Oncology Clinical Pathways
Bladder Cancer

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Bladder Cancer – Clinical Presentation and Evaluation

Primary Evaluation

- CT urogram
- Cystoscopy
- Tobacco use and exposure history
- Order cytology
- Family history

Secondary Evaluation

Muscle invasive disease?

- No
  - Follow appropriate NMIBC Risk pathway
- Yes
  - Follow appropriate Muscle Invasive pathway

Clinical trial(s) always considered on pathway.

- In patients unable to receive IV contrast, order alternative upper tract imaging.
- Exposure Agent Orange, burn pits, and other occupational/environmental toxins.
- Cytology order if results would change clinical management
- Family History family or personal malignancy history, suspicion for Lynch syndrome; age under 60 years
- TURBT Transurethral Resection of Bladder Tumor (TURBT) with Exam Under Anesthesia (EUA) and blue-light cystoscopy if clinically appropriate
- Intravesical gemcitabine for known or presumed low grade
Bladder Cancer – Non-Muscle Invasive Surgical Evaluation

Non-Muscle Invasive Surgical Evaluation

Visually complete resection?

Yes

T1 disease?

No

Follow appropriate NMIBC Risk Group pathway

Yes

Follow appropriate MIBC pathway

No

Follow NMIBC Risk Group pathway

Repeat TURBT

Muscle invasive disease?

No

Yes

Repeat TURBT

American Urological Association Non-Muscle Invasive Risk Stratification

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Papillary urothelial neoplasm of low malignant potential Or • Low grade urothelial carcinoma ▪ Ta and ▪ ≤3 cm and ▪ Solitary</td>
<td>• Low grade urothelial carcinoma ▪ T1 or ▪ &gt;3 cm or ▪ Multifocal or ▪ Recurrence within 1 year Or • High grade urothelial carcinoma ▪ Ta and ▪ &lt;3 cm and ▪ Solitary</td>
<td>• High grade urothelial carcinoma ▪ CIS or ▪ T1 or ▪ &gt;3 cm or ▪ Multifocal Or • Very high risk features (any) ▪ BCG unresponsive ▪ Variant histologies ▪ Lymphovascular invasion ▪ Prostatic urethral involvement</td>
</tr>
</tbody>
</table>

*Variant histologies includes micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid, squamous or glandular predominant.

TURBT Transurethral Resection of Bladder Tumor
Bladder Cancer – Non-Muscle Invasive Low Risk

Clinical trial(s) always considered on pathway.

TURBT Transurethral Resection of Bladder Tumor
Bladder Cancer – Non-Muscle Invasive Intermediate Risk

**Non-Muscle Invasive Intermediate Risk**

- **Intravesical therapy**
- **Cystoscopy 3 mo post TURBT**
- **Recurrence?**
  - **Yes** → Follow NMIBC Surgical Evaluation pathway
  - **No** → Cystoscopy in 3-6 mo

**Clinical trial(s) always considered on pathway.**

**Intravesical therapy** BCG weekly instillations for 6 weeks preferred for high grade disease; if low grade or not available, gemcitabine once a week for six weeks within 3-4 weeks of TURBT; BCG or gemcitabine maintenance should be continued for one year.

**TURBT** Transurethral Resection of Bladder Tumor

**Follow NMIBC Surgical Evaluation pathway**

**Cystoscopy post TURBT:**
- Year 1: at 3, 6, and 12 mo
- Year 2: every 6 mo
- Years 3-4: every 12 mo
- Years ≥5: annually
Bladder Cancer – Non-Muscle Invasive High Risk

Non-Muscle Invasive High Risk

BCG naïve ?

Yes

No very high risk features ?

No

Patient received adequate BCG ?

Yes

BCG induction for 6 weeks ?

Cystoscopy & cytology 3 mo post TURBT ?

Recurrence tumor?

Yes

Follow stage appropriate pathway

No

Patient preference after shared decision making

Radical Cystectomy

Maintenance BCG with cystoscopy and cytology post TURBT ?

Recurrent tumor?

Yes

No

Patient preference after shared decision making

Radical Cystectomy

Salvage Intravesical therapy

Pembrolizumab

Clinical trial(s) always considered on pathway.

*BCG naïve BCG non-exposed or greater than one year since last BCG

**Very high risk features include BCG unresponsive, variant histologies, lymphovascular invasion, or prostatic urethral invasion

*B C G Induction only one repeat induction BCG course

*Cystoscopy and Cytology Post TURBT surveillance schedule: years 1-2: every 3 months; years 3-4: every 6 months; years >5: annually

*BCG maintenance 3 week instillations at 3, 6, 12, 18, 24, 30, and 36 months (3 years) after start of induction BCG

*Adequate BCG >5 induction doses and ≥2 maintenance doses

*BCG unresponsive Persistent high-grade disease or recurrence within 6 months of receiving at least 2 courses of intravesical BCG (at least 5 of 6 induction and at least 2 of 3 maintenance doses of BCG)

