Non Muscle-Invasive Bladder Cancer: Guidelines-based Approach

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Management of Bladder Cancer

- Bladder Cancer
  - “Caged” Tiger
  - “Uncaged” Tiger
- Bladder Preservation
- Cystectomy
66 yo man is found to have a solitary 2cm LG Ta bladder tumor. Upper tract imaging is negative. The next step is:

1. Surveillance cystoscopy and cytology q 3 months X 2 years then q 6 months
2. Surveillance cystoscopy only q 3-4 months X 2 years then q 6 months
3. Surveillance cystoscopy only at 3 and 12 months then yearly
4. Induction BCG
5. Re-TURBT
58 yo woman is found to have a recurrent Ta HG tumor 3 months after completing BCG for a Ta HG tumor. The next step is:

1. Induction mitomycin C
2. Induction valrubicin
3. Repeat induction BCG
4. Re-TURBT
5. Radical cystectomy
52 yo man is found to have a T1 HG micropapillary tumor at the dome. CTU is negative. The next step is:

1. Induction BCG
2. Induction mitomycin C
3. Re-TURBT
4. Partial cystectomy
5. Radical cystectomy
Objective

Understanding of the 2016 AUA-SUO guidelines-based approach to NMIBC from diagnosis, risk-stratification, and treatment
Bladder Cancer

- 74,100 new cases in 2015
  - 4th most common in men
  - 80% cases are NMIBC

- 16,000 deaths per year in the U.S.

- 500,000 survivors in U.S.

- Overall incidence stable over past 30 years
  - Ta increasing
  - T1, Tis slight decrease
Epidemiology

- Male predominance (3:1)
- Caucasians : African Americans (2:1)
Clinical Presentation

• Hematuria – >80% of UC
  – Gross
  – Microscopic (2.6% pts with AMH have malignancy)

• Bladder irritability
  – Most with CIS
  – Frequency, urgency, dysuria

• Sometimes asymptomatic
Histology

- 90% urothelial carcinoma (UC)
  - + / - squamous differentiation or adenocarcinoma

- 10% variants
  - Squamous cell ca
  - Adenocarcinoma
  - Small cell ca
  - Sarcoma, melanoma
  - Metastases (colorectal, lung, cervix, ovarian)
Clinical Staging

- **T1** affects the lamina propria
- **Ta** affects the epithelium
- **Carcinoma in situ**

- **Mucosa**
- **Lamina propria**
- **Superficial muscle**
- **Deep muscle**
- **Peritoneum**
- **Prostate**

- **T2a** affects superficial muscle
- **T2b** affects deep muscle
- **T3a** affects vesical tissue (microscopically)
- **T3b** affects vesical fat or peritoneum
- **T4** affects contiguous organs
World Health Organization (WHO) Classification of Urothelial Neoplasms

Reuter V. Urology 2006; 67;3A 11-18
### Grading

<table>
<thead>
<tr>
<th>2004 World Health Organization/ International Society of Urologic Pathologists: Classification of Non-muscle Invasive Urothelial Neoplasia\textsuperscript{ix}</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>
Prognosis

- 10-year CSS for HG NMIBC = 70-85%
- Ta LG: 55% recurrence + 6% progression
- Ta HG: 45% recurrence + 17% progression
Non-muscle Invasive Bladder Cancer

- Patients with noninvasive bladder are evaluated for:
  - Risk of Recurrence
  - Risk of Progression

- The ability to predict recurrence and progression is based on patient-specific disease characteristics
2007 Panel members
M. Craig Hall, M.D., Chair
Sam S. Chang, M.D.
Guido Dalbagni, M.D.
Raj S. Pruthi, M.D.
Paul F. Schellhammer, M.D.
John D. Seigne, M.D.
Eila C. Skinner, M.D.
J. Stuart Wolf, Jr., M.D.

