Urothelial Carcinoma of Bladder and Upper Tract

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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)

- Positive for upper tract tumor
- Positive for bladder cancer
- Negative for bladder cancer

Treat as indicated

INITIAL SCREEN STAGING

• Transurethral resection (TUR)
• Exam under anesthesia (EUA)
• Consider single dose peri-operative chemotherapy instillation

Less than T2

See Page 2

T2-4 (Muscle Invasion)

See Page 3

See Page 5

1 Consider 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

2 If persistent microhematuria recommend repeat of History and Physical, office cystoscopy, imaging (CT Urogram or IVU) in 2-3 years
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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
    - Ta: Follow Ta - Multifocal path
    - Tis, T1-3: Follow appropriate path
  - No
    - 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
        - Radical cystectomy or
        - Clinical trial
        - See Surveillance on Page 6
      - 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
            - See Surveillance on Page 6
          - No
            - BCG (weekly for 6 weeks) plus maintenance for 3 years
            - Patient refuses
            - Consider early cystectomy
            - See Page 3

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
- T1 - re-biopsy to exclude T2
- Ta, HG - consider re-biopsy
- Persistent carcinoma in situ at 6 months?
  - Yes
    - Radical cystectomy or
    - Clinical trial
    - Salvage intravesical therapy
    - See Surveillance on Page 6
  - 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)

High-grade Ta or T1 Unifocal
- Muscle in pathology specimen?
  - Yes
    - Muscle in pathology specimen?
  - No

High risk T1\(^2\)
- Carinoma 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
      - Salvage intravesical therapy
      - See Surveillance on Page 6
    - No
      - 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
      - T1 - re-biopsy to exclude T2
      - Ta, HG - consider re-biopsy
      - Persistent carcinoma in situ at 6 months?
        - Yes
          - Radical cystectomy or
          - Clinical trial
          - Salvage intravesical therapy
          - See Surveillance on Page 6
        - 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)

\(^1\)Cystoscopy 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

\(^2\)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.
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TREATMENT AND FOLLOW-UP

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., DDMVC, IAG, etc.). Refer to chemotherapy principles on Page 7)

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Page 3 of 12
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
3. Any T, N+, M+

CHEMOTHERAPY

- Consider metastatic clinical trial if available
- CT chest, abdomen, and pelvis
- Bone scan
- Cystoscopy
- EUA
- Imaging

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

CT = computed tomography
EUA = endoscopic ultrasound for American college of surgery

RESPONSE:

1. Response at 6 weeks greater than 30%?
   - Yes: Continue same chemotherapy for additional 6 weeks
   - No: Re-stage

2. Re-stage
   - Response greater than 90%?
     - Yes: Two additional cycles of same chemotherapy regimen
     - No: Second regimen?
       - Yes: Consider surgical consolidation or Observation or Clinical trial to delay progression
       - No: Select alternate regimen from chemotherapy in Box A.

RESPONSIBLE 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
GTA = gemcitabine, paclitaxel, and doxorubicin
GCTx = gemcitabine and cyclophosphamide
GVinorelbine = gemcitabine and vinorelbine
GTP = gemcitabine, paclitaxel, and cisplatin
CGI = cisplatin, gemcitabine, and ifosfamide
TMP = paclitaxel, methotrexate, and cisplatin

MD Anderson’s specific patient population, MD Anderson’s services and structure, and MD Anderson’s clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. This algorithm should not be used to treat pregnant women.

1. 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.

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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
- High grade or stage, sessile architecture, or a measurable mass on CT
- Metastatic disease

TREATMENT AND FOLLOW-UP

- Patient suitable for conservative management
- Surgical removal
  - Nephroureterectomy with bladder cuff
  - Occasionally may consider segmental resection
  - Regional node dissection (if high grade or stage)
- Neoadjuvant chemotherapy
- Clinical trial

- Holmium laser ablation;
- Consider adjuvant instillation of BCG (2-3 weeks later) or intraluminal chemotherapy
- Greater than or equal to pT2, N+, or selected G3 regardless of stage?

- Yes
  - Consider adjuvant chemotherapy
- No
  - Observation

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

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Department of Clinical Effectiveness V8
Approved by The Executive Committee of the Medical Staff on 04/25/2017
## SURVEILLANCE AFTER RADICAL CYSTECTOMY

<table>
<thead>
<tr>
<th>Less than or equal to pT1 (no variant histology)²</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>History / PE / Laboratory⁴</td>
<td>x</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>x</td>
</tr>
<tr>
<td>CT Urogram</td>
<td>x</td>
</tr>
<tr>
<td>CT abdomen and pelvis</td>
<td>x²</td>
</tr>
</tbody>
</table>

| pT2 NO: |
|-----------------------------------------------|--------|
| History / PE / Laboratory⁴ | x | x | x | x | x | x | x | x | x |
| Chest X-ray | x | x | x | x | x | x | x | x | x |
| CT Urogram | x | x | x | x | x | x | x | x | x |
| CT abdomen and pelvis | x | x |

| pT3/T4 or pTxN+: |
|-----------------------------------------------|--------|
| History / PE / Laboratory⁴ | x | x | x | x | x | x | x | x | x |
| Chest X-ray | x | x | x | x | x | x | x | x | x |
| CT Urogram | x | x | x | x | x | x | x | x | x |
| CT abdomen and pelvis | x | x | x | x | x |

¹After 5 years, follow guidelines every 1-2 years at the discretion of the treating physician.
²Patients with adverse pathologic features, e.g. micropapillary disease, presence of lymphovascular invasion (LVI), sacromatoid de-differentiation, or those who have been downstaged after neoadjuvant chemotherapy, may be followed as pT2 patients.
³History should include urethral discharge/bloody mucus.
⁴Laboratory tests include CBC, electrolytes, BUN, creatinine, and LFTs. Cytology is optional if imaging is routinely obtained.
⁵As 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. These patients are characterized by more than one of the following:
  - Comorbid conditions
  - Poor performance status
  - Liver or bone metastases
  - High alkaline phosphatase
  - High LDH
  - Poor renal function
- Immunotherapy with atezolizumab has been approved for patients failing frontline chemotherapy.

TRANURETHRAL 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, 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.

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APPENDIX A: Standard Chemotherapy Regimens

**Dose-dense MVAC (DDMVAC):**
- Methotrexate 30 mg/m² IV
- Vinblastine 3 mg/m² IV
- Doxorubicin 30 mg/m² IV
- 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
- 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
Urothelial Carcinoma of Bladder and Upper Tract

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SUGGESTED READINGS – continued from previous page

MUSCLE INVASIVE BLADDER CANCER- continued


CHEMOTHERAPY


Suggested readings continued on next page
RARE BLADDER TUMORS

SMALL CELL

PŁASMACYTOID

MICROPAPILLARY

UPPER TRACT

URACHAL

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Urothelial Carcinoma of Bladder and Upper Tract

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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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