



**Alberta Genito-Urinary Oncology Group
Clinical Guidelines: Bladder Cancer
April 2005**

Stage O/A (Ta / T₁)

Indications	Recurrent or multifocal disease.
Staging	As clinically indicated.
Induction	Primary therapy at time of TURBT: Epirubicin 100mg instillation @ TURBT. If there is a recurrence, proceed to intravesical BCG ¹ .
First line	Induction intravesical BCG at dosage prescribed in the pre-written orders that are available from ACB pharmacies. <i>Maintenance therapy if disease-free at three months</i> On-going maintenance therapy consists of three weekly treatments at months three, six, and 12. Therapy may be continued at 18, 24, 30, and 36 months, at which time a clinical decision should be made as to whether or not to proceed with maintenance. Dosage prescribed in the pre-written orders, available from ACB pharmacies.
Second line	<i>BCG failure</i> In the event of BCG failure, defined as persistent disease after two courses of BCG or intolerance, the following treatment options are available. <ul style="list-style-type: none">• Surgery• Intravesical chemotherapy:<ul style="list-style-type: none">• Single agent interferon. Induction: Interferon Alpha –2b (Intron –A). Dosage prescribed in the pre-written orders available from ACB pharmacies and is delivered intravesically, weekly for eight weeks.
Maintenance	Interferon at dosage as prescribed in the pre-written orders available from ACB pharmacies. <ul style="list-style-type: none">• Interferon combined with low dose BCG. Induction BCG with Alpha 2b interferon: Dosage prescribed in the prewritten orders that are available from the ACB pharmacies.• Maintenance BCG with Alpha 2b interferon: Dosage prescribed in the prewritten orders available from ACB pharmacies.• Mitomycin C: Mitomycin is administered intravesically at a dose of 40 mg weekly for four weeks.
F/U	Cystoscopic evaluation every three months for the first year and then at increasing intervals. Consider upper tract evaluation as clinically indicated.

Duration of F/U As clinically indicated.

Cysto and chest x-ray (CXR) q three months for first year, and then at increasing intervals.

T1 high-grade and TCIS BCG failure

In the event of BCG failure, defined as persistent disease after two courses of BCG (with or without interferon) or intolerance, the following treatment options are available.

- Surgery, if fit for cystectomy.
- Radiotherapy

Renal, pelvic & ureteric TCC

Surgical excision

F/U Cystoscopic evaluation every three months for the first year, then at increasing intervals. A CT scan every year for primary node metastases, and every two years in the evaluation of lymph nodes. Need a CXR at time of cystoscopies.

Clinical Stage T2a,b, T3a,b, T4a,b

Indications Muscle invasive bladder cancer.

Staging CT abdomen / pelvis, CBC, renal function tests, and CXR.

Management *Therapy with curative intent.*
As there are no modern-era randomized trials to support either a surgical (radical cystectomy) or an organ preservation approach over the other, either treatment can be considered. In individual patients, there may be medical reasons for offering one modality over the other. The bladder preservation approach consists of radiotherapy combined with either cisplatin or carboplatin.

Chemotherapy dose and schedule

For combined modality therapy, cisplatin 50 mg/M² is administered every two weeks during RT. Alternatively, usually for impaired renal function, carboplatin at an AUC of 1.5 weekly can be administered. Alternative regimens consist of cisplatin 20mg/m² days one through five every three weeks while receiving radiotherapy or, for patients in whom cisplatin is contraindicated, carboplatin administered at AUC=5 q 21 days can be considered.

It should be noted that bladder preservation is not preferred in patients with hydronephrosis or in patients with significant irritative symptoms. It is important to remember that prior to bladder preservation there should be a complete resection of the bladder tumor.

In selected cases (medically unfit) the bladder cancer can be managed by a TUR +/- radiotherapy for local control.

Neoadjuvant chemotherapy:

Most bladder cancer related deaths are due to systemic relapse. Administration of chemotherapy in either the adjuvant or neoadjuvant setting can be considered to reduce the risk of recurrence. Clinical trials of neoadjuvant chemotherapy followed by either radical cystectomy or radiotherapy have been performed with mixed results. Recently, a meta-analysis of neoadjuvant chemotherapy followed by either surgery or radiotherapy demonstrated a survival advantage for neoadjuvant treatment. To obtain benefit, three to four cycles of chemotherapy must be given and combination chemotherapy must be given (*i.e.* not single agent cisplatin). Patients with contraindications to cisplatin can be considered for carboplatin + gemcitabine.