2016 Panel members
Sam S. Chang, M.D., Chair
Jim McKiernan, M.D., Vice Chair
Steve Boorjian, M.D.
Peter Clark, M.D.
Sia Danshmand, M.D.
Badri Konety, M.D.
Raj S. Pruthi, M.D.
Diane Quale, Patient Advocate
Chad Ritch, M.D.
John D. Seigne, M.D.
Eila C. Skinner, M.D.
Norm Smith, M.D.
Methodology

• Systematic review from AHRQ and supplementation by the authors and consultant methodologists.

• Database searches resulted in 3,740 articles. After dual review of abstracts and titles, 643 articles were selected for full-text dual review, and 192 met inclusion criteria and were included.

• The NMIBC Panel was created in 2014 by the AUA.

• Draft guidelines distributed to 128 peer reviewers. The Panel reviewed and discussed all submitted comments and revised. Approved by the AUA Board of Directors. Funding was provided by the AUA; panel received no remuneration for their work.
TABLE 1: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength

<table>
<thead>
<tr>
<th>Statement Type</th>
<th>Evidence Strength A (High Certainty)</th>
<th>Evidence Strength B (Moderate Certainty)</th>
<th>Evidence Strength C (Low Certainty)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong Recommendation</td>
<td>Benefits &gt; Risks/Burdens (or vice versa)</td>
<td>Benefits &gt; Risks/Burdens (or vice versa)</td>
<td>Benefits &gt; Risks/Burdens (or vice versa)</td>
</tr>
<tr>
<td>(Net benefit or harm substantial)</td>
<td>Net benefit (or net harm) is substantial</td>
<td>Net benefit (or net harm) is substantial</td>
<td>Net benefit (or net harm) appears substantial</td>
</tr>
<tr>
<td></td>
<td>Applies to most patients in most circumstances and future research is unlikely to change confidence</td>
<td>Applies to most patients in most circumstances but better evidence could change confidence</td>
<td>Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)</td>
</tr>
<tr>
<td>Moderate Recommendation</td>
<td>Benefits &gt; Risks/Burdens (or vice versa)</td>
<td>Benefits &gt; Risks/Burdens (or vice versa)</td>
<td>Benefits &gt; Risks/Burdens (or vice versa)</td>
</tr>
<tr>
<td>(Net benefit or harm moderate)</td>
<td>Net benefit (or net harm) is moderate</td>
<td>Net benefit (or net harm) is moderate</td>
<td>Net benefit (or net harm) appears moderate</td>
</tr>
<tr>
<td></td>
<td>Applies to most patients in most circumstances and future research is unlikely to change confidence</td>
<td>Applies to most patients in most circumstances but better evidence could change confidence</td>
<td>Applies to most patients in most circumstances but better evidence is likely to change confidence</td>
</tr>
<tr>
<td>(No apparent net benefit or harm)</td>
<td>Best action depends on individual patient circumstances</td>
<td>Best action appears to depend on individual patient circumstances</td>
<td>Alternative strategies may be equally reasonable</td>
</tr>
<tr>
<td></td>
<td>Future research unlikely to change confidence</td>
<td>Better evidence could change confidence</td>
<td>Better evidence likely to change confidence</td>
</tr>
<tr>
<td>Clinical Principle</td>
<td>A statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expert Opinion</td>
<td>A statement, achieved by consensus of the Panel, that is based on members’ clinical training, experience, knowledge, and judgment for which there is no evidence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Evaluation

- Cystoscopy
- Urinary Cytology
- Imaging of Upper Tracts
  - (IVP)
  - CT urogram
  - MRI
Guidelines

1. At the time of resection, a clinician should perform a thorough cystoscopy documenting tumor size, location, configuration, number, and any mucosal abnormalities. (Clinical Principle)

2. At initial diagnosis, should perform complete visual TURBT, when technically feasible. (Clinical Principle)

3. A clinician should perform upper tract imaging as a part of initial evaluation. (Clinical Principle)

4. In a patient with a history of NMIBC with normal cystoscopy and positive cytology, should consider prostatic urethral bx and upper tract imaging, enhanced cystoscopic techniques (when available), ureteroscopy, or random bladder biopsies. (Expert Opinion)
Risk Stratification

