MUSCLE INVASIVE AND LOCALLY ADVANCED/METASTATIC BLADDER CANCER

Effective Date: October 2013

The recommendations contained in this guideline are a consensus of the Alberta Provincial Genitourinary 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.
BACKGROUND

Urinary bladder cancer is the fourth most common cancer among men and accounts for 7% of all new male cancer cases. Urinary bladder cancer is far less common among women (ranked 11th) and accounts for less than 3% of all new female cancer cases. Bladder cancer is the ninth leading cause of cancer deaths, among men, accounting for 3%.\(^1\) Statistics Canada estimates that there were 7,100 new cases in Canada in 2010. The five-year survival rate for urinary bladder cancer, overall, is about 80%; however, the recurrence rate is nearly 80%.\(^2\)

There are several histological types of bladder cancer. Urothelial carcinoma is the most common, accounting for more than 90% of all cases; other 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.\(^3\) Staging of bladder cancer is currently based on the seventh edition (2010) of the American Joint Committee on Cancer’s AJCC Cancer Staging Manual.\(^4\) A detailed description of the staging can be found in the Appendix. The objective of this guideline is to provide physicians with the latest, evidence-based, management strategies for bladder cancer in Alberta.

GUIDE QUESTION

- What work-up is required for bladder cancer?
- What is the appropriate stage-specific treatment (i.e., surgery, systemic therapy, radiotherapy) for patients with bladder cancer?
- Following treatment for bladder cancer, how often should patients be followed and what tests are appropriate during the follow-up period?

DEVELOPMENT PANEL

This guideline was reviewed and endorsed by the Alberta Provincial Genitourinary Tumour Team. Members of the Alberta Provincial Genitourinary Tumour Team include medical oncologists, radiation oncologists, urologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Genitourinary Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

SEARCH STRATEGY AND REVISION HISTORY

The original guideline, which was developed in 2005 and updated in 2009, 2010, and 2011, was divided into two distinct documents during the 2013 update: a guideline on noninvasive bladder cancer (GU-009) and a guideline on muscle-invasive and locally advanced or unresectable/metastatic disease (GU-002). The guideline on noninvasive disease includes an update of the original search strategy and recommendations, as well as new literature and more in-depth recommendations on bacillus calmette-guerin (BCG) therapy. The guideline on invasive disease includes an update of the literature, using the Medline and EMBASE databases. The search term bladder cancer was used and results were limited to clinical trials, randomized controlled trials, and phase III studies. The 2011 literature update produced a total of 15 relevant citations, which were included in the review.
The guideline was again updated in 2013. The literature review was updated with new clinical trials published between 2010 December and 2013 March. For this update, the PubMed database was searched using the terms (“transitional cell carcinoma” or “urothelial carcinoma”) AND “bladder.” Results were limited to clinical trials published in English, leaving a total of 80 citations. Phase I clinical trials, as well as irrelevant citations (i.e., studies on primaries other than bladder cancer, studies on lifestyle interventions, etc.) were subsequently removed, leaving a total of five phase III clinical trials, two additional randomized controlled trials, and eight phase II trials, all of which were included in the review.

TARGET POPULATION

The target population for this guideline is patients with muscle invasive bladder cancer (i.e., stages T2a/b, T3a/b, T4a and N0-X, M0).

RECOMMENDATIONS

Management of Stage T2a/b

Staging
- CT abdomen and pelvis or MRI as clinically indicated.
- Examination under anesthesia and/or cystoscopy, if clinically indicated
- CXR
- Alkaline phosphatase
- Bone scan, if elevated alkaline phosphatase or symptoms

Preparation for therapy
- Baseline CBC
- Baseline Cr

Therapy with curative intent
- Complete resection or adequate tissue sampling including muscularis propria
- Either a surgical (radical cystectomy with full bilateral pelvic LN dissection) or a bladder preservation approach can be considered.
- Patients should be considered on an individual basis:
  - Bladder preservation is not preferred in patients with hydronephrosis or in patients with significant irritative symptoms.
  - Bladder preservation therapy is best suited for those with a solitary early-stage lesion, no CIS, no evidence of hydronephrosis, adequate renal function for delivery of concurrent platinum-based chemotherapy, adequate bladder volume and absence of significant lower urinary tract symptoms.
  - Non-transitional cell histologies (i.e. adenocarcinoma, squamouscell carcinoma) are generally insensitive to chemotherapy; these patients should not be considered for a neoadjuvant treatment.
  - In patients unable to tolerate either a surgical or bladder-preserving approach due to medical comorbidities, poor performance status, or unwillingness, consider TURBT ± radiotherapy or chemotherapy, TURBT alone, radiotherapy alone, or chemotherapy alone.

