Guideline Resource Unit
guru@ahs.ca

Muscle-Invasive Bladder Cancer

(T2a-T4a, N0-1, M0)

Effective Date: October 2024

Cancer Care Alberta

Clinical Practice Guideline GU–013 Version 9
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 muscle-invasive bladder cancer in Alberta. Guidelines for non-muscle-invasive bladder cancer, locally advanced/metastatic bladder cancer, and upper tract urothelial cancer are available separately.

Guideline Questions

1. What work-up is required for muscle invasive bladder cancer?
2. What is the appropriate stage-specific treatment for patients with muscle invasive bladder cancer?

Following treatment for muscle invasive 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

Adult patients (age ≥18 years) with a diagnosis of non-metastatic, muscle-invasive bladder cancer, including patients with a single regional lymph node metastasis in the true pelvis (T2a-T4a, N0-1, M0).

Recommendations

1. Staging:

A. Cystoscopy with transurethral resection of bladder tumour (TURBT) to establish if disease is muscle-invasive.
B. CT of chest, abdomen, and pelvis.
C. MRI abdomen/pelvis as clinically indicated.
D. Alkaline phosphatase.
E. Bone scan if elevated alkaline phosphatase or symptoms.
F. Where available and if clinically indicated, PET/CT can provide valuable staging information.
G. Additional blood work (e.g. CBC, LFTs, creatinine, HBV screening) may be required if neoadjuvant chemotherapy is being considered, but should be done at the time of medical oncologist consult.

2. Therapy with Curative Intent:

- All patients should be discussed in a multidisciplinary setting, and be made aware of their curative intent treatment options.
- Either a surgical (radical cystectomy with bilateral and extended lymph node dissection with urinary diversion or neobladder reconstruction[5-11] OR trimodality bladder-preserving approach can be considered.[12-17]
- In patients unable to tolerate either a surgical or bladder-preserving approach due to medical comorbidities, poor performance status, or patient choice, consider TURBT +/- radiotherapy or chemotherapy, TURBT alone, radiotherapy alone, or chemotherapy alone, although the odds of cure are low.

A. Neoadjuvant chemotherapy

i. Neoadjuvant chemotherapy is considered standard of care prior to radical cystectomy in patients with muscle-invasive urothelial bladder cancer. It may also be considered on a case-by-case basis for patients who are planned to receive a bladder preservation / trimodality therapy.
ii. Where possible, neoadjuvant chemotherapy is strongly preferred over adjuvant chemotherapy.

iii. Neoadjuvant chemotherapy should be cisplatin-based combination therapy. Options include cisplatin-gemcitabine or dose-dense MVAC.[18, 19] A total of 4 cycles should be planned.[20, 21] A standard dosing option for each regimen is provided below:

a. Cisplatin-gemcitabine (21-day cycle): cisplatin 70 mg/m^2 day 1, gemcitabine 1250 mg/m^2 days 1 and 8 (total dose per cycle = 2500 mg/m^2)

b. 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

iv. Consideration for split-dose cisplatin (cisplatin dose divided over 2 separate days) can be considered for patients who are otherwise good candidates for neoadjuvant chemotherapy but have a creatinine clearance between 45-60 mL/min.[22, 23] Standard dosing options for split-dose regimens are provided below:

a. Split-dose cisplatin-gemcitabine (21-day cycle): cisplatin 35 mg/m^2 days 1 and 8, gemcitabine 1250 mg/m^2 days 1 and 8 (total dose per cycle = 2500 mg/m^2)

b. Split-dose ddMVAC (14-day cycle): methotrexate 30 mg/m^2 day 1, cisplatin 35 mg/m^2 days 1 and 2, vinblastine 3 mg/m^2 day 2, doxorubicin 30 mg/m^2 day 2, plus GCSF support

v. Patients with contraindications to cisplatin should proceed directly to definitive locoregional therapy – routine use of carboplatin-based neoadjuvant combinations is not advised.

vi. For patients receiving cisplatin-gemcitabine, a CT scan of abdomen and pelvis should be performed after 2 cycles to exclude progression. If disease progression has occurred, then neoadjuvant chemotherapy should be abandoned, and the patient should be taken to surgery if feasible.