• EORTC and CUETO risk calculators
• Limited by lack of applicability to current populations
  – Few patients received BCG maintenance, re-staging TURBT, or post-operative mitomycin C.
• EORTC uses 1973 WHO grading
• Unique to the AUA/SUO risk stratification is incorporating prior BCG, etc
• Risk groups used to predict outcomes of patients felt to be similar to one another
• Use of C-index (0.5 = coin flip; higher is better)
  – EORTC = 0.66 / 0.75
  – CUETO = 0.64 / 0.70
Bladder Cancer Prognosis Calculator

Calculate Probabilities

Probability of Recurrence
Probability of Progression


Programmed by Richard Sylvester

Version 1.0. January 2006

Denis L. Newling DWW, Brussels, Belgium.
Risk Stratification

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  - EORTC = 0.66 / 0.75
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### TABLE 4: AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>LG(^a) solitary Ta ≤ 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, ≤ 3cm</td>
<td>Any CIS</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(^d)</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; \(^d\)LVI = lymphovascular invasion;

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

- Micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid, pure glandular or squamous; LVI
- At TURBT, 86% (vs. 53%) patients with variant histology present with muscle-invasive disease.
- At cystectomy, 64% (vs. 34%) of patients with variant histology were found to have pT3-T4 disease

6. An experienced GU pathologist should review variant or suspected variant (Moderate Recommendation; Evidence Strength: Grade C)

7. If a bladder sparing approach is considered, should perform a restaging TURBT within 4-6 weeks. (Expert Opinion)

8. Due to high rate of upstaging, clinician should consider offering initial radical cystectomy. (Expert Opinion)
Urine Markers

5 markers approved by the FDA and/or commercially available in U.S.: NMP22® and BTA® tests are protein-based, while UroVysion® FISH, ImmunoCyt™ and Cxbladder™ are cell-based

<table>
<thead>
<tr>
<th>Marker</th>
<th>Avg. sens (range)</th>
<th>Avg. spec (range)</th>
<th>Avg. cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dipstick</td>
<td>68% (40-93)</td>
<td>68% (62-98)</td>
<td>$0.92</td>
</tr>
<tr>
<td>Cytology</td>
<td>48% (16-89)</td>
<td>96% (81-100)</td>
<td>$35</td>
</tr>
<tr>
<td>NMP22</td>
<td>67% (21-100)</td>
<td>75% (54-93)</td>
<td>$125-150</td>
</tr>
<tr>
<td>BladderChek</td>
<td></td>
<td></td>
<td>$10-30</td>
</tr>
<tr>
<td>BTA stat</td>
<td>68% (51-100)</td>
<td>74% (51-95)</td>
<td>$15</td>
</tr>
<tr>
<td>UroVysion (FISH)</td>
<td>79% (44-96)</td>
<td>88% (46-100)</td>
<td>$600 - $1200</td>
</tr>
<tr>
<td>ImmunoCyt</td>
<td>77% (18-100)</td>
<td>76% (62-86)</td>
<td>$300-400</td>
</tr>
</tbody>
</table>
Urine Markers

9. In surveillance, should **not** use urinary biomarkers in place of cystoscopy. (Strong Recommendation; Evidence Strength: Grade B)

10. History of low-risk cancer and a normal cystoscopy, should **not** routinely use a urinary biomarker or cytology during surveillance. (Expert Opinion)

11. May use biomarkers to assess response to intravesical BCG (UroVysion® FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™). (Expert Opinion)
Atypical cytology and FISH