Surgical Approach
- Ileal neobladder reconstruction can be considered in carefully selected patients with bladder-confined, node-negative urothelial carcinoma with good kidney and liver function.
Radical cystectomy with bilateral pelvic lymph node dissection (PLND), followed by urinary diversion. Options for urinary diversion include continent reservoir and conduit diversion. There is insufficient data to recommend one procedure over another.

Extended template PLND to include the presacral and common iliac lymph nodes to the aortic bifurcation.

All patients who are eligible for cisplatinum-based combination chemotherapy should have the opportunity to discuss neoadjuvant therapy with a medical oncologist either before surgery or as combined modality therapy.

Consider adjuvant chemotherapy based on pathological criteria (pT3-4, positive nodes), if no neoadjuvant chemotherapy is given.

Bladder-Preserving Approach

Bladder preservation consists of radiotherapy combined with platinum-based chemotherapy.

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 TURBT prior to initiation of concurrent chemoradiation if safely possible.

Consider surgical intervention (i.e. decompression) if hydronephrosis is present.

Radiotherapy should be delivered to the whole bladder and regional nodes to at least 40 Gy, followed by a bladder/tumour boost to at least 60 Gy in conventional fractionation; altered fractionation regimens, such as 50-52.5 Gy in 20 fractions, may also be considered.

In cystectomy candidates, second-look cystoscopy ± biopsy and urine cytology is recommended after 40-50 Gy to ensure complete response.

Salvage cystectomy should be performed in patients with residual disease.

Neoadjuvant / Adjuvant Chemotherapy Peri-Cystectomy

Chemotherapy is usually given as cisplatinum-based combination therapy (e.g. cisplatinum, 70 mg/m² day 1 and gemcitabine, 1000-1250 mg/m² day 1 and 8 q 21 days); patients with contraindications to cisplatinum should proceed directly to definitive therapy—routine use of carboplatinum-based neoadjuvant combinations cannot be advised.

Following neoadjuvant chemotherapy patients should have a CT scan of abdomen and pelvis, prior to the cystectomy.

The standard of care for patients who have already undergone cystectomy is to offer adjuvant chemotherapy (same as neoadjuvant chemotherapy regimen) T2 and T3 lesions or worse; if patients are ineligible for cisplatinum-based combination therapy in the adjuvant setting, carboplatinum-based combination therapy can be considered.

Chemotherapy dose and schedule for combined modality approach

For combined modality therapy, regimens include:

- cisplatinum 50 mg/m² is administered every two weeks during RT; alternatively, usually for impaired renal function, carboplatinum (AUC 1.5) weekly can be administered.
- cisplatinum 20 mg/m² days 1-4 q21 days while receiving radiotherapy or, for patients in whom cisplatinum is contraindicated, carboplatinum administered at (AUC 5) q 21 days can be considered.
- 5-fluorouracil (5-FU; 500 mg/m² per day) during fractions 1-5 and 16-20 of RT and mitomycin C (12 mg/m²) on day 1 can be considered.

In patients who are candidates for a cystectomy a second look cystoscopy is recommended after 40-45 Gy to ensure appropriate therapeutic response.
Follow-up

Surgical Approach
- Urine cytology q 3-6 months for 3 years, then at increasing intervals
- CT Abdomen and Pelvis at 6 months as clinically indicated
- CXR q 6 months for 3 years, then at increasing intervals
- Duration: as clinically indicated; if there is no evidence of recurrence, could probably stop at five years

Bladder Preservation Approach
- Cystoscopy ± biopsy and cytology q 3 months for 1 year, then at increasing intervals
- CT abdomen and pelvis q 3-6 months for 2 years, then at increasing intervals
- CXR q 6 months for 3 years, then at increasing intervals
- Duration: as clinically indicated; if there is no evidence of recurrence, could probably stop at five years

Management of Stages T3, T4 and/or N1-3 M0

Indications include lymph node metastases or locally advanced cancer found at time of cystectomy.

