Urothelial Carcinoma of Bladder and Upper Tract

Note: Consider Clinical Trials as treatment options for eligible patients.

CLINICAL PRESENTATION
- Hematuria
- Recurrent unexplained urinary tract infection
- Other unexplained lower urinary tract symptoms

INITIAL DIAGNOSIS
- History and Physical
- Office cystoscopy
- Imaging: CT urogram or intravenous urogram (IVU)

INITIAL SCREEN STAGING
- Transurethral resection (TUR)
- Exam under anesthesia (EUA)
- Consider single dose perioperative chemotherapy instillation

Positive for upper tract tumor
- See Page 5

Positive for bladder cancer
- See Page 2

Negative for bladder cancer
- Treat as indicated

Less than T2
- See Page 3

T2-4 (Muscle Invasion)
- See Page 2

1Consider urinary cytology or other urinary markers https://www.mdanderson.org/content/dam/mdanderson/documents/for-physicians/algorithms/clinical-management/clin-management-biomarkers-web-algorithm.pdf

2If persistent microhematuria recommend repeat of History and Physical, office cystoscopy, imaging (CT Urogram or IVU) in 2-3 years

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Urothelial Carcinoma of Bladder and Upper Tract

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TREATMENT AND FOLLOW-UP

STAGE

Ta-Unifocal (low-grade solitary tumor)
- Transurethral resection (TUR) and surveillance cystoscopy\(^1\) at 3 months and if clear, then 9 months later (at 12 months after initial) and then annually
- Recurrence?
  - Yes
    - BCG (weekly for 6 weeks) with or without maintenance or
    - Intravesical chemotherapy with maintenance for 1 year
    - Observation (in selected cases)
    - Clinical trial
    - Repeat cystoscopy to assess response (with or without biopsy if indicated) at 3 months
    - Residual disease?
      - Yes
        - Ta: Follow Ta - Multifocal path
        - Tis, T1-3: Follow appropriate path
      - No
        - Continue surveillance cystoscopy\(^1\) (every 3 months for 2 years; every 6 months for 2 years; then annually)
  - No

Ta-Multifocal (low-grade)
- BCG (weekly for 6 weeks) with or without maintenance or
- Intravesical chemotherapy with maintenance for 1 year
- Observation (in selected cases)
- Clinical trial
- Consider repeating resection in 4-6 weeks, especially with T1
- Cystoscopy.
- Consider repeat biopsy to assess response at 3 months (if positive cystoscopy or no initial TUR)
- Residual disease?
  - Yes
    - Radical cystectomy or
    - Clinical trial
  - No
    - See Surveillance on Page 6

High-grade Ta or T1 Unifocal
- Muscle in pathology specimen?
  - Yes
    - Consider early cystectomy
  - No
    - Cystoscopy.
    - Consider repeat biopsy to assess response at 3 months (if positive cystoscopy or no initial TUR)
    - Residual disease?
      - Yes
        - Radical cystectomy or
        - Clinical trial
      - No
        - See Surveillance on Page 6

High risk T1\(^2\)
- Carcinoma In-Situ
  - BCG (weekly for 6 weeks) plus maintenance for 3 years
  - Cystoscopy\(^1\) at 3 and 6 months
  - Persistent carcinoma in-situ at 6 months?
    - Yes
      - Radical cystectomy or
      - Clinical trial or
      - Salvage intravesical therapy
    - No
      - Continue BCG as per SWOG protocol
      - Continue surveillance cystoscopy\(^1\) (every 3 months for 2 years; every 6 months for 2 years; then annually)

1Cystoscopy combined with either cytology or FISH (fluorescence in situ hybridization) cytology as indicated. In selected patients, fluorescent cystoscopy should be considered. T1 multifocal, variant histology with concurrent carcinoma in situ (CIS), lymphovascular invasion (LVI), and/or resectable tumor 3 cm or greater with poor prognosticator or too large to resect completely.

BCG = Bacillus Calmette-Guerin therapy

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Approved by The Executive Committee of the Medical Staff on 04/25/2017
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**TREATMENT AND FOLLOW-UP**

- **Neoadjuvant chemotherapy**
- **Clinical trial**
- **Assess response by cystoscopy/EUA/imaging, as indicated**
- **Resectable?**
  - Yes → **Radical cystectomy**
  - No → **Salvage therapy**

- **Presence of poor risk factors?**
  - Yes → **Cystectomy**
  - No → **Upstaged at surgery?**
    - Yes → **Consider metastatic chemotherapy or ifosfamide-based chemotherapy**
    - No → **Observation**

- **Patient accepts surgery?**
  - Yes → **Bladder sparing treatment**
    - Chemoradiation or Clinical Trial
  - No → **Resectable?**
    - Yes → **Radical cystectomy**
    - No → **Additional chemotherapy**

---

1. Presence of poor risk factors:
   - Lymphovascular invasion
   - Inability to assess depth of invasion
   - Variant histology such as small cell
   - Hydronephrosis
   - Tumor involving bladder diverticulum

2. Consider neoadjuvant/adjuvant cisplatin or ifosfamide-based systemic chemotherapy (i.e., DDMVAC, IAG, etc.). Refer to chemotherapy principles on Page 7
**Urothelial Carcinoma of Bladder and Upper Tract**

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### CLINICAL PRESENTATION

1. **Positive pelvic nodes or Nodes below aortic bifurcation**
2. **Nodes above aortic bifurcation or Visceral metastasis**

**Any T, N+, M+**

1. **CT chest, abdomen, and pelvis**
2. **Bone scan**

**Chemotherapy**
- Consider metastatic clinical trial if available

**Assess response:**
- **CT chest, abdomen, and pelvis**
- **Bone scan**
- **Cystoscopy**
- **EUA**
- **Imaging**

**CT chest, abdomen, and pelvis**

**Bone scan**

**Systemic chemotherapy on clinical trial or chemotherapy**

- **Frontline** based on creatinine clearance:
  - Greater than or equal to 50 mL/min: full dose cisplatin or ifosfamide-based combinations. (i.e., DDMVAC, GC, IAG, ITP, IV, GTP)
  - Greater than or equal to 40 mL/min and less than 50 mL/min: modified cisplatin-combinations including split-dose scheduling (i.e., CGI, TMP)
  - Less than 40 mL/min: nephron-sparing combinations (i.e., GTA, GCtx, GVInorelbine)
  - Second-line: atezolizumab

**Response at 6 weeks greater than 30%?**

- **Yes** Continue same chemotherapy for additional 6 weeks

**Response greater than 90%?**

- **Yes** Two additional cycles of same chemotherapy regimen

- **No** Re-stage

**Response at 6 weeks greater than 90%?**

- **Yes** Two additional cycles of same chemotherapy regimen

- **No** Re-stage

**Response at 6 weeks greater than 90%?**

- **Yes** Two additional cycles of same chemotherapy regimen

- **No** Re-stage

- **Yes** Consider surgical consolidation or Observation or Clinical trial to delay progression

- **No** Select alternate regimen from chemotherapy in Box A. If no response after 2 or more different regimens, consider palliative care or Phase I clinical trials.

**Patients are generally considered surgically resectable if no tumor present in the bladder and near complete response in lymph nodes. If tumor still present on cystoscopy or on biopsy of nodes consider additional chemotherapy prior to considering surgical consolidation.**

**See Appendix A for Standard Chemotherapy Regimens**

DDMVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin

GC = gemcitabine and cisplatin

IAG = ifosfamide, doxorubicin, and gemcitabine

ITP = ifosfamide, paclitaxel, cisplatin

IV = ifosfamide and vinblastine

GTP = gemcitabine, paclitaxel, and cisplatin

CGI = cisplatin, gemcitabine, and ifosfamide

TMP = paclitaxel, methotrexate, and cisplatin

GTA = gemcitabine, paclitaxel, and doxorubicin

GCtx = gemcitabine and cyclophosphamide

GVInorelbine = gemcitabine and vinorelbine

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Urothelial Carcinoma of Bladder and Upper Tract

**Note:** Consider Clinical Trials as treatment options for eligible patients.

**CLINICAL PRESENTATION**

- Upper tract (renal pelvis or ureter) tumor
- CT urogram
- Cystoscopy
- Ureteroscopy
- Biopsy (forcep or brush) strongly recommended
- Washing adequate only if positive for high grade
- Low grade or stage

**TREATMENT AND FOLLOW-UP**

- Patient suitable for conservative management
  - Yes
  - Holmium laser ablation; Consider adjuvant instillation of BCG (2-3 weeks later) or intraluminal chemotherapy
  - No

- Surgical removal
  - Nephroureterectomy with bladder cuff
  - Occasionally may consider segmental resection
  - Regional node dissection (if high grade or stage)
  - Greater than or equal to pT2, N+, or selected G3 regardless of stage?
  - Yes
  - Considier adjuvant chemotherapy
  - No
  - Observation

- High grade or stage, sessile architecture, or a measurable mass on CT
- Neoadjuvant chemotherapy
  - Yes
  - Clinical trial
  - No

- Metastatic disease
  - See Box A on Page 4

---

1 Conservative management is based on individual patient status and clinical findings.

2 Consider neoadjuvant/adjuvant cisplatin or ifosfamide-based systemic chemotherapy (i.e.: DDMVAC, IAG, etc.) Refer to chemotherapy principles on Page 7)
### SURVEILLANCE AFTER RADICAL CYSTECTOMY

<table>
<thead>
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<th>Months</th>
<th>3</th>
<th>6</th>
<th>12</th>
<th>18</th>
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<th>48</th>
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<tr>
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<tr>
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1. After 5 years, follow guidelines every 1-2 years at the discretion of the treating physician.
2. Patients with adverse pathologic features, e.g. micropapillary disease, presence of lymphovascular invasion (LVI), sarcomatoid de-differentiation, or those who have been downstaged after neoadjuvant chemotherapy, may be followed as pT2 patients.
3. History should include urethral discharge/bloody mucus.
4. Laboratory tests include CBC, electrolytes, BUN, creatinine, and LFTs. Cytology is optional if imaging is routinely obtained.
5. As clinically indicated.

Note: For all patients with urinary diversion, imaging study 6-8 weeks after surgery to confirm patency of anastomosis is at treating surgeon’s discretion. Choices include: loopogram (or cystogram), IVU, renal ultrasound.
BLADDER CANCER TREATMENT PRINCIPLES

PRINCIPLES OF RADIATION THERAPY MANAGEMENT

OF INVASIVE DISEASE

- External beam radiation is rarely appropriate for patients with superficial tumors or carcinoma in situ (CIS). Surgery remains the standard of care.
- Precede radiation by maximal transurethral resection (TUR) of the tumor when safely possible.
- Combining concurrent chemotherapy with radiation is encouraged for added tumor cytotoxicity.
- Simulate and treat patients with the bladder empty.
- Use multiple fields from high-energy linear accelerator beams.
- Treat the whole bladder with 40-55 Gy and then boost bladder tumor to a total dose of 64-66 Gy excluding, if possible, normal areas of bladder from the high-dose volume.

PRINCIPLES OF CHEMOTHERAPY MANAGEMENT

Active agents:
- Two-to-three drug combinations based on cisplatin, docetaxel, paclitaxel, ifosfamide, gemcitabine or MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) are used for treatment of metastatic disease.
- Adjuvant or neoadjuvant therapy is also considered for patients at high risk of recurrence.
- Patients at increased risk for morbidity from more toxic regimens (e.g., MVAC) may be treated with combinations of lower toxicity profiles.
- Immunotherapy with atezolizumab has been approved for patients failing first-line chemotherapy.

TRANSURETHRAL RESECTION OF BLADDER TUMOR (TURBT)

- The first step in surgical management of bladder tumors is a complete TUR of the tumor. Muscle must be present in the TUR specimen to appropriately stage the tumor; if no muscle is present in the specimen, re-resection/biopsy of tumor base should be discussed with patient.
- Repeat TUR at 4-6 weeks is to be strongly considered if incomplete initial resection, no muscle in specimen, or T1 stage. It must also be considered if first TURBT does not allow adequate staging or attribution of risk factor for treatment selection or when using bladder-preserving treatment by chemotherapy and/or radiation therapy.
- In cases of positive cytology with no evidence of tumor, patient should undergo multiple biopsies of the bladder mucosa (if visibly abnormal with or without use of fluorescent cystoscopy) as well as prostate urethral biopsies and evaluation of upper tracts.

RADICAL CYSTECTOMY

- Radical cystectomy should include bilateral pelvic node resection with goal of at least 10 nodes removed.
- Nerve sparing and type of diversion selected depends on many factors, several of which are patient specific.

PRINCIPLES OF INTRAVESICAL TREATMENT

- Immunotherapy
  - Bacillus Calmette-Guerin (BCG) immunotherapy is the most effective treatment for non muscle invasive bladder cancer.
  - It is ideal to wait 14-21 days after TURBT (no gross hematuria).
  - BCG induction (6 weekly treatments) should be followed by maintenance therapy (weekly for 3 weeks at months 3 and 6, and then every 6 months for a total of 3 years).
  - Dose reduction of BCG is preferable to shorter duration of maintenance.
  - If patient fails 2 courses of BCG, strongly consider radical cystectomy (or clinical trial).
- Chemotherapy
  - Peri-operative intravesical chemotherapy is most effective when given right after TUR (ideally within 6 hours).
  - Induction and maintenance chemotherapy in selected patients if indicated.
  - Agents include gemcitabine and mitomycin.
APPENDIX A: Standard Chemotherapy Regimens

Dose-dense MVAC (DDMVAC):
- Methotrexate 30 mg/m² IV and
- Vinblastine 3 mg/m² IV and
- Doxorubicin 30 mg/m² IV and
- Cisplatin 70 mg/m² IV.
  Cisplatin followed with D5 1/4 NS IV plus mannitol 40 g/L with appropriate potassium and magnesium, typically for 3 liters.
  This regimen is given every 2 weeks with growth factor support.

Gemcitabine, cisplatin (GC):
- Gemcitabine 900 mg/m² IV over 90 minutes on Day 1 and Day 8 and
- Cisplatin 70 mg/m² IV on Day 1.
  Cisplatin followed with D5-1/4 NS IV plus mannitol 40 g/L with appropriate potassium and magnesium, typically for 3 liters.
  This regimen is repeated every 3 weeks with growth factor support as needed.

Atezolizumab 1,200 mg IV every 3 weeks.
SUGGESTED READINGS

NON-MUSCLE INVASIVE BLADDER CANCER


MUSCLE INVASIVE BLADDER CANCER


Suggested readings continued on next page
SUGGESTED READINGS – continued from previous page

MUSCLE INVASIVE BLADDER CANCER - continued


CHEMOTHERAPY


RARE BLADDER TUMORS

SMALL CELL

PLASMACYTOID

MICROPAPILLARY

UPPER TRACT

URACHAL

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DEVELOPMENT CREDITS

This practice algorithm is based on majority expert opinion of the Genitourinary Center Faculty at the University of Texas MD Anderson Cancer Center. It was developed using a multidisciplinary approach that included input from the following medical, radiation, and urologic oncologists:

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