Diagnosis & Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guidelines

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DISCLOSURES

NONE
PURPOSE

The survival rate for the majority of patients with non-muscle invasive bladder cancer (NMIBC) is favorable; however, the rates of recurrence and progression to muscle-invasive bladder cancer (MIBC) are major determinants of long-term outcome. The recurrence and progression probability rates depend on several clinical and pathologic factors. Therefore, the ability to predict risk of recurrence and progression and treat the disease appropriately is important. This guideline provides a risk-stratified clinical framework for the management of NMIBC.
AHRQ SYSTEMATIC REVIEW
• January 1990-October 2014
• 149 studies (192 publications)

REPORT SUPPLEMENTATION
• AHRQ Report Publication-September 2015
• 29 studies

A
• Well conducted RCT’s
• Exceptional observational studies

B
• RCT’s and/or observational studies with some weaknesses

C
• Observational studies that are inconsistent -difficult to interpret
Staging for bladder cancer is separated into clinical and pathologic stage, as outlined by the American Joint Committee on Cancer (AJCC), also known as the Tumor-Node-Metastases (TNM) classification. Clinical stage reflects the histologic findings at TURBT; the clinician’s physical exam, including bimanual exam under anesthesia; and findings on radiologic imaging.

### Staging of primary tumors (T) in bladder cancer

<table>
<thead>
<tr>
<th>Staging</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>Ta</td>
<td>Noninvasive papillary carcinoma</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ (CIS)</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades lamina propria</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscularis propria</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumor invades superficial muscularis propria (inner half)</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumor invades deep muscularis propria (outer half)</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades perivesical tissue/fat</td>
</tr>
<tr>
<td>T3a</td>
<td>Tumor invades perivesical tissue/fat microscopically</td>
</tr>
<tr>
<td>T3b</td>
<td>Tumor invades perivesical tissue fat macroscopically (extravesical mass)</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades prostate, uterus, vagina, pelvic wall, or abdominal wall</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor invades adjacent organs (uterus, ovaries, prostate stoma)</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor invades pelvic wall and/or abdominal wall</td>
</tr>
</tbody>
</table>
Tumor grade is an important prognostic factor for determining risk of recurrence and progression in bladder cancer. The WHO/ISUP 2004 grading system is now the most widely accepted and utilized system in the United States.

<table>
<thead>
<tr>
<th>2004 World Health Organization/ International Society of Urologic Pathologists: Classification of Non-muscle Invasive Urothelial Neoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplasia (flat and papillary)</td>
</tr>
<tr>
<td>Reactive atypia</td>
</tr>
<tr>
<td>Atypia of unknown significance</td>
</tr>
<tr>
<td>Urothelial dysplasia</td>
</tr>
<tr>
<td>Urothelial CIS</td>
</tr>
<tr>
<td>Urothelial papilloma</td>
</tr>
<tr>
<td>Papillary urothelial neoplasm of low malignant potential</td>
</tr>
<tr>
<td>Non-muscle invasive low-grade papillary urothelial carcinoma</td>
</tr>
<tr>
<td>Non-muscle invasive high-grade papillary urothelial carcinoma</td>
</tr>
</tbody>
</table>
The survival prognosis for patients with NMIBC is relatively favorable, with the cancer-specific survival (CSS) in high-grade disease ranging from approximately 70-85% at 10 years and a much higher rate for low-grade disease.

The rates of recurrence and progression to MIBC are important surrogate endpoints for prognosis in NMIBC, as these are major determinants of long-term outcome.

Risk stratification in NMIBC aids personalized treatment decisions and surveillance strategies as opposed to a generalized ‘one-size fits all’ approach.

Palou 2012; Cookson 1997; Leblanc 1999
### AUA RISK STRATIFICATION SYSTEM

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>LG$^a$ solitary Ta $\leq$ 3cm</td>
<td>Recurrence within 1 year, LG Ta</td>
<td>HG T1</td>
</tr>
<tr>
<td>PUNLMP$^b$</td>
<td>Solitary LG Ta $&gt;$ 3cm</td>
<td>Any recurrent, HG Ta</td>
</tr>
<tr>
<td></td>
<td>LG Ta, multifocal</td>
<td>HG Ta, $&gt;$3cm (or multifocal)</td>
</tr>
<tr>
<td></td>
<td>HG$^c$ Ta, $\leq$ 3cm</td>
<td>Any CIS$^d$</td>
</tr>
<tr>
<td></td>
<td>LG T1</td>
<td>Any BCG failure in HG patient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any variant histology</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any LVI$^e$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any HG prostatic urethral involvement</td>
</tr>
</tbody>
</table>

$^a$LG = low grade; $^b$PUNLMP = papillary urothelial neoplasm of low malignant potential; $^c$HG = high grade; $^d$CIS = carcinoma in situ; $^e$LVI = lymphovascular invasion
1. At the time of resection of suspected bladder cancer, a clinician should perform a thorough cystoscopic examination of a patient’s entire urethra and bladder that evaluates and documents tumor size, location, configuration, number, and mucosal abnormalities. (Clinical Principle)

2. At initial diagnosis of a patient with bladder cancer, a clinician should perform complete visual resection of the bladder tumor(s), when technically feasible. (Clinical Principle)

Incomplete TURBT is likely a significant contributing factor to early bladder cancer recurrences, as tumors are seen at first surveillance cystoscopy in up to 45% of patients

Brausi 2002
3. A clinician should perform upper urinary tract imaging as a component of the initial evaluation of a patient with bladder cancer. (Clinical Principle)

4. In a patient with a history of NMIBC with normal cystoscopy and positive cytology, a clinician should consider prostatic urethral biopsies and upper tract imaging, as well as enhanced cystoscopic techniques (blue light cystoscopy, when available), ureteroscopy, or random bladder biopsies. (Expert Opinion)
GUIDELINE: RISK STRATIFICATION

5. At the time of each occurrence/recurrence, a clinician should assign a clinical stage and classify a patient accordingly as “low-,” “intermediate-,” or “high-risk.” (Moderate Recommendation; Evidence Strength: Grade C)

EORTC/CUETO Model → Tumor size, tumor focality, grade, stage, recurrence pattern, number

AUA/SUO Additions → Lymphovascular invasion, prostatic urethral involvement, variant histology, poor response to BCG
6. An experienced genitourinary pathologist should review the pathology of a patient with any doubt in regards to variant or suspected variant histology (e.g., micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid), extensive squamous or glandular differentiation, or the presence/absence of lymphovascular invasion. (Moderate Recommendation; Evidence Strength: Grade C)

7. If a bladder sparing approach is being considered in a patient with variant histology, then a clinician should perform a restaging TURBT within four to six weeks of the initial TURBT. (Expert Opinion)

8. Due to the high rate of upstaging associated with variant histology, a clinician should consider offering initial radical cystectomy. (Expert Opinion)
GUIDELINE: URINE MARKERS

9. In surveillance of NMIBC, a clinician should not use urinary biomarkers in place of cystoscopic evaluation. (Strong Recommendation; Evidence Strength: Grade B)

Direct comparisons between markers are difficult, and given the uncertainty in sensitivity, these tests cannot be used to replace cystoscopy.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Description</th>
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<tbody>
<tr>
<td>NMP22®</td>
<td>Protein-based; identifies nuclear matrix protein involved in the mitotic apparatus</td>
</tr>
<tr>
<td>BTA®</td>
<td>Protein-based; identifies a basement membrane antigen related to complement factor H</td>
</tr>
<tr>
<td>UroVysion® FISH</td>
<td>Cell-based; identifies altered copy numbers of specific chromosomes using fluorescent probes</td>
</tr>
<tr>
<td>ImmunoCyt™</td>
<td>Cell-based; identifies three cell surface glycoproteins</td>
</tr>
<tr>
<td>Cxbladder™</td>
<td>Cell-based; identifies the presence of five mRNA fragments</td>
</tr>
</tbody>
</table>

Tomasini 2013; O’Sullivan 2012
10. In a patient with a **history of low-risk cancer and a normal cystoscopy**, a clinician should not routinely use a urinary biomarker or cytology during **surveillance**. (Expert Opinion)

11. In a patient with NMIBC, a clinician may use biomarkers to assess response to intravesical BCG (UroVysion® FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™). (Expert Opinion)
12. In a patient with non-muscle invasive disease who underwent an incomplete initial resection (not all visible tumor treated), a clinician should perform repeat transurethral resection or endoscopic treatment of all remaining tumor if technically feasible. (Strong Recommendation; Evidence Strength: Grade B)

13. In a patient with high-risk, high-grade Ta tumors, a clinician should consider performing repeat transurethral resection of the primary tumor site within six weeks of the initial TURBT. (Moderate Recommendation; Evidence Strength: Grade C)

14. In a patient with T1 disease, a clinician should perform repeat transurethral resection of the primary tumor site to include muscularis propria within six weeks of the initial TURBT. (Strong Recommendation; Evidence Strength: Grade B)
15. In a patient with suspected or known low- or intermediate-risk bladder cancer, a clinician should consider administration of a single postoperative instillation of intravesical chemotherapy (e.g., mitomycin C or epirubicin) within 24 hours of TURBT. In a patient with a suspected perforation or extensive resection, a clinician should not use postoperative chemotherapy. (Moderate Recommendation; Evidence Strength: Grade B)
16. In a low-risk patient, a clinician should not administer induction intravesical therapy. (Moderate Recommendation; Strength of Evidence Grade C)

17. In an intermediate-risk patient a clinician should consider administration of a six week course of induction intravesical chemotherapy or immunotherapy. (Moderate Recommendation; Evidence Strength: Grade B)

18. In a high-risk patient with newly diagnosed CIS, high-grade T1, or high-risk Ta urothelial carcinoma, a clinician should administer a six-week induction course of BCG. (Strong Recommendation; Evidence Strength: Grade B)
GUIDELINE: INTRAVESICAL THERAPY

There is insufficient evidence to recommend one particular strain of BCG
• Several small studies suggest that different strains may have different efficacies

There is insufficient evidence to prescribe a particular strength of BCG
• EORTC 30962 recommends full dose for three years for high-risk patients
• For lower-risk patients, no difference in recurrence free survival between full or 1/3 dose at 1 or 3 years

There is insufficient evidence to recommend using BCG in combination with other intravesical agents
• Several ongoing trials are currently examining synergistic combinations

Rentsch 2014; Oddens 2013; Houghton 2013
19. In an intermediate-risk patient who completely responds to an induction course of intravesical chemotherapy, a clinician may utilize maintenance therapy. (Conditional Recommendation; Evidence Strength: Grade C)

20. In an intermediate-risk patient who completely responds to induction BCG, a clinician should consider maintenance BCG for one year, as tolerated. (Moderate Recommendation; Evidence Strength: Grade C)

21. In a high-risk patient who completely responds to induction BCG, a clinician should continue maintenance BCG for three years, as tolerated. (Moderate Recommendation; Evidence Strength: Grade B)
GUIDELINE: INTRAVESICAL THERAPY

Oddens 2013
22. In an intermediate- or high-risk patient with persistent or recurrent disease or positive cytology following intravesical therapy, a clinician should consider performing prostatic urethral biopsy and an upper tract evaluation prior to administration of additional intravesical therapy. (Conditional Recommendation; Evidence Strength: Grade C)

23. In an intermediate- or high-risk patient with persistent or recurrent Ta or CIS disease after a single course of induction intravesical BCG, a clinician should offer a second course of BCG. (Moderate Recommendation; Strength of Evidence C)

24. In a patient fit for surgery with high-grade T1 disease after a single course of induction intravesical BCG, a clinician should offer radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)
25. A clinician should not prescribe additional BCG to a patient who is intolerant of BCG or has documented recurrence on TURBT of high-grade, non-muscle-invasive disease and/or CIS within six months of two induction courses of BCG or induction BCG plus maintenance. (Moderate Recommendation; Evidence Strength: Grade C)

26. In a patient with persistent or recurrent intermediate- or high-risk NMIBC who is unwilling or unfit for cystectomy following two courses of BCG, a clinician may recommend clinical trial enrollment. A clinician may offer this patient intravesical chemotherapy when clinical trials are unavailable. (Expert Opinion)
27. In a patient with Ta low- or intermediate-risk disease, a clinician should not perform radical cystectomy until bladder-sparing modalities (staged TURBT, intravesical therapies) have failed. (Clinical Principle)

28. In a high-risk patient who is fit for surgery with persistent high-grade T1 disease on repeat resection, or T1 tumors with associated CIS, LVI, or variant histologies, a clinician should consider offering initial radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)

29. In a high-risk patient with persistent or recurrent disease within one year following treatment with two induction cycles of BCG or BCG maintenance, a clinician should offer radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)
30. In a patient with NMIBC, a clinician should offer blue light cystoscopy at the time of TURBT, if available, to increase detection and decrease recurrence. (Moderate Recommendation; Evidence Strength: Grade B)

31. In a patient with NMIBC, a clinician may consider use of NBI to increase detection and decrease recurrence. (Conditional Recommendation; Evidence Strength: Grade C)
32. After completion of the initial evaluation and treatment of a patient with NMIBC, a clinician should perform the first surveillance cystoscopy within three to four months. (Expert Opinion)

33. For a low-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent surveillance cystoscopy six to nine months later, and then annually thereafter; surveillance after five years in the absence of recurrence should be based on shared-decision making between the patient and clinician. (Moderate Recommendation; Evidence Strength: Grade C)

34. In an asymptomatic patient with a history of low-risk NMIBC, a clinician should not perform routine surveillance upper tract imaging. (Expert Opinion)

35. In a patient with a history of low-grade Ta disease and a noted sub-centimeter papillary tumor(s), a clinician may consider in-office fulguration as an alternative to resection under anesthesia. (Expert Opinion)
35. For an intermediate-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent cystoscopy with cytology every 3-6 months for 2 years, then 6-12 months for years 3 and 4, and then annually thereafter. (Expert Opinion)

36. For a high-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent cystoscopy with cytology every three to four months for two years, then six months for years three and four, and then annually thereafter. (Expert Opinion)

37. For an intermediate- or high-risk patient, a clinician should consider performing surveillance upper tract imaging at one to two year intervals. (Expert Opinion)
The future of NMIBC will likely be driven forward by basic science, novel technologies, new therapeutics and clinical trials.