Staging
- CT abdomen / pelvis
- CBC, biochemical profile
- CXR

Primary Therapy
- Radical cystectomy; if at the time of radical cystectomy the patient is found to have locally advanced disease or lymph node metastases, adjuvant chemotherapy can be considered.
- If cystectomy is abandoned because of locally extensive disease, concurrent chemoradiation can be considered as in the organ preservation approach, combined with 4 cycles of adjuvant chemotherapy; the patient should be made aware that the use of adjuvant chemotherapy is controversial in this setting.
- If surgery is abandoned because of unresectable N+ or T4b, the patient should be managed as for metastatic disease.
- Patients with muscle invasive disease who have not had surgical intervention may still be candidates for a combined modality approach.
  - These patients should also be considered for neoadjuvant chemotherapy prior to definitive local management.
  - The chemotherapy choice would be the same as described in the section, Chemotherapy dose and schedule for combined modality approach, and should consist of a cisplatin-based regimen.
- Some patients may also be treated with single modality therapy, i.e. chemotherapy or radiotherapy for palliation and or survival prolongation.

Follow-up

Surgical Approach
- Cystectomy: clinical evaluation every 6, 12, and 24 months with a CXR, for 3 years
- CT scan of abdomen and pelvis at 6 months post completion of therapy
- Duration: as clinically indicated; if there is no evidence of recurrence, could stop at five years

Bladder Preservation Approach
- Cystoscopic evaluation every 3 months for the first year with a CXR every 6 months for 3 years and
then at increasing intervals
- CT scan of the abdomen and pelvis should be done at six months post completion of therapy
- Duration: as clinically indicated; if there is no evidence of recurrence, could stop at five years

**Management of Advanced Unresectable Metastatic Disease (T4b, N1-3, M1)**

Indications include the development of metastatic disease post radical therapy or presents with advanced unresectable or metastatic disease.

**Staging**
As clinically indicated:
- CT abdomen / pelvis
- CBC, renal and liver function tests
- Bone scan if clinically indicated

**Primary Therapy**
- In patients who present with *de novo* metastatic disease or for those that develop metastatic disease after a definitive local therapy, the mainstay of treatment is systemic chemotherapy.
  - Sequential cisplatinum and gemcitabine at the schedule described above, plus paclitaxel (80 mg/m² days 1 and 8), every 3 weeks.
  - Cisplatinum in combination with gemcitabine is the primary chemotherapy combination at the dose and schedule described above; an alternative to cisplatinum if clinically indicated is carboplatinum in combination with gemcitabine; patients who respond should be treated for a maximum of six cycles.
- For patients with their bladder *in situ*, radiotherapy to the bladder either as a single modality therapy or combined with a platinum can be administered for (1) palliation in patient unable to receive chemotherapy or (2) in attempt to reduce the risk of local recurrence as an adjunct to systemic chemotherapy in selected patients who wishes for aggressive treatment after discussion of lack of high level evidence in this area.
- Radiotherapy is of value in the management of symptomatic local disease and symptomatic metastases.

**Second-line**
- There is no phase III data to support recommending one agent over another.
- If patients treated with cisplatinum (carboplatinum) + gemcitabine relapse within six months, consider treating with agents not previously administered such as CMV or MVAC, depending on performance status, or single agents. If relapses are greater than six months, then the patient could be considered for re-treatment with original regimen or alternatively with CMV or MVAC.
- Paclitaxel in combination with a platinum agent could be considered as second line therapy.

**Follow-up**
- Post-chemotherapy: CT scan to evaluate tumour response and then as clinically indicated to follow the course of the disease
- If relapses are to occur, they are likely to happen early; therefore, follow closely for two years, and then as clinically indicated.
DISCUSSION

Management of Stage T2a/b

For muscle invasive bladder cancer (T2-T4a and N0, 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 adjuvant 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, T2 tumour <5 cm, no CIS, pT0 after a second TURBT, good performance status and with a proper bladder capacity and function) 18 may be better suited for bladder preservation while others (i.e. those with non-transitional cell histologies) 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 is 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; 19 Bader, et. al. reported 24% for extended; 20 Allaf, et. al. reported 3% for extended vs. 1% for limited; 21 and Dhar, et. al. reported 26% for extended vs. 13% for limited. 22 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). 22 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). 23 A retrospective comparative study looking at recurrence rates following extended (i.e., up to the mid-upper third of the common iliac vessels) or super extended (i.e., up to the inferior mesenteric artery) LN dissections in patients with clinically organ confined bladder cancer demonstrated no significant difference in 5-year recurrence-free survival for pT2pN0-2 patients (57% vs. 67%; p=.55) or pT3pN0-2 patients (32% vs. 34%; p=.44). The overall recurrence rate was equal for both procedures (38%). 24 Therefore, extended template PLND may be pivotal when considering adjuvant therapies. 25

