This guideline is a statement of consensus of the GU Disease Site Team regarding their views of currently accepted approaches to treatment. It is not intended to replace the independent medical judgment of the physician in the context of individual clinical circumstances to determine any patient’s care or treatment.
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Bladder Cancer
GU Practice Guidelines

1) OVERVIEW

Bladder cancer is the 4th most common cancer among men and 13th in women. The incidence in males is about three times that in females. Incidence is highest in white populations in developed countries, most notably in Western Europe and North America. Within Canada, Nova Scotia and Quebec have the highest incidence and Ontario has the lowest.

The vast majority of bladder cancers are transitional cell carcinomas (over 90%), with about 3% each of squamous cell carcinomas and adenocarcinomas.

Risk factors for bladder carcinoma include smoking, chronic irritation and exposure to naphthylamines, benzidines, amino biphenyl and cytoxan.

Patients most commonly present with hematuria but may also experience urinary frequency, urgency, dysuria or pain and obstruction in more advanced cases.

2) INVESTIGATIONS

Appropriate investigations for bladder cancer include the following:

1. history and physical exam
2. routine blood work including CBC, urea, creatinine and electrolytes. Liver function tests, BHCG, and alkaline phosphatase ideally should be included for muscle-invasive disease.
3. urinalysis, urine cytology
4. assessment of the upper tracts with IVP, CT or retrograde pyelograms
5. cystoscopy and examination under anesthesia
6. Metastatic work up including CXR, CT scan of abdomen and pelvis and a bone scan in all patients with muscle invasive disease
3) STAGING

Table 1: American Joint Committee on Cancer (AJCC) TNM Staging System for Bladder Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Pathologic Type</th>
<th>Histopathologic Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Papillary</td>
<td>Urothelial (transitional cell) carcinoma in situ</td>
</tr>
<tr>
<td>T2</td>
<td>Flat</td>
<td>With squamous metaplasia</td>
</tr>
<tr>
<td>T3</td>
<td>With squamous metaplasia</td>
<td>With glandular metaplasia</td>
</tr>
<tr>
<td>T4</td>
<td>With squamous and glandular metaplasia</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>N0</td>
<td>Adenocarcinoma</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>N1</td>
<td>Undifferentiated carcinoma</td>
<td>The predominant cancer is undifferentiated (transitional cell) carcinoma.</td>
</tr>
<tr>
<td>N2</td>
<td></td>
<td>Histopathologic Grade (G)</td>
</tr>
<tr>
<td>N3</td>
<td></td>
<td>G1: Well differentiated</td>
</tr>
<tr>
<td>M0</td>
<td></td>
<td>G2: Moderately differentiated</td>
</tr>
<tr>
<td>M1</td>
<td></td>
<td>G3: Poorly differentiated or undifferentiated</td>
</tr>
</tbody>
</table>

**Staging**

**Primary Tumor (T)**
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ (flat tumor)
- T1: Tumor invades subepithelial connective tissue
- T2: Tumor invades muscle
- T2a: Tumor invades superficial muscle (inner half)
- T2b: Tumor invades deep muscle (outer half)
- T3: Tumor invades perivesical tissue
- T3a: Microscopically
- T3b: Microscopically (extravesical mass)
- T4: Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
  - T4a: Tumor invades prostate, uterus, vagina
  - T4b: Tumor invades pelvic wall, abdominal wall

**Regional Lymph Nodes (N)**
- N0: No regional lymph node metastases
- N1: Metastasis in a single lymph node, 2 cm or less in greatest dimension
- N2: Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension
- N3: Metastasis in a lymph node more than 5 cm in greatest dimension

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

**Clinical Staging**
Primary tumor assessment includes bimanual examination under anesthesia before and after endoscopic surgery (transurethral resection) and histologic verification of the presence or absence of tumor when indicated. Bimanual examination following endoscopic surgery is an indicator of clinical stage. The finding of bladder wall thickening, a mobile mass, or a fixed mass suggests the presence of T3a, T3b, and T4b disease, respectively. Appropriate imaging techniques for lymph node evaluation should be used. When indicated, evaluation for distant metastases includes imaging of the chest, biochemical studies, and isotopic studies to detect common metastatic sites.

**Pathologic Staging**
Microscopic examination and confirmation of extent are required. Total cystectomy and lymph node dissection generally are required for this staging. Laceration does not affect the N classification.
4) TREATMENT - Superficial bladder cancer (Tis, Ta, T1 disease)

- After total transurethral resection (TURBT) of low-grade tumour(s) confined to the basement membrane or superficial connective tissue, selected and random biopsies plus urine cytology should be performed to rule out carcinoma in-situ.
- Intravesical BCG therapy is recommended if further biopsies are positive, there are too many superficial low-grade lesions to resect endoscopically, or recheck cystoscopies reveal recurrent low-grade superficial tumours (see Appendix B).
- If carcinoma in-situ is detected the risk of progression to muscle invasive disease and subsequent metastases ranges from 40 to 80% depending on the extent of the disease therefore the standard treatment recommendation is cystectomy.
- Radiation is not recommended as carcinoma in-situ does not respond reliably to radiotherapy.
- For selected patients with high grade tumors, focal disease and functional bladders, consideration may be given to intravesical chemotherapy as an option to cystectomy (Appendix D).
- If resection is incomplete, the staging is inadequate or uncertain, there is no muscle in the specimen or there is lymphvascular invasion then consideration should be given to re-resection or cystectomy.
- Patients who have recurrence of disease either on maintenance BCG or within 6 months of the last BCG treatment should be considered for more aggressive treatment such as chemoradiation or cystectomy.
- Patients with T1G3 are at high risk of occult/incipient muscle invasive bladder cancer and should be considered for early cystectomy.
Treatment - Muscle invasive disease (T2-T3)

Radical cystectomy remains the gold standard in North America with five year survival rates of 40-80% (Appendix D).

- Neo-adjuvant chemotherapy prior to radical cystectomy has shown a 5% survival advantage in 2 recent meta-analysis
- Adjuvant Chemotherapy has less supporting data and may be used in individual cases of high risk patients (T3/T4, positive nodes)

External Beam Radiation Therapy (EBRT) may be used in selected bladder preservation protocols or for those patients unsuitable for surgery due to advanced age or concurrent medical problems (Appendix C).

- It may be used alone for local control or in combination with chemotherapy (see next section)
- Five-year survival range for EBRT alone is 20-40% in large series.

Combined Modality Treatment with chemotherapy and radiation

- Radical Concurrent Chemotherapy & EBRT after TURBT is recommended for patients who are non-surgical candidates.
- Hypofractionated Concurrent Chemotherapy and EBRT is a good option for the elderly patient who cannot tolerate radical chemo/radiation or a cystectomy.

- Tridomality therapy for bladder preservation
  - o comprises aggressive TURBT followed by induction chemoradiotherapy, cystoscopic reassessment with immediate cystectomy for those not in complete remission, and further chemoradiotherapy for those in remission.
  - o this approach is being assessed at a number of centres but is not yet recommended for routine practice
Locally advanced or metastatic (T4b/N+/M+)

There are many treatment options dependant on the patient’s age, performance status and the aggressiveness of the disease therefore each case should be considered individually.

Options include chemotherapy alone, radiation alone, combination treatment with chemotherapy and radiation or surgery or best supportive care.
5) FOLLOW-UP

Superficial bladder cancer

- Follow up cystoscopy every three months for the first three years and then annually is recommended.
- Subsequent resections, institution of intravesical chemotherapy or consideration of radical cystectomy may be indicated.
- Voided urine cytology should be assessed at the same intervals as cystoscopy. Upper tract imaging should be performed every two years.
Muscle invasive bladder cancer

- Cystoscopy every three months for the first 2 years, then every six months for three years then annually is recommended.
- Voided urine cytology should be assessed at the same intervals.
- Upper tract imaging should be considered in high risk patients.
APPENDIX A – PATHOLOGY GUIDELINES

Transurethral Resection

For TURBT specimens the pathology report should include the following information:

1. Presence or absence of tumour
2. Growth pattern, papillary or flat
3. Grade (I,II,III,) – highest grade clone determines overall tumour grade
4. Presence of and extent of subepithelial connective tissue invasion. If possible, attempt to delineate muscularis mucosa and determine if just lamina propria or submucosal stromal invasion.
5. Presence or absence of muscularis propria (sometimes impossible to distinguish between muscularis propria and hypertrophical muscularis mucosa)
6. If muscularis propria is seen, the presence or absence of invasion (depth of muscle invasion) cannot generally be reliably determined.
7. Submucosa may contain adipose tissue which may intermingle with muscularis propria, so interpretation of perivesical soft tissue extension in TUR specimens may be difficult.
8. Invasion of lymphatics, vascular or perineural spaces
9. Extension into prostate, either along ducts or as a result of prostatic stromal infiltration.