Therefore, patients with muscle invasive disease who are candidates for either radical cystectomy or combined modality treatment should be considered for neoadjuvant chemotherapy prior to definitive local management.

F/U	Cystectomy: clinical evaluation at six months with a CXR for three years. CT scan of abdomen at six, 12, and 24 months.
Bladder preservation approach	Cystoscopic evaluation every three months for the first year with a CXR every six months for three years and then at increasing intervals. CT scan of abdomen/pelvis at six, 12, and 24 months.
Duration of F/U:	As clinically indicated. If there is no evidence of recurrence, could probably stop at five years.

Pathological Stage T3, T4 and/or N1-3

Indications	Lymph node metastases <i>or locally advanced cancer</i> found at time of cystectomy.
Staging	CT abdomen / pelvis, CBC, biochem profile, CXR
Management	If at the time of radical cystectomy the patient is found to have locally advanced disease or lymph node metastases, then adjuvant chemotherapy can be considered. If the cystectomy is abandoned because of locally extensive or metastatic disease, then the same therapy can be considered as in the organ preservation approach, combined with adjuvant chemotherapy for four cycles. The patient should be made aware that adjuvant chemotherapy is controversial in bladder cancer. If N+ and surgery are abandoned, 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. If this is undertaken, they should also be considered for neoadjuvant chemotherapy prior to definitive local management. Chemotherapy should consist of three to four cycles of cisplatin + gemcitabine chemotherapy. Patients with contraindications to cisplatin can be considered for carboplatin + gemcitabine.

	Some patients may also be treated with single modality therapy, <i>i.e.</i> chemotherapy or radiotherapy for palliation and or survival prolongation.
F/U	Cystectomy: clinical evaluation every six, 12, and 24 months with a CXR, for three years.
Bladder preservation approach:	Cystoscopic evaluation every three months for the first year with a chest x-ray every six months for three years and then at increasing intervals. A CT scan of the abdomen and pelvis should be done at six months post completion of chemotherapy.
Duration of F/U	As clinically indicated. If there is no evidence of recurrence, could stop at five years.

Metastatic Disease (N1-3, M1)

Indications	Development of metastatic disease post radical therapy or presents with metastatic disease. If age and clinical situation warrant, patient should be investigated and treated.
Staging	As clinically indicated: CT abdomen / pelvis, CBC, renal and liver function tests, and bone scan if clinically indicated.
Management	In patients who present with <i>de novo</i> metastatic disease or for those that develop metastatic disease after a definitive local therapy, the mainstay of treatment is systemic chemotherapy. For patients with their bladder <i>in situ</i> radiotherapy to the bladder either as a single modality therapy or combined with a platin can be administered for palliation in patient unable to receive chemotherapy or 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. Combination chemotherapy with gemcitabine + cisplatin should be offered for improvements in quality of life as well as survival. Patients with contraindications to cisplatin can be offered carboplatin + gemcitabine. Patients who respond should be treated for a maximum of six cycles. Single agent gemcitabine can be considered for poor performance status patients who are not eligible for platinum-based chemotherapy.
F/U	Evaluation post-chemotherapy with a CT scan to evaluate tumour response and then as clinically indicated to follow the course of the disease.
Duration of F/U	If relapses are to occur, they are likely to happen early; therefore, follow closely for two years, and then as clinically indicated. If patients treated with cisplatin (carboplatin) + gemcitabine relapse within six months, consider treating with agents not previously administered such as CMV or MVAC depending on performance status. 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

For muscle invasive disease, neoadjuvant treatment of three to four cycles of cisplatin + gemcitabine should be considered prior to cystectomy.

References

1. Rajala,P., Liukkonen, T., Raitanen, M., Rntala, E., Kaasinen, M., Lukkarinen,O., The Finnbladder Group(1999). Transurethral resection with perioperative instillation of Interferon or Epirubicin for the prophylaxis of recurrent primary superficial bladder cancer: A prospective randomized multicenter study- Finnbladder III. *Journal of Urology* v.161, 1133-1136.