*Salvage Intravesical therapy gemcitabine and docetaxel preferred

*Pembrolizumab indicated for treatment of patients with BCG-unresponsive, high-risk NMIBC with Tis tumors who are ineligible for or have elected not to undergo cystectomy

TURBT Transurethral Resection of Bladder Tumor
Bladder Cancer – Non-Muscle Invasive Positive Urine Cytology

Non-Muscle Invasive Positive Urine Cytology →
- Repeat cytology within 3 mo a
- Selective upper tract cytology, transurethral biopsy of prostate, and cystoscopy with bladder biopsies b

Carcinoma identified?
- Yes
  - Bladder
  - Prostate
  - Upper Tract
    - Follow appropriate MIBC or NMIBC Risk pathway
    - Follow Urothelial Carcinoma of Prostatic Urethra pathway
    - Follow Upper GU Tract Carcinoma pathway
- No
  - Follow appropriate NMIBC Risk pathway

Clinical trial(s) always considered on pathway.

a Cytology Review clinical history with cytopathologist
b Cystoscopy Use enhanced technology if available
**Bladder Cancer – Urothelial Carcinoma of Prostatic Urethra**

Clinical trial(s) always considered on pathway.

- **Urothelial Carcinoma of Prostatic Urethra**: solely isolated prostatic urethra involvement
  - Ta, Tis, T1 based on TUR, confirm subepithelial involvement

- **Cystoscopy and Cytology Post TURBT**: 6 months; surveillance schedule: years 1-2: every 3 months; years 3-4: every 6 months; years ≥5: annually

- **If cisplatin eligible**, prescribe gemcitabine and cisplatin followed by avelumab maintenance therapy; **if cisplatin ineligible**, prescribe gemcitabine and carboplatin followed by avelumab maintenance therapy

- **If only prior pelvic metastatic disease**, reimage with PET to ensure no metastatic disease prior to proceeding with surgery

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**Staging confirmation?**

- Mucosal (Ta, Tis, T1) followed by BCG
  - CT chest/abdomen/pelvis → Metastatic?
    - Yes → Systemic therapy
    - No → Cystoprostatectomy and urethrectomy

- Ductal + acini (Ta, Tis, T1)
  - CT chest/abdomen/pelvis → Metastatic?
    - Yes → Systemic therapy
    - No → Cystoprostatectomy and urethrectomy

- Stromal Invasion (T2)
  - CT chest/abdomen/pelvis → Metastatic?
    - Yes → Systemic therapy
    - No → Cystoprostatectomy and urethrectomy

**Follow NMIBC High Risk pathway**: if only prior pelvic metastatic disease, reimage with PET to ensure no metastatic disease prior to proceeding with surgery.
Bladder Cancer – Upper GU Tract Carcinoma

CT urogram
Cytology
Cystoscopy and ureteroscopy with selective washing + single-dose intravesical gemcitabine
Family history *

Location?
Renal pelvis, upper ureter, or mid ureter
Low volume and low grade?

Yes
Endoscopic resection
Residual disease?
Yes
Mitomycin gel instillation
Surveillance ureteroscopy
No
Surveillance ureteroscopy

No
Nephroureterectomy with single-dose intravesical gemcitabine
Grade/stage from nephroureterectomy?
Low grade
Follow NMIBC
High Risk pathway
High grade
Follow NMIBC
High Risk pathway
Stage ≥T2 or N+
Adjuvant platinum and gemcitabine

No
Distal ureter
Low volume and low grade?

Yes
Endoscopic resection
Residual disease?
Yes
Mitomycin gel instillation
Surveillance ureteroscopy
No
Surveillance ureteroscopy

No
Nephroureterectomy or distal ureterectomy with reimplantation and single-dose intravesical gemcitabine

No

Stage ≥T2 or N+
Adjuvant platinum and gemcitabine

Clinical trial(s) always considered on pathway.

*Family History family or personal malignancy history, suspicion for Lynch syndrome; age under 60 years
* Consider neoadjuvant gemcitabine and cisplatin for select high grade patients; consider Tumor Board discussion
* For high grade include regional lymphadenectomy
* Adjuvant therapy cisplatin if renal function allows; carboplatin if not a cisplatin candidate
Bladder Cancer – Muscle Invasive Stage II, IIIA, IIIB
Predominantly Urothelial Carcinoma

<table>
<thead>
<tr>
<th>Muscle Invasive Stage II, IIIA, IIIB Predominantly Urothelial Carcinoma</th>
<th>Chest, abdominal, and pelvic imaging</th>
<th>Multidisciplinary discussion and/or tumor board</th>
<th>Candidate for cystectomy?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Systemic chemotherapy candidate?</td>
<td>Yes</td>
<td>Patient prefers bladder preservation and is candidate?</td>
</tr>
<tr>
<td>No</td>
<td>Cystectomy alone</td>
<td>No</td>
<td>Bladder preservation with concurrent 5FU and mitomycin and radiotherapy</td>
</tr>
<tr>
<td>Yes</td>
<td>Bladder preservation with concurrent 5FU and mitomycin and radiotherapy</td>
<td>Yes</td>
<td>Neoadjuvant (4 cycles) gemcitabine and cisplatin and radical cystectomy</td>
</tr>
<tr>
<td>No</td>
<td>Radiotherapy</td>
<td>No</td>
<td>Adjuvant nivolumab</td>
</tr>
</tbody>
</table>

*Imaging perform bone scan if clinically indicated
*Patients with clinical node positive disease should have resolution of adenopathy post chemo to become eligible for cystectomy
*Candidate Avoid bladder preservation in patients with hydronephrosis and extensive or multifocal carcinoma in situ
*Consider Platinum-based chemotherapy (4 cycles) if not given as neoadjuvant
*Adjuvant nivolumab for patients at high risk for recurrent MIBC following radical cystectomy with negative margins regardless of PD-L1 status

Clinical trial(s) always considered on pathway.