Radical Cystectomy

Radical cystectomy specimens should be marked at all excisional margins and these should be sampled generously. Obvious tumour should be sampled and random sections of apparently normal mucosa should be taken. The pathology report should include the following information:

1. Presence or absence of tumour
2. Histologic grade, I-III
3. Number, location and size of tumours
4. Depth of invasion relative to the total thickness of the wall i.e. lamina propria, submucosa and inner vs. outer muscularis-propria involvement.
5. Extravesical extension
6. Relationship to perivesical soft tissue margins and vesical serosal surface
7. Invasion of lymphatics, vascular or perineural spaces
8. Marginal extension including urethra and ureters
9. Presence of nodes, with number positive and measurement of involvement, including extranodal extension.
10. Extension into prostate (ducts vs. stromal invasion)
11. Presence of CIS remote from primary tumour.
APPENDIX B - CHEMOTHERAPY GUIDELINES

LRCP Conventions for Systemic Therapy

ADVANCED AND METASTATIC DISEASE

Chemotherapy – First Line
- Gemcitabine – Cisplatin
- Intensified MVAC Dose-intense MVAC + GCSF
- Carboplatin – Gemcitabine
- Clinical Trial

Considerations for Regime Selection:
1. goal of therapy (e.g. local control only, palliation)
2. age and performance status
3. renal function
4. marrow function
5. previous therapy
6. co-morbid illnesses
7. feasibility
8. available clinical trial

References:
1. PEBC: Use of Chemotherapy in Advanced Unresectable or Metastatic Transitional Cell Carcinoma of the Bladder or Urothelium # 3-12, 2002.

**Chemotherapy – Second Line**
- Paclitaxel – Carboplatin
- Docetaxel
- Ifosphamide

**Considerations for Regime Selection**
1. goal of therapy (symptomatic vs. not; palliative goals)
2. age performance status
3. renal function
4. previous therapy (including prior platinum regimens)
5. marrow function/reserve
6. available clinical trial

**References:**

**NEoadjuvant Chemotherapy**

**Indications for Neoadjuvant Chemotherapy**
1. Clinical stage T2 – T4a
2. No nodal or metastatic disease
3. Urothelial histology only
4. Candidate for radical cystectomy

**Regimens:**
To receive 3-4 cycles
Possible (not evaluated in RCT):
1. Gemcitabine + cisplatin/carboplatin
2. Dose-intense MVAC
Provision: Include repeat cystoscopic assessment after 2 cycles. If progression, proceed to cystectomy. If response, proceed with additional 2 cycles of chemotherapy. Book surgery.

References:
1. PEBC: Use of Neoadjuvant chemotherapy in Transitional Cell Carcinoma of the Bladder #3.2.2, 2005.

ADJUVANT CHEMOTHERAPY

Indications for Adjuvant Chemotherapy
Not standard of care for patients following radical cystectomy BUT to be considered when:
1. pathological T2b, T3, T4a
2. pathological N+ disease

Regimens:
To receive 4-6 cycles

Possible (not evaluated in RCT):
1. Gem-cisplatin
2. Dose-intense MVAC

References:
1. PEBC: Use of adjuvant Chemotherapy following Cystectomy in Patients with deep Muscle-Invasive Transitional Cell Carcinoma of the Bladder #3.2.1, 2003


APPENDIX C – RADIATION GUIDELINES

Simulation

- Maximal TURBT should be performed prior to simulation
- Patients are generally simulated in the supine position
- Patients being treated to the pelvis plus bladder should be simulated and treated with the bladder full
- Patients being treated to the bladder only should be simulated and treated with the bladder empty
- Contrast may be used at the discretion of the treating physician

Treatment

1) Radical treatment

- Target volume- bladder and regional nodes (external and internal iliac nodes) with boost to bladder and/or partial bladder plus a 2 cm margin
- Traditional borders-pelvic field
  - Lateral-2 cm to either side of the widest section of the bony pelvis
  - Inf-inferior border of obturator foramen
  - Sup-L5-S1
  - Ant-1-1.5 cm anterior to the pubic symphysis or 2 cm anterior to the bladder
  - Post-2-2.5 cm posterior to the bladder
- Traditional borders-bladder field or partial bladder
  - Sup, inf, lat, ant and post-2 cm beyond bladder or GTV
- Technique
  - Four field box preferred
  - May require unequal weighting
  - Boost may require 3 or 4 fields
- Dose
  - Pelvis should receive doses of 44-45 Gy in 1.8-2.0 Gy fractions (1.8 Gy fractions are preferred)
  - Whole bladder should receive doses of 60-63 Gy in 1.8-2.0 Gy fractions (1.8 Gy fractions are preferred)
  - If a partial bladder boost is being used, doses up to 66 Gy are recommended
- Concurrent chemotherapy
  - Low dose concurrent cisplatin or carboplatin given once weekly

