall, abdominal wall
REGIONAL LYMPH NODES (N)	
NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node)
N2	Multiple regional lymph node metastases in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node metastases)
N3	Lymph node metastasis to the common iliac lymph nodes
DISTANT METASTASIS (M)	
M0	No distant metastasis
M1	Distant metastasis
M1A	Distant metastasis limited to lymph nodes beyond the common iliacs
M1B	Non-lymph node distant metastases

PROGNOSTIC STAGE GROUPS			
WHEN T IS…	*And N is…*	*And M is…*	*Then the stage group is…*
TA	N0	M0	0a
TIS	N0	M0	0is
T1	N0	M0	I
T2A-T2B	N0	M0	II
T3A, T3B, T4A	N0	M0	IIIA
T1-T4A	N1	M0	IIIA
T1-T4A	N2, N3	M0	IIIB
T4B	Any N	M0	IVA
ANY T	Any N	M1a	IVA
ANY T	Any N	M1b	IVB

Development and Revision History

This guideline was developed by a multidisciplinary working group comprised of members from the Alberta Provincial GU Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. The draft guideline was externally reviewed and endorsed by members of the Alberta Provincial GU Tumour Team who were not involved in the guideline's development, including surgical oncologists, radiation oncologists, medical oncologists, urologists, nurses, pathologists, and pharmacists. 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.

Maintenance

A formal review of the guideline will be conducted in 2025. 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; AJCC, American Joint Committee on Cancer; CCA, Cancer Care Alberta; MVAC, Methotrexate, vinblastine sulfate, doxorubicin hydrochloride; TURBT, Transurethral resection of a bladder tumor.

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.

Funding Source

Financial support for the development of Cancer Care Alberta's evidence-based clinical practice guidelines and supporting materials comes from the Cancer Care Alberta operating budget; no outside commercial funding was received to support the development of this document.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the *Outpatient Cancer Drug Benefit Program Master List*.

Conflict of Interest Statements

***Dr. Nimira Alimohamed** reports receiving grants from Astellas, AstraZeneca, Janssen, Merck & Pfizer.
Dr. Shaan Dudani has nothing to disclose.
Derek Tilley has nothing to disclose.

Citation

Alimohamed N (lead), Dudani S, Tilley D. Cancer Care Alberta, Alberta Health Services (2024). Clinical Practice Guideline on Advanced/Metastatic Bladder Cancer v4. Accessed [Month, Year]. Available from: www.ahs.ca/guru