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. A trial among stage T2-T4a 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. 26 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. 27 In the adjuvant setting, patients (n=327) with stage T3a-T4a and/or pathologic node-positive disease who had undergone radical cystectomy received either chemotherapy, either three cycles of cisplatin (70 mg/m² on day 1) and methotrexate (40 mg/m² on days 8 and 15) every three weeks or three cycles of methotrexate (30 mg/m² on days 1, 15, and 22), vinblastine (3 mg/m² on days 2, 15, and 22), epirubicin (45 mg/m² on day 2), and cisplatin (70 mg/m² on day 2) every four weeks; there were no differences in 5-year progression-free survival (46.3 vs. 48.8%), tumour-specific survival (52.0 vs.
52.3%), and overall survival (46.1 vs. 45.1%). However, grade 3/4 leukopenia was significantly lower in patients treated with cisplatin and methotrexate (7.0 vs. 22.2%; P<.0001). Other cisplatin-based regimens have been investigated. The International Collaboration of Trialists BA06 30894 trial compared three cycles of neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) with no neoadjuvant chemotherapy, followed by cystectomy and/or radiotherapy, among patients with muscle-invasive bladder cancer (n=976). After 10 years of follow-up, the overall survival rate was 36% for CMV versus 30% for control (HR 0.84; 95% CI 0.72-0.99; p=.037). 36

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 transitional cell carcinoma (TCC: T2-T3, Nx, M0; n=33) who underwent maximum TURBT followed by three cycles of adjuvant chemotherapy (e.g. methotrexate, vinblastin, 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). 37 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. 38 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). 39 Salvage cystectomy should be performed in patients with invasive residual disease or recurrence. 40,41

As an alternative to radical cystectomy, concurrent chemoradiotherapy may be considered. 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/m² during fractions 1-5 and 16-20 and mitomycin-C; 12 mg/m² 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). 42 Cisplatin or carboplatin are also acceptable for use with a combined modality approach. 43 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/m²), 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. 44 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 usually given as cisplatinum-based combination therapy (e.g. cisplatinum, 70 mg/m² day 1 and gemcitabine, 1000-1250 mg/m² day 1 and 8 q 21 days); patients with contraindications to cisplatinum should proceed directly to definitive therapy, as the routine use of
Carboplatinum-based neoadjuvant combinations is not advised. A CT scan of the abdomen and pelvis should precede cystectomy. In patients who have already undergone cystectomy, adjuvant cisplatinum-based combination chemotherapy (as above) should be offered. As most bladder cancer related deaths are due to systemic relapse, chemotherapy in either the adjuvant or neoadjuvant setting can be expected to improve overall survival and disease free survival. 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. As well, neoadjuvant chemotherapy may spare the patient unnecessary radical therapy due to the evolution of microscopic disease into overt clinical disease in the interim between diagnosis and further staging after neoadjuvant therapy. In cases where a cystectomy has already been performed, there is less rigorous evidence for adjuvant chemotherapy. 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; however, power was limited in this study so the meta-analysis was not as strong as that done on neoadjuvant therapy; therefore neoadjuvant therapy is still the preferred option, if feasible.

**Management of Stages T3, T4 and/or N1-3 M0**

In patients with lymph nodes metastases (T3-T4 and/or N1-3 / M0), primary therapy includes radical cystectomy with the option of adjuvant chemotherapy. A retrospective study among patients (n=85) with lymph node positive disease at the time of radical cystectomy showed that, among those who received adjuvant chemotherapy (versus those who did not), overall survival, disease specific survival, and recurrence free survival were each significantly improved (P=.031, P=.028, P=.004, respectively) at a median follow up of 46 months. Another retrospective study among patients with T3-T4 or lymph node positive disease (n=78) undergoing radical cystectomy showed that among those who received adjuvant chemotherapy (versus observation) 5-year recurrence free survival and mean overall survival time were better (51.1 vs. 27.6%, respectively; 31 vs. 22 months, respectively). In the event of locally extensive disease, concurrent chemoradiation can be considered as an alternative to radical cystectomy but should be combined with adjuvant chemotherapy for four cycles. Patients with muscle invasive disease who have not had surgical intervention may be candidates for a combined modality approach; however, neoadjuvant cisplatinum-based combination chemotherapy should be considered, prior to definitive local management. Some patients may also be treated with chemotherapy alone or radiotherapy alone for palliation and/or survival prolongation.