B. Radical cystectomy with bilateral pelvic lymph node dissection

i. Radical cystectomy with bilateral pelvic lymph node dissection (PLND), followed by urinary diversion. Options for urinary diversion include continent reservoir and conduit diversion. There are insufficient data to recommend one procedure over another.

ii. Ileal neobladder reconstruction can be considered in carefully selected patients with bladder-confined, node-negative urothelial carcinoma with good kidney and liver function.[24, 25]

iii. Extended template PLND can include the presacral and common iliac lymph nodes to the aortic bifurcation.[26-30]

iv. Non-urothelial histologies should be considered on a case-by-case basis and discussed in multi-disciplinary tumor boards/rounds.

v. All patients who are eligible for cisplatin-based chemotherapy should have the opportunity to discuss neoadjuvant therapy with a medical oncologist before surgery, as this has been shown to result in improved survival versus surgery alone[31, 32] (see section A above).

vi. In cases where neoadjuvant chemotherapy was not received and/or completed, adjuvant chemotherapy can be considered on a case-by-case basis pending post-surgical pathology (see section D below).

C. Bladder preservation / combined modality approach

i. Bladder preservation therapy is best suited for those with a solitary lesion which has been maximally resected with TURBT and the following features: no CIS, no evidence of hydronephrosis, urothelial histology, adequate bladder volume, clinically negative lymph nodes, and absence of significant lower urinary tract irritative symptoms.[20, 21, 33]

ii. Optimal bladder preservation strategies consist of radiotherapy combined with concurrent chemotherapy following a maximal TURBT.[34]

iii. Prior to bladder preservation there should be a complete resection of the bladder tumour. If more than eight weeks have elapsed since TURBT, or symptoms are recurrent, consider repeat cystoscopy/ TURBT prior to initiation of concurrent chemoradiation if safely possible.

viii. Prior to definitive chemoradiation, neoadjuvant chemotherapy may be considered on a case-by-case basis, although there is no level I evidence to support this (see section A above).

iv. Radiotherapy should be delivered to the whole bladder (+/- regional nodes to at least 40-44 Gy), followed by a bladder/ tumour boost to at least 60 Gy in conventional fractionation. Altered fractionation regimens, such as 50-55 Gy in 20 fractions may also be considered.[35]

v. In cystectomy candidates, second-look cystoscopy +/- biopsy and urine cytology can be considered after 40-50 Gy to ensure lack of progression. If there is evidence of progression, bladder preservation approach should be abandoned, and salvage cystectomy should be considered.

vi. Commonly used concurrent chemotherapy regimens include: weekly cisplatin, 5-FU plus Mitomycin C.[36, 37] Standard dosing options are provided below:

- **a.** Weekly cisplatin (7-day cycle): cisplatin 40 mg/m^2 day 1
- **b.** 5-FU + MMC: MMC 12 mg/m^2 day 1, 5-fluorouracil 500 mg/m^2/day days 1-5 and 16-20

vii. If patients are ineligible for weekly cisplatin or 5FU+ MMC, or the patient refuses, weekly gemcitabine can be considered.

- **a.** Weekly gemcitabine: gemcitabine 100mg/m2 day 1 q7 days, during radiation therapy[38]

viii. Salvage cystectomy should be performed in patients with residual disease post completion of combined modality therapy.

D. Adjuvant chemotherapy

i. Referral to medical oncology should be considered for consideration of adjuvant therapy if neoadjuvant treatment was not received.

ii. Adjuvant chemotherapy should be considered for patients with resected urothelial carcinoma with either pT3-T4 or pN1-3 disease on the surgical specimen.

iii. Adjuvant chemotherapy with a cisplatin-based regimen is recommended.[39, 40] For cisplatin-ineligible patients (CrCl <60 ml/min, PS ≥ 2, NYHA ≥ 3 heart failure, ≥ Grade 2 peripheral neuropathy, ≥ Grade 2 hearing loss), adjuvant chemotherapy is not recommended. [41 41 40 40 39 40]