- **Bladder Cancer Genome Atlas Project**
- **Novel agents to improve BCG efficacy or manage BCG failures**
- **New technologies**
  - [A Study of Blue Light Flexible Cystoscopy With Cysview in the Detection of Bladder Cancer in the Surveillance Setting](https://clinicaltrials.gov/ct2/show/NCT02560584)
  - [Transurethral Resection of Bladder Tumors Using PK Button Vaporization Electrode or Monopolar Loop Electrocautery in Treating Patients with Bladder Cancer](https://clinicaltrials.gov/ct2/show/NCT01567462)
- **Therapeutic Trials in Surgery/Radiation**
  - [Intracorporeal or Extracorporeal Urinary Diversion during Robotic Assisted Radical Cystectomy in Reducing Complications in Patients with Bladder Cancer](https://clinicaltrials.gov/ct2/show/NCT02252393)
  - [Radiation Therapy and Cisplatin or Mitomycin and Fluorouracil in Treating Patients with Non-Muscle Invasive Stage I Bladder Cancer](https://clinicaltrials.gov/ct2/show/NCT00981656)
- **Surveillance**
  - [Surveillance Guidelines in Monitoring Patients with Non-muscle Invasive Bladder Cancer](https://clinicaltrials.gov/ct2/show/NCT02298998)
Non-Muscle Invasive Bladder Cancer: AUA/SUO Treatment Algorithm

TURBT

Int. Risk
- Others
- T1 and/or incomplete TUR
  - Re-TURBT +/− Chemo
  - BCG
- T1, LVI, +/− variant
  - Cystectomy

Low Risk
- Postoperative Chemo
  - Complete response
  - Surveillance
- Recurrence within 1 year
  - Reassess as Int. Risk
  - Partial or no response

Induction Chemo
- Complete response
  - Surveillance
  - Maintenance (1 yr)
  - Recurrence

BCG
- Complete response
- Reinduce
- Partial or no response
  - <1 yr
  - If unfit or unwilling to undergo surgery
  - Cystectomy
- T1, LVI, +/− variant
  - Re-TURBT +/− Chemo

High Risk
- Re-TURBT +/− Chemo
  - Others
  - Partial or no response
  - Reinduce
  - Complete response

If trial is unavailable
- Clinical Trial
- Intravesical Chemo
Non-Muscle Invasive Bladder Cancer: AUA/SUO Treatment Algorithm

TURBT

Int. Risk

Others

TI and/or incomplete TUR

Re-TURBT+/- Chemo

Induction Chemo

Complete response

Partial or no response

BCG

Complete response

Maintenance (1 yr)

Surveillance

Recurrence

Clinical Trial

If trial is unavailable

Intravesical Chemo

Cystectomy

If unfit or unwilling to undergo surgery

T1, LVI, +/variant

High Risk

Re-TURBT+/- Chemo

T1, LVI, +/variant

Others

T1

Others

Partial or no response

Reinduce

Complete response

BCG

Partial or no response

Reinduce

Complete response

Maintenance (3 yrs)

*Consider fulguration in low-volume disease recurrence; otherwise re-assess as intermediate risk.

†Timely re-TURBT (within six weeks) should be performed if there are concerns regarding an incomplete resection and/or if bladder sparing treatment (e.g., intravesical therapy or surveillance) is being planned.
WHAT’S NEXT

• AUA, ASTRO, ASCO and SUO have formed a guidelines committee that will publish the first multi-organization endorsed guidelines on Muscle Invasive Bladder Cancer

• Panel members includes: Kamat, Lerner, Holzbeierlein, Bochner, Zietman, Dreicer, Rosenberg, Quale et al

• Presentation date: AUA 2017, Boston by Dr. Holzbeierlein

• Important concepts:
  • Neoadjuvant chemotherapy
  • Multi-modality bladder preserving therapy
  • Surveillance
ACKNOWLEDGEMENTS

Non-muscle Invasive Bladder Cancer Panel
Sam S. Chang, MD, MBA (Chair)
James McKiernan, MD (Vice Chair)
Peter Clark, MD (PGC Rep)
Diane Zipursky Quale (Patient Adv)
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Siamak Daneshmand, MD
Badrinath Konyet, MD
Raj Pruthi, MD
Chad Ritch, MD
John Seigne, MD
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Norm Smith, MD

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Erin Kirkby
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THANK YOU!