Schlommer BJ et al. J. Urol. 2010
## FISH and response to BCG

<table>
<thead>
<tr>
<th></th>
<th>Recurrence if post BCG FISH</th>
<th>% ≥T2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Kipp</td>
<td>100%</td>
<td>52%</td>
</tr>
<tr>
<td>Whitson</td>
<td>89%</td>
<td>26%</td>
</tr>
<tr>
<td>Mengual</td>
<td>52%</td>
<td>25%</td>
</tr>
<tr>
<td>Savic</td>
<td>76%</td>
<td>26%</td>
</tr>
</tbody>
</table>

- Post BCG FISH predicts for rec and prog.
- FISH useful if post BCG cytology equivocal

Incomplete resection is likely a significant contributing factor early recurrences, as tumors have been noted at the first follow-up cystoscopic evaluation in up to 45% of patients.

12. In patient who underwent an incomplete initial resection (not all visible tumor treated), perform repeat TURBT of all remaining tumor if feasible. (Strong Recommendation; Evidence Strength: Grade B)

13. Patient with high-risk, high-grade Ta tumors, consider performing repeat TUR of primary tumor site within 6 weeks. (Moderate Recommendation; Evidence Strength: Grade C)

14. With T1 disease, perform repeat TUR of primary tumor site to include muscularis propria within 6 weeks. (Strong Recommendation; Evidence Strength: Grade B)
Intravesical Therapies

15. Low- or intermediate-risk, consider single postoperative instillation of intravesical chemotherapy (e.g., mitomycin C or epirubicin) within 24 hours of TURBT -- **EXCEPT** with suspected perforation or extensive resection (Moderate Recommendation; Evidence Strength: Grade B)

16. Low-risk - should not administer induction intravesical therapy. (Moderate Recommendation; Strength of Evidence Grade C)

17. Intermediate-risk - consider administration of a 6 week induction intravesical chemotherapy or immunotherapy. (Moderate Recommendation; Evidence Strength: Grade B)

18. High-risk patient with CIS, high-grade T1, or high-risk Ta, should administer 6-week induction course of BCG. (Strong Recommendation; Evidence Strength: Grade B)
19. Intermediate-risk who completely responds to induction BCG, should consider maintenance BCG for one year, as tolerated. (Moderate Recommendation; Evidence Strength: Grade C)

20. High-risk who completely responds to induction BCG, should continue maintenance BCG for three years, as tolerated. (Moderate Recommendation; Evidence Strength: Grade B)
21. Intermediate- or high-risk with persistent or recurrent disease or positive cytology following intravesical therapy, should consider performing prostatic urethral biopsy and an upper tract evaluation prior to administration of additional intravesical therapy. (Conditional Recommendation; Evidence Strength: Grade C)

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

- 50% patients with persistent/ recurrent NMIBC following first induction course of BCG respond to a second course of BCG
BCG Relapse

23. In patient fit for surgery with recurrent HG T1 after a single induction BCG, should offer radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)

24. Should not prescribe additional BCG if patient is intolerant or has recurrence on TURBT of high-grade, non-muscle-invasive disease and/or CIS within 6 months of 2 induction courses of BCG or induction BCG plus maintenance. (Moderate Recommendation; Evidence Strength: Grade C)

25. With persistent or recurrent intermediate- or high-risk NMIBC who is unwilling or unfit for cystectomy following two courses BCG, a clinician may recommend clinical trial enrollment. May offer intravesical chemotherapy when clinical trials are unavailable. (Expert Opinion)
Role of Cystectomy

• Early, high-risk recurrences are at significant risk of progression; salvage intravesical therapies have poor success rates.

• Rationale for “early” cystectomy:
  – Understaging (50% T1 are upstaged to >=T2 at cystectomy
  – Significant “late” failure rate
  – Potential survival benefit from avoiding delay of cystectomy
Role of Cystectomy

26. 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)

27. High-risk who is fit for surgery with persistent HG T1 disease on re-TUR, or T1 tumors with CIS, LVI, or variant histologies, should consider initial radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)

28. In high-risk with persistent/recurrent disease within one year following treatment with two inductions of BCG or BCG maintenance, should offer radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)
Enhanced Cystoscopy

Use of fluorescent cystoscopy improves the detection of urothelial carcinoma, especially CIS and can decrease recurrence rates.

29. In NMIBC, should offer blue light cystoscopy at the time of TURBT, if available, to increase detection and decrease recurrence. (Moderate Recommendation; Evidence Strength: Grade B)

30. In NMIBC, may consider use of NBI to increase detection and decrease recurrence. (Conditional Recommendation; Evidence Strength: Grade C)
At time of first evaluation, none of existent risk stratification tools or urinary biomarkers is sufficiently sensitive and specific to predict which patient will have an early recurrence. Most reliable way is by cystoscopic visualization.

31. 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)
Follow Up

32. For a low-risk whose 1st surveillance cystoscopy is negative, should perform next cystoscopy 6 – 9 months later, and then annually; surveillance after 5 years should be based on shared-decision making between the patient and clinician. (Moderate Recommendation; Evidence Strength: Grade C)

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

34. In a patient with a history of low-grade and a noted sub-centimeter papillary tumor(s), may consider in-office fulguration as an alternative to TURBT. (Expert Opinion)
Follow Up

35. For an intermediate-risk whose first surveillance cystoscopy is negative, 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 whose first cystoscopy is negative, should perform subsequent cystoscopy with cytology every 3 – 4 months for two years, then 6 months for years three and four, and then annually thereafter. (Expert Opinion)

37. For an intermediate- or high-risk patient, should consider performing surveillance upper tract imaging 1 – 2 year intervals. (Expert Opinion)
Future Directions

• Likely driven forward by basic science, novel technologies, new therapeutics and clinical trials.

• The bladder cancer genome atlas project provided analysis of 131 muscle-invasive urothelial carcinomas in an effort to describe molecular alterations and, ideally, provide insight into use of molecularly targeted agents.

• NMIBC fortunate to have increasing number of clinical trials, vast majority are studying novel agents to improve outcomes of BCG or treat BCG failures, but also investigating new technology, surgical techniques, radiation, and surveillance schedules.
Non-Muscle Invasive Bladder Cancer: AUA/SUO Treatment Algorithm

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

- **Int. Risk**
  - TURBT
  - Others
  - T1 and/or incomplete TUR
  - Re-TURBT† +/− Chemo
  - Partial or no response

- **Induction Chemo**
  - Complete response

- **BCG**
  - Partial or no response
  - Complete response

- **maintenance (1 yr)**
  - Surveillance

- **Reurrence**
  - Clinical Trial
  - Intravesical Chemo

- **High Risk**
  - Re-TURBT† +/− Chemo
  - T1, LVI, +/− variant

- **Cystectomy**
  - If unfit or unwilling to undergo surgery

- **BCG**
  - Partial or no response

- **Reinduce**
  - T1
  - Others

- **Maintenance (3 yrs)**

---

*Consider fulguration in low-volume disease recurrence; otherwise reassess 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.
66 yo man is found to have a solitary 2cm LG Ta bladder tumor. Upper tract imaging is negative. The next step is:

1. Surveillance cystoscopy and cytology q 3 months X 2 years then q 6 months
2. Surveillance cystoscopy only q 3-4 months X 2 years then q 6 months
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58 yo woman is found to have a recurrent Ta HG tumor 3 months after completing BCG for a Ta HG tumor. The next step is:

1. Induction mitomycin C
2. Induction valrubicin
3. Repeat induction BCG
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5. Radical cystectomy
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1. Induction mitomycin C
2. Induction valrubicin
3. *Repeat induction BCG*
4. Re-TURBT
5. Radical cystectomy
52 yo man is found to have a T1 HG micropapillary tumor at the dome. CTU is negative. The next step is:

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52 yo man is found to have a T1 HG micropapillary tumor at the dome. CTU is negative. The next step is:

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3. Re-TURBT
4. Partial cystectomy
5. **Radical cystectomy**