E. Adjuvant immunotherapy

i. Adjuvant immunotherapy can be considered for high-risk patients. The Phase III Checkmate 274 trial demonstrated an improvement in disease-free survival in patients with urothelial carcinoma with high-risk muscle-invasive disease after surgery with one-year of adjuvant nivolumab compared to placebo. [39] Eligibility criteria included:

- Patients with ypT2-ypT4a or ypN+ MIUC who had neoadjuvant cisplatin chemotherapy OR
- Patients with pT3-4a or pN+ MIUC without prior neoadjuvant cisplatin chemotherapy and not eligible/refused adjuvant cisplatin-based chemotherapy
- Radical surgery within the past 120 days
- Disease-free status within 4 weeks of dosing

ii. Nivolumab was delivered as 240mg IV q2weekly x 1 year in the Checkmate 274 study

iii. Nivolumab is Health Canada approved for this indication and is currently funded and available. Dosing can be 240mg q2weekly or 480 mg q4weekly.

F. Adjuvant radiotherapy

i. Adjuvant radiotherapy following cystectomy is generally not recommended.

3. Follow-up

A. Surgical approach

i. A stage-specific follow-up strategy has been endorsed by a consensus group from the Canadian Urologic Oncology Group, Canadian Urological Association and Bladder Cancer Canada.[42] Follow-up is recommended according to these guidelines.

Table 1. Recommended stage-specific surveillance protocol after radical cystectomy (adapted from Yafi et al[262])

≤pT2 N0														
Months	3	6	9	12	15	18	21	24	30	36	42	48	54	60
Office visit	X	X		X				X		X		X		X
Chest X-ray				X				X		X		X		X
Lab studies	X	X		X				X		X		X		X
Triphasic CT abdomen/pelvis				X				X		X				X
Urine cytology*				X				X		X		X		X
pT3-4 N0														
Months	3	6	9	12	15	18	21	24	30	36	42	48	54	60
Office visit	X	X		X		X		X		X		X		X
Chest X-ray		X		X		X		X		X		X		X
Lab studies	X	X		X		X		X		X		X		X
Triphasic CT abdomen/pelvis		X		X				X		X		X		X
Urine cytology*				X				X		X		X		X
pTx N+														
Months	3	6	9	12	15	18	21	24	30	36	42	48	54	60
Office visit	X	X	X	X		X		X	X	X	X	X	X	X
Chest X-ray	X	X		X		X		X	X	X	X	X	X	X
Lab studies	X	X	X	X		X		X	X	X	X	X	X	X
Triphasic CT abdomen/pelvis	X	X		X		X		X		X		X		X
Urine cytology*				X				X		X		X		X

*Urine washings/cytology once a year is optional. Vitamin B12 is recommended when clinically indicated and upper tract imaging to assess the uretero-ileal anastomosis at 6–8 weeks from time of RC is recommended in all groups. Baseline CT abdomen/pelvis at 3–6 months following radical cystectomy may be considered for all patients. CT: computed tomography.

(Adapted from Kassouf et al. 2016[42])

B. Bladder preservation approach

i. Patients undergoing a bladder preservation, combined modality approach should be followed in similar fashion to patients treated with a surgical approach, with the addition of regular, lifelong cystoscopic surveillance as per the following schedule:

a. Cystoscopy +/- biopsy and cytology q3 months for first 2 years, then every 6 months for the next 2 years, then annually thereafter.

ii. Superficial recurrences of bladder cancer may be treated as per other non–muscle-invasive bladder cancers (see separate guidelines) or with salvage cystectomy with bilateral pelvic lymphadenectomy.

iii. Muscle-invasive recurrences are recommended to be treated with salvage cystectomy and bilateral pelvic lymphadenectomy (see section 2B above).

4. 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. Given that pure non-urothelial histologies are generally less sensitive to chemotherapy, (neo)adjuvant treatment is generally not recommended. The major exceptions to this are small cell carcinoma (see below) and micropapillary histology.

iv. Radical cystectomy is strongly preferred over bladder-preserving, combined modality approaches for pure non-urothelial histologies.

B. Urachal adenocarcinomas

i. Partial cystectomy may be considered as an alternative to radical cystectomy, provided that adequate margins can be maintained.

ii. Cystectomy should be performed with en bloc resection of the urachal ligament and umbilicus. Bilateral pelvic lymphadenectomy should also be performed.

iii. As with other non-urothelial histologies, neoadjuvant chemotherapy and bladder-preserving, combined modality approaches are not recommended.

iv. It is recommended that these patients are discussed at multidisciplinary rounds post-operatively and are referred to medical oncology for consideration of adjuvant chemotherapy, though there is no level I evidence to support the use of adjuvant chemotherapy.

C. Small cell carcinoma of the bladder

i. Small cell carcinoma (including any percentage small cell histology, and early stage (i.e T1) disease) of the bladder is recommended to be managed as follows:

a) All patients should be discussed in multidisciplinary rounds. Treatment recommendations include neoadjuvant chemotherapy with platinum etoposide followed by definitive surgical resection or combined modality therapy analogous to pulmonary small cell carcinoma.[43, 44]

b) For patients who did not receive neoadjuvant chemotherapy prior to definitive local therapy, adjuvant chemotherapy with 4 cycles of platinum-etoposide is recommended.

c) Baseline staging brain imaging can be considered in asymptomatic patients given the higher risk of brain metastases versus conventional urothelial bladder cancer. It is recommended in patients with higher-risk disease (e.g. T3+, N+ or M+).

d) The role of prophylactic cranial irradiation (PCI) following definitive therapy is unclear. In the absence of data demonstrating clear benefit, PCI is generally not recommended in this setting.

e) For patients who develop metastatic disease, guidelines for management of metastatic small cell carcinoma of the lung should be followed.

Discussion

For muscle-invasive bladder cancer (T2-T4a, N0-1, M0), therapy with curative intent typically includes either a radical cystectomy with full bilateral pelvic LN dissection, followed by urinary diversion or neobladder reconstruction[5-11] or a bladder preservation approach (i.e. complete tumour resection followed by radiotherapy and concurrent chemotherapy).[12-17] There are no modern-era randomized trials to support one approach over the other; however, some patients (e.g. those with adequate renal function, no hydronephrosis, urothelial histology, T2 tumour <5 cm, no CIS, pT0 after a second TURBT, and with a proper bladder capacity and function)[45] may be better suited for bladder preservation while others (i.e. not meeting criteria above) are better suited for radical cystectomy. For patients unable to tolerate or unwilling to undergo either approach, options include: TURBT ± radiotherapy or chemotherapy, TURBT alone, radiotherapy alone, or chemotherapy alone.

Pelvic LN dissection should include the presacral and common iliac lymph nodes to the aortic bifurcation (i.e., extended template). There are data to show that the lymph node metastasis detection rate is higher with extended template pelvic LN dissection than with limited or standard pelvic LN dissection: Heidenreich, et. al. reported 27% detection for extended vs. 12% for standard;[26] Bader, et. al. reported 24% for extended;[27] Allaf, et. al. reported 3% for extended vs. 1% for limited;[28] and Dhar, et. al. reported 26% for extended vs. 13% for limited.[29] The 5-year recurrence-free survival rate for extended is higher than that of limited (71% vs. 63% for pT2pN0-2 and 49% vs. 19% for pT3pN0-2; p<.0001).[29] These results were confirmed in a meta-analysis of 2,824 patients which showed a significantly better recurrence-free survival in extended pelvic LN dissection vs. non-extended pelvic LN dissection (HR 0.65; p<.001).[46]

In patients for whom the surgical approach is appropriate, and who are eligible for cisplatin-based combination chemotherapy, the option of neoadjuvant chemotherapy should be discussed; if chemotherapy in the neoadjuvant setting is deemed inappropriate, adjuvant administration should instead be considered (see below).

In patients for whom the bladder-preserving approach is recommended, TURBT should be performed prior to the initiation of concurrent chemoradiation. A prospective study among patients with urothelial carcinoma (T2-T3, Nx, M0; n=33) who underwent maximum TURBT followed by three cycles of adjuvant chemotherapy (e.g. methotrexate, vinblastine, adriamycin and cisplatin; MVAC), followed by radical radiotherapy, demonstrated a response rate of 46.4% overall (39.3% complete; 7.1% partial) and disease free and overall survival rates of 39.3% and 64.3%, respectively, after 12 months of follow-up. Response and survival were positively associated with a lower tumour stage (P=.001) and completeness of TURBT (P=.001).[47] Similar results were reported in another study among patients with T2-T4 bladder cancer (n=74) who underwent either: three cycles of neoadjuvant methotrexate, cisplatin, and vinblastine (MCV) chemotherapy followed by radiotherapy (60 Gy) or concurrent chemoradiotherapy (64.8 Gy with weekly cisplatin). With a mean follow-up of 54 months, the actuarial 5-year overall survival and overall survival with bladder preservation rates were 72% and 60%,

respectively; there were no significant differences in the incidence of superficial, muscle-invasive, or distant recurrences.[48] In patients (n=123) with muscle-invasive bladder cancer (T2-T4a), the addition of neoadjuvant chemotherapy (two cycles) with methotrexate, cisplatin, and vinblastine did not improve overall survival or distant metastases rates, as compared to pelvic irradiation (39.6 Gy) with concurrent cisplatin (two cycles q three weeks) alone. The actuarial 5-year overall survival rate was 48% for patients receiving neoadjuvant chemotherapy (versus 49% for those who didn't); the 5-year distant metastasis rate was 33% for those who received neoadjuvant chemotherapy (versus 39% for those who didn't).[20] Salvage cystectomy should be performed in patients with invasive residual disease or recurrence.[49, 50]

A multicenter, phase III trial among patients with muscle-invasive bladder cancer (N=360) compared radiotherapy alone to radiotherapy with concurrent chemotherapy (5-fluorouracil; 500 mg/m^2 during fractions 1-5 and 16-20 and mitomycin-C; 12 mg/m^2 on day 1). Two-year locoregional disease-free survival was 67% (95% CI 59-74) for chemoradiotherapy and 54% (95% CI 46-62) for radiotherapy alone. Five-year overall survival was 48% (95% CI 40-55) for chemoradiotherapy and 35% (95% CI 28-43) for radiotherapy alone (p=0.16).[37] A recent randomized controlled trial compared post-TURBT (maximal) whole-pelvis concurrent chemoradiotherapy with bladder-only concurrent chemoradiotherapy (45 Gy in 25 fractions plus 20 Gy boost, with weekly cisplatin 40 mg/m^2), among patients with muscle-invasive, node-negative disease (n=230). The 5-year disease-free survival rates (47.1% vs. 46.9%; p=.5), 5-year overall survival rates (52.9% vs. 51.0%; p=.8), and bladder preservation rates (58.9% vs. 57.1%; p=.8) were not different between groups.[12] These data suggest that bladder-only concurrent chemoradiotherapy may be an option for patients with potentially lower morbidity than whole-pelvis chemoradiotherapy.

Neoadjuvant chemotherapy is cisplatin-based combination therapy (e.g. cisplatin-gemcitabine or dose-dense MVAC).

A trial among stage T2-T4a, N0 patients (n=307) who were treated with radical cystectomy alone or preceded by three cycles of neoadjuvant chemotherapy (e.g. methotrexate, vinblastine, doxorubicin, and cisplatin) showed that median survival was increased among patients who received neoadjuvant chemotherapy (77 vs. 46 months; P=.06); furthermore, the presence of residual disease was decreased significantly (15 vs. 38%; P<.001) among those who received neoadjuvant chemotherapy.[31] Another study in patients with T2-T4aNXM0 disease (n=309) showed that neoadjuvant chemotherapy with three courses of cisplatin and methotrexate also increased overall survival (53 vs. 46%) at a median follow-up of 5.3 years.[51] However, given that both cisplatin-gemcitabine and dose-dense MVAC have been shown to have improved tolerability with similar outcomes as compared to conventional MVAC in the advanced/metastatic setting for urothelial cancer,[52, 53] these regimens have been adopted as standard of care neoadjuvant regimens, despite the lack of level I evidence..[54, 55] Two single-arm phase II studies of ddMVAC which suggest this regimen is feasible and effective, with pathologic downstaging to non-muscle invasive disease in

49%-52% of patients.[18, 19] The VESPER study was a phase 3 randomized (N=437) trial of peri-operative chemotherapy in patients with MIBC and randomized patients to receive 4 cycles of cisplatin-gemitabine vs 6 cycles of ddMVAC. The study demonstrated improvements in pCR rates off 42% with ddMVAC compared to 36% with cisplatin and gemcitabine in those patients who received neoadjuvant therapy (p=0.2). PFS was also improved with ddMVAC. However, 6 cycles of ddMVAC is not standard therapy. In summary, it is currently recommended that neoadjuvant chemotherapy consist of either 4 cycles of cisplatin-gemcitabine or 4 cycles of ddMVAC.[56]

A meta-analysis of over 3000 T2-T4a patients in whom definitive therapy (surgery or radiotherapy) was given either by itself or with neoadjuvant chemotherapy demonstrated a survival advantage for neoadjuvant treatment. Neoadjuvant chemotherapy, regardless of the type of local treatment that followed, resulted in a 14% reduction in the risk of death and 5% absolute increase in overall survival at five years.[32]

Patients with contraindications to cisplatin should proceed directly to definitive therapy, as the use of carboplatin-based neoadjuvant combinations is not advised.[31, 32, 57-71] Pure non-urothelial histologies are generally less sensitive to chemotherapy and therefore neoadjuvant chemotherapy is generally avoided in this patient population. The major exception to this is micropapillary bladder cancer, which should be treated similarly to urothelial bladder cancer in terms of perioperative chemotherapy.

A CT scan of the abdomen and pelvis should precede cystectomy. In patients who have already undergone cystectomy, adjuvant cisplatin-based combination chemotherapy (using the same regimens as outlined for neoadjuvant chemotherapy above) should be offered. In cases where a cystectomy has already been performed, there is less rigorous evidence for adjuvant chemotherapy. A Canadian population-based outcome study demonstrated that use of adjuvant chemotherapy was associated with improved OS (HR 0.71, 95% CI 0.62-0.81) and cancer-specific survival (HR 0.73, 95% CI 0.64-0.84).[72] In addition, a Cochrane Collaboration meta-analysis of adjuvant chemotherapy for invasive bladder cancer reported a 25% relative reduction in the risk of death for chemotherapy compared to that on control;[73] however, power was limited in this study.

The phase III double-blind CheckMate 274[41] randomized (N=709) patients with muscle-invasive urothelial carcinoma who had undergone radical surgery (1:1) and remained high-risk to receive nivolumab or placebo every 2 weeks for up to 1 year (cisplatin-based chemotherapy before trial entry was allowed). After a median follow-up of 20.9 months, median DFS was 20.8 months with nivolumab vs 10.8 months with placebo HR: 0.70 (95%CI: 0.55-0.90; p<0.001). This study included patients with muscle-invasive or node-positive disease after receiving neoadjuvant chemotherapy, or those with extravesicular extension or node-positive disease who did not receive neoadjuvant chemotherapy and were ineligible for or refused adjuvant cisplatin-based chemotherapy. Treatment-associated grade ≥3 adverse events were 17.9% in the nivolumab group and 7.2% in the placebo group. A presentation at the European Urology Association annual meeting reported overall survival data after additional follow-up and found that nivolumab improved overall survival in the entire

population (median 69.5 months vs 50.1 months) HR: 0.76 (95%CI: 0.61-0.95) and in the PD-L1 >1% population HR: 0.56 (95%CI: 0.36-0.86) [link]. This has been Health Canada approved and is funded.

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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)[72]

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; CBC, Complete blood count; CT, Computed tomography; HBV, Hepatitis B virus; LFT, Liver function test; MVAC, Methotrexate, vinblastine sulfate, doxorubicin, hydrochloride; PET, Positron emission tomogrphay; PLND, Pelvic lymph node dissection; TURBT, Transurethral resection of bladder tumour

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 other from Astellas, other from Pfizer, other from Merck, other from AstraZeneca, other from Janssen, outside the submitted work.

Dr. Shaan Dudani has nothing to disclose.

Derek Tilley has nothing to disclose.

Citation

Alimohamed N, (lead), Shaan D, Tilley D. Cancer Care Alberta, Alberta Health Services (2024). Clinical Practice Guideline on MIBC, Version 9]. Accessed [Month, Year]. Available from: www.ahs.ca/guru