If predominantly squamous cell carcinoma or adenocarcinoma, consider cystectomy or radiation as no proven role for adjuvant/neoadjuvant chemotherapy for pure squamous cell carcinoma of bladder; if predominantly small cell, follow appropriate SCLC Pathway
Bladder Cancer – Muscle Invasive Stage IVA
Predominately Urothelial Carcinoma

Muscle Invasive Stage IVA Predominately Urothelial Carcinoma

- Chest, abdominal, and pelvic imaging
- Comprehensive genetic profiling on tissue with PD-L1 through NPOP

Multidisciplinary discussion

Patient preference after shared decision making

Chemotherapy alone (gemcitabine and cisplatin)

Concurrent 5FU and mitomycin and radiation

Palliative radiation alone

Reassess with EUA, cystoscopy, and CT chest/abdomen/pelvis, every 2-3 cycles

Reassess tumor 2-3 months post treatment

Follow up as clinically indicated

Tumor present?

Yes

Consolidation systemic therapy or chemoradiotherapy

Follow appropriate Post Follow Up pathway

No

Systemic therapy or chemoradiotherapy

Clinical trial(s) always considered on pathway.

* If predominantly squamous cell carcinoma or adenocarcinoma, consider cystectomy or radiation as no proven role for adjuvant/neoadjuvant chemotherapy for pure squamous cell carcinoma of bladder; if predominantly small cell, follow appropriate SCLC Pathway

* Imaging perform bone scan if clinically indicated

* If patient not a cisplatin candidate, recommend carboplatin

* If no previous radiation therapy and/or cystectomy EUA Exam Under Anesthesia

NPOP National Precision Oncology Program
Bladder Cancer – Stage IVB Metastatic

Stage IVB Metastatic

- Chest, abdominal, and pelvic imaging *
- Comprehensive genetic profiling on tissue with PD-L1 through NPOP
- Patient preference after shared decision making

Criteria for Use

**Erdafitinib:** exclude patients with retinal/corneal abnormality at baseline or serum phosphate greater than upper limits of normal at baseline; perform ophthalmological exams at baseline and then monthly for the first 4 months of therapy, then every 3 months thereafter.

**Enfortumab Vedotin:** exclude patients with preexisting neuropathy ≥ Grade 2, baseline ocular disorders, or uncontrolled diabetes at baseline.
## Bladder Cancer – Post Cystectomy Follow Up

<table>
<thead>
<tr>
<th></th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Year 5-10</th>
<th>Year &gt;10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Imaging NMIBC</strong></td>
<td>CT urogram at 3 &amp; 12 mo</td>
<td>Annual CT urogram</td>
<td></td>
<td></td>
<td>Annual renal ultrasound</td>
<td>As clinically indicated</td>
<td></td>
</tr>
<tr>
<td><strong>Imaging MIBC</strong></td>
<td>CT chest and CT urogram every 3-6 mo</td>
<td>Annual CT chest/abdomen/pelvis</td>
<td></td>
<td></td>
<td>Annual renal ultrasound</td>
<td>As clinically indicated</td>
<td></td>
</tr>
<tr>
<td><strong>Blood Tests</strong></td>
<td>CMP &amp; CBC every 6 mo</td>
<td>Annual CMP and B₁₂ levels</td>
<td></td>
<td></td>
<td>Annual B₁₂ levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Urine Tests</strong></td>
<td>Urine cytology every 6-12 mo; consider urethral wash every 6-12 mo</td>
<td></td>
<td></td>
<td></td>
<td>Urine cytology as clinically indicated</td>
<td>Urethral wash cytology as clinically indicated</td>
<td></td>
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### Bladder Cancer – Muscle Invasive Post Bladder Preservation Follow Up

#### Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 5-10 | Year >10
--- | --- | --- | --- | --- | --- | ---
**Cystoscopy** | Every 3 mo | Every 6 mo | Annually | As clinically indicated
**Imaging** | CT chest and CT urogram every 3-6 mo | Annual CT chest/abdomen/pelvis | As clinically indicated
**Blood Tests** | CMP & CBC every 6 mo | | | Annual CMP
**Urine Tests** | Urine cytology every 6-12 mo | | | Urine cytology as clinically indicated

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**Muscle Invasive Post Bladder Preservation Follow Up**
Questions?

Contact VHAOncologyPathways@va.gov