2) Hypofractionated treatment

- Target volume-bladder only
- Borders
  - 2 cm margins around CTV (bladder)
• Technique
  • 3 or 4 field
• Dose
  • 3750 cGy in 15 fractions
• Concurrent chemotherapy
  • Low dose concurrent cisplatin or carboplatin given once weekly

3) Palliative treatment
• target volume is the bladder only with a 2 cm margin
• may be treated with a 2, 3 or 4 field technique depending on intent
• common doses include: 2000/5, 3000/10 or 2400/3 (given on day 0, 7 and 21)
APPENDIX D - SURGERY GUIDELINES

Risk Assessment

- Cystoscopy and transurethral resection (TUR) with bimanual examination under anesthesia should be performed to determine the size of tumor and the presence of extravesical extension or invasion into adjacent organs.
- TUR should be deep enough to include muscle in order to stage appropriately
- Biopsies, if feasible should be large enough to avoid heat artifact; alternatively “cold cup” biopsies should be performed to avoid the use of cautery

Low risk disease

- Can be treated with TUR using a resectoscope and electrocautery or a laser
- If laser is used then separate biopsies should be performed first since laser treatment does not yield specimens adequate for histology
- The bladder is irrigated with sterile water in order to minimize implantation of cells
- If patients have high risk features such as recurrent tumors, large, multifocal, poorly differentiated tumors or carcinoma in-situ is present, then BCG or intravesical chemotherapy should be used
- Patients with carcinoma-in-situ should have multiple random biopsies and well as prostate urethral biopsies where indicated.
- Patients with carcinoma in-situ should be treated with intravesical therapy preferentially.

Intravesical therapy

- BCG is administered weekly over a period of 6 weeks. It must not be given to immunocompromised individuals, after a traumatic catheterization or when there is active hematuria. In these cases treatment should be post-poned.
- Mitomycin C and interleukin-alpha are options for second-line intravesical therapy

Muscle invasive disease or intravesical therapy failures or salvage

- Radical Cystectomy and pelvic lymphadenectomy (common iliac, external iliac, hypogastric and obturator nodes) is the treatment of choice although partial cystectomy may be chosen for select patients (solitary lesion in region amenable to resection with adequate margin and no carcinoma-in-situ)
- In men, the bladder is removed along with the pelvic peritoneum, ureteric remnants, prostate and seminal vesicles
- In women, the bladder is usually removed along with the uterus, ovaries, fallopian tubes, vaginal vault and urethra
• There are two types of urinary diversions that can be performed after surgery
  o Incontinent diversion
    ▪ This is more commonly performed in older (>65 yr old) and more infirmed patients and is accomplished with a conduit derived from the distal ileum to which the ureters are anastomosed
    ▪ An ostomy is then created by attachment of the distal end of the ileum to the anterior abdominal wall
  o Continent diversion
    ▪ Orthotopic reservoirs connect neobladders (pouch of intestine) to the membranous male urethra.
      • Approximately 80% of patients can void relatively normally with good control
      • 10% of patients experience “hypercontinence” and require intermittent catheterization to evacuate the neobladder
      • The remaining 10% of patients have little or no continence
    ▪ Stomal reservoirs may be formed that require intermittent catheterization.
      • These stomal reservoirs use a pouch of intestine with a constructed “sphincter” mechanism to maintain continence.
      • they include the cecoappendicostomy, the cecoileostomy (Indiana pouch) and the ileostomy (Kock pouch)
      • the pouch is associated with a 2% mortality, 5% incidence of serious complications and 30% reoperative rate so patients must be selected with care

• If radical chemo/RT or bladder preservation is being considered then the patient should undergo a complete TUR prior to initiation of therapy and radical cystectomy would be reserved for salvage if medically fit
REFERENCES

1. NCCN clinical guidelines. www.nccn.org
2. BCCA clinical guidelines. www.bccancer.bc.ca
12. Cochrane Meta-analysis 2007: Adjuvant chemo
Authors, Contact Information

Scott Ernst, MD, FRCPC (Medical Oncologist)
Head Division of Medical Oncology
Associate Professor, University of Western Ontario
London Regional Cancer Program
London Health Sciences Centre
790 Commissioners Road East
London, Ontario, Canada N6A 4L6
Telephone: 519.685.8600 Ext. 58640

Tracy Sexton, MD, PhD. FRCPC (Radiation Oncologist)
Assistant Professor, Department of Oncology
London Regional Cancer Program
London Health Sciences Centre
790 Commissioners Road East
London, Ontario, Canada N6A 4L6
Telephone: 519.685.8600 Ext. 58650

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