**Management of Advanced Unresectable or Metastatic Disease (T4b, N1-3, M1)**

Unresectable metastatic disease (T4b, N1-3, M1) should be treated primarily with systemic chemotherapy. Cisplatinum in combination with gemcitabine (six cycles) is the standard regimen; however, if clinically indicated, carboplatin can be substituted for cisplatin. Single agent gemcitabine can be considered for poor performance status patients who are not eligible for platinum-based chemotherapy. MVAC has also been investigated. For patients with good performance status, paclitaxel in combination with a platinum agent can be considered for second line therapy. The EORTC 30987 trial compared cisplatin/gemcitabine combination therapy with or without paclitaxel in 513 patients with locally advanced or metastatic urothelial cancer. Median overall survival was longer in the paclitaxel group (15.9 months vs. 11.9 months; HR 0.80; p=.025); however progression-free survival was not different (8.3 months vs. 7.6 months (HR 0.87; p=.113). Although both treatments were well tolerated, there was more thrombocytopenia and bleeding on cisplatin/gemcitabine regimen than the paclitaxel combination
(11.4% vs. 6.8%; p=.05) and more febrile neutropenia on the paclitaxel combination than the cisplatin/gemcitabine regimen (13.2% vs. 4.3%; p<.001).  

Radiotherapy alone or in combination with a platinum can be considered for palliation or to reduce the risk of local recurrence. In patients who fail first-line platinum-based combination chemotherapy within six months, CMV (cisplatin, methotrexate, vinblastine) or MVAC (methotrexate, vinblastine, adriamycin, and cisplatinum) can be considered. Patients with urothelial carcinoma (n=255) who were treated with combination chemotherapy (e.g. MVAC) every 28 days (versus cisplatin alone) experienced superior overall survival (6.8 vs. 1.6%; P=.00015); however, only 3.7% of patients treated with MVAC were alive and continuously disease-free at six years follow-up. A phase III randomized controlled trial (AUO AB 20/99) comparing short-term gemcitabine and paclitaxel (GP) with long-term GP in patients with metastatic disease who had failed 1st line treatment with cisplatin-based chemotherapy found no difference in median overall survival (7.8 months vs. 8.0 months, respectively) or progression-free survival (4.0 months vs. 3.1 months, respectively). However, severe grade III/IV anemia was less in the short-term group (6.7% vs. 26.7%; p=.011). Failures that occur after six months may be treated with the original regimen, CMV or MVAC, or a platinum-paclitaxel combination.

**GLOSSARY OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>AUC</td>
<td>area under the curve</td>
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<tr>
<td>BCG</td>
<td>Bacillus Calmette-Guerin</td>
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<tr>
<td>CBC</td>
<td>complete blood count</td>
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<tr>
<td>CIS</td>
<td>carcinoma in situ</td>
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<tr>
<td>CMV</td>
<td>cisplatin, methotrexate, vinblastine</td>
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<td>Cr</td>
<td>creatinine</td>
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<td>CT</td>
<td>computer tomography</td>
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<tr>
<td>CXR</td>
<td>chest x-ray</td>
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<tr>
<td>CUA</td>
<td>Canadian Urology Association</td>
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<tr>
<td>Gy</td>
<td>unit of radiation dose</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>MVAC</td>
<td>methotrexate, vinblastine, adriamycin, and cisplatinum</td>
</tr>
<tr>
<td>PLND</td>
<td>pelvic lymph node dissection</td>
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<tr>
<td>TURBT</td>
<td>transurethral resection of bladder tumour</td>
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**CONFLICT OF INTEREST**

Participation of members of the Alberta Provincial Genitourinary Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Genitourinary Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.
DISSEMINATION

• Present the guideline at the local and provincial tumour team meetings and weekly rounds.
• Post the guideline on the Alberta Health Services website.
• Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2015. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

REFERENCES


32 Galsky, MD, Scher, HI. Bladder cancer "adjuvant-lite": tastes great (works as well) and less filling (less toxic)?. J Clin Oncol 2005; 23:4823.


APPENDIX

Cancer Staging Manual (American Joint Committee on Cancer, 2010) 1

Primary Tumour (T)
Tx: primary tumour cannot be assessed
T0: No evidence of primary tumour
Ta: Non-invasive papillary carcinoma
Tis: Carcinoma in situ: “flat tumour”
T1: Tumour invades 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 tissue
  • pT3a: Microscopically
  • pT3b: Macroscopically (extra vesical mass)
T4: Tumour invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
  • T4a: Tumour invades prostatic stroma, uterus, vagina
  • T4b: 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 (hypogastric, obturator, external iliac, or presacral lymph node)
N2: Multiple regional lymph node metastases in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
N3: Lymph node metastases to the common iliac lymph nodes

Distant Metastasis (M)
M0: No distant metastasis
M1: Distant metastasis