Updates in the New AJCC TNM Staging of Bladder Cancer: Issues Pertaining to Application in Routine Surgical Pathology

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Dr. Gladell Paner declares he/she has no conflict(s) of interest to disclose.

8th Edition AJCC TNM Staging Urinary Bladder

8th Edition AJCC TNM Staging for Bladder Cancer: Summary of Changes

<table>
<thead>
<tr>
<th>Change</th>
<th>Details of Change</th>
<th>Level of Evidence</th>
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<tbody>
<tr>
<td>Definition of Regional LN (N)</td>
<td>Perivesical LN involvement is classified as N1.</td>
<td>II</td>
</tr>
<tr>
<td>Definition of Distant Metastasis (M)</td>
<td>M1 is subdivided into M1a and M1b.</td>
<td>II</td>
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<tr>
<td>AJCC Prognostic Groups</td>
<td>Stage III is subdivided into IIIA and IIIB.</td>
<td>II</td>
</tr>
<tr>
<td>AJCC Prognostic Groups</td>
<td>Stage IV is subdivided intoIVA and IVB.</td>
<td>II</td>
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8th Edition AJCC TNM Staging for Bladder Cancer

- No changes in the actual T stage categories, however, the AJCC:
  1. Recommended T1 subcategorization (Level of evidence II).
  2. Clarified T staging schema for bladder cancer with prostatic stromal invasion.
  3. Recognized T staging approach for diverticular cancer of “skipping” T2.
- No official AJCC staging for urachal cancers nor urachal cancers be staged as bladder cancer.

pT1 Subcategorization

- Significant upstaging of (LP-invasive) pT1 tumors at RC with 48%-50% upstaged to ≥pT2 and 33% upstaged to ≥pT3 or pN+.
- Prognostic factors in pT1 tumors include grade, tumor size, CIS, multiplicity and recurrence.
- Subcategorization may stratify pT1 tumors in TURs:
  1. Histoanatomic approach
  2. Micrometric approach - 0.5 mm or other cut-offs
- The 2017 AJCC recommended attempting pT1 subcategorization, but acknowledged the need for optimization.

Histoanatomic pT1 Subcategorization

- Uses muscularis mucosae (MM) and/or vascular plexus layer as landmarks.
- 3-tiered:
  - Above (pT1a), into (pT1b) and below (pT1c).
- 2-tiered:
  - Above (pT1a) or below (pT1b).
- Estimated 5-year CSS
  - 88% in pT1a
  - 85% in pT1b (p=0.02)

>30 Histoanatomic pT1 subcategorization studies since 1990

<table>
<thead>
<tr>
<th>1990's</th>
<th>2000's</th>
<th>2010's</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younes et al. 1990</td>
<td>Kondylis et al. 2000</td>
<td>Orsola et al. 2010</td>
</tr>
<tr>
<td>Heus et al. 1994</td>
<td>Shehadi et al. 2000</td>
<td>Paino d'Ance et al. 2010⇑</td>
</tr>
<tr>
<td>Angulo et al. 1995</td>
<td>Bernardini et al. 2001</td>
<td>Birmo et al. 2013</td>
</tr>
<tr>
<td>Smids et al. 1998</td>
<td>Andius et al. 2007</td>
<td>Cher et al. 2012⇑</td>
</tr>
</tbody>
</table>

- Varying end points – progression, recurrence, overall survival, disease-specific survival

Histoanatomic pT1 Subcategorization

- Largest study (6 centers) divided 587 TURs into pT1a (66%)/pT1b (34%).
- pT1b independently associated with RFS, PFS and CSS.
- In the only prospective study by Orsola et al., pT1 substaging was an independent risk for progression (5.6% vs. 23.6%).
- In the study that accounted re-TUR staging by Patriarca et al., pT1 subcategorization was not predictive of recurrence (R).

(TURBT) ⇨ pT1 ⇨ Re-TURBT ⇨ pT1 a/b ⇨ NS diff in R
(current management for pT1)


Histoanatomic pT1 Subcategorization in 31 Studies

• Overall, pT1 subcategorization was feasible or assessable in 43%-100% (median 93%) of the tumors.
• Overall, pT1 subcategorization predictive of outcome in 68% of the studies (48% by multivariate and 19% by univariate).
• Varying feasibility, technical difficulties and inconsistent prognostic ability may be attributed, at least in part, to the structural variations of the lamina propria layer.

Lamina Propria Histoanatomic Variances

• MM layer discernable (discontinuous and near-continuous) in ~40% cystectomy sections; least seen in trigone.
• Disposition of vascular plexus may vary.


Micrometric pT1 Subcategorization: 0.5 mm or 1 HPF cut-off

• Divides pT1 into pT1<0.5 mm and pT1>0.5 mm or as referred by van der AA et al. as pt1m (for microinvasive) or pt1e (for extensive).
• Multifocal (>1 foci) invasion or invasion by tumor areas that would not fit within 1 HPF also regarded as pT1e.


• Decreasing cut-off criteria for “microinvasive” urothelial carcinoma proposed over the years

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farrow et al.</td>
<td>1976</td>
<td>5 mm from basement membrane</td>
</tr>
<tr>
<td>Amin et al.</td>
<td>1997</td>
<td>2 mm from basement membrane</td>
</tr>
<tr>
<td>Lopez-Beltran et al.</td>
<td>2002</td>
<td>&lt;20 invading cells from the stromal-epithelial interface</td>
</tr>
<tr>
<td>van der AA et al.</td>
<td>2005</td>
<td>0.5 mm (1 HPF or 40X obj.) parallel to overlying neoplastic urothelium</td>
</tr>
</tbody>
</table>

• Other cut-offs, but with fewer studies:
  1. 1 mm (X200 field)
  2. 1.5 mm
  3. Depth (3 mm) and diameter (6 mm)
  4. Aggregate dimension of invasion (5 mm)

• Depth and variations of lamina propria should be factored in implementation and future proposals for pT1 subcategorization.

Micrometric pT1 Subcategorization: Other Cut-offs

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>n</th>
<th>Feasibility</th>
<th>pT1&lt;0.5 mm</th>
<th>pT1&gt;0.5 mm</th>
<th>FF-up, months</th>
<th>Significant</th>
<th>Significant Cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>van der AA et al</td>
<td>2005</td>
<td>53</td>
<td>100%</td>
<td>45/56</td>
<td>55/44</td>
<td>Median 55</td>
<td>Yes, Multi</td>
<td>P</td>
</tr>
<tr>
<td>Bertz et al.</td>
<td>2011</td>
<td>309</td>
<td>100%</td>
<td>38/62</td>
<td>40/47</td>
<td>Median 77</td>
<td>Yes, Multi</td>
<td>R, P</td>
</tr>
<tr>
<td>Van Rhijn et al.</td>
<td>2012</td>
<td>134</td>
<td>100%</td>
<td>30/70</td>
<td>Median 77</td>
<td>Yes, Multi*</td>
<td>P, DSS</td>
<td></td>
</tr>
<tr>
<td>Chang et al.</td>
<td>2012</td>
<td>609</td>
<td>100%</td>
<td>35/65</td>
<td>63/37</td>
<td>Median 81/39</td>
<td>Yes, Multi*</td>
<td>R, P, DSS, OS</td>
</tr>
<tr>
<td>Nishiyama et al.</td>
<td>2013</td>
<td>79</td>
<td>100%</td>
<td>53/47</td>
<td>Median 74</td>
<td>Yes, Uni</td>
<td>R, P</td>
<td></td>
</tr>
<tr>
<td>Di Marco et al.</td>
<td>2014</td>
<td>68</td>
<td>100%</td>
<td>30/70</td>
<td>Median 114</td>
<td>Nu*</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Patriarca et al.</td>
<td>2016</td>
<td>314</td>
<td>100%</td>
<td>35/65</td>
<td>Median 44</td>
<td>Nu*</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

* 5 studies also applied histoanatomic subcategorization in the same cohort - only 1 histoanatomic study had significant association to outcome.

P, progression; R, recurrence; DSS, disease-specific survival; OS, overall survival; NS, non-significant
Validation Studies for Exclusion of Intraurethral PSI from pT4a

- Intraurethral PSI compared to pT4a had:
  - Lower rates of LN+ (14.6% vs. 81.2%, p<0.001) and SM+ (18.7% vs. 61.2%, p<0.001).
  - Better OS (64 mos vs. 84 mos, p<0.001) and CSS (not achieved vs. 16.5 mos, p<0.001).
- 48 patients with intraurethral PSI
- 49 patients with transurethral PSI
- Median follow-up 12.8 mos


Bladder Cancer with Prostatic Stromal Invasion (PSI)

- Involvement of prostate occurs in 13%-29% of bladder cancers.
- PSI occurs via 2 routes: intraurethral and transmural.
- Several studies have shown that intraurethral PSI has better survival than transmural PSI.
- The 2010 AJCC excluded intraurethral PSI from pT4a, but with no specification on how to categorize.


Validation Studies for Exclusion of Intraurethral PSI from pT4a

- Intraurethral CIS (pTis), intraurethral PSI (pT2) and pT4a had 5-year CSS of 73%, 57% and 21%, respectively (p<0.001).

Knoedler et al. BJU Int 2014;114:832.
Bladder Cancer with Prostatic Stromal Invasion (PSI)

- The 2017 AJCC clarified that intraurethral PSI should be staged as pT2 (per urethral cancer staging) and bladder proper tumor given a separate pT stage (per bladder cancer staging).

- 65 yo M had TURBT
- MP-invasive CA (at least pT2)
- Residual LP-invasive CA in Bladder
- Intraurethral PSI

Cystoprostatectomy

Should We Stage Prostatic Stromal Invasion with Concomitant Bladder in TURP?

- Some transmural PSI may not be visualized by cystoscopy.
- In 2008 ENUP survey, 74% of pathologists would assign pT4a to PSI in TUR specimens.
- In TUR prostate chips, we recommend not to automatically stage PSI, unless transmural extension is clinically detected (pT4a).
- Explain that in the absence of transmural spread, PSI should be staged as (at least) pT2 based on urethral cancer staging. Presence of transmural spread qualifies the tumor as pT4a bladder cancer.

Irregular Outer Muscularis Propria Boundary

- Boundary between MP and perivesical tissue not well-delineated, complicating distinction between pT2b and pT3a.
- Current oncology guidelines and clinical trials consider giving adjuvant chemotherapy for bladder cancer with at least microscopic perivesical tissue invasion (pT3a).
- Accuracy in distinction of pT2b vs. pT3a important.
- Studies investigating outcome of pT2b and pT3a has so far been showing conflicting results.

How to define the outer MP boundary?

- We asked 17 expert GU pathologists to stage 20 difficult or ambiguous pT2b/pT3a cases, and agreement was only fair (κ=0.281).
- The study calls for use of a common criterion in defining the outer bounder of MP layer.

pT3a/b Subcategorization – Impact of Gross Prosector

- Several large and multi-institutional studies have shown poorer outcome of pT3b (macroscopic perivesical tissue involvement [PVTI]) over pT3a (microscopic).
- Staging relies on the meticulousness of the prosector’s inspection and documentation:
  - Inconsistent documentation or undersampling of PVTI leads to understaging.
  - Overestimation of reactive changes and inflammation may lead to overstaging.
- Awareness of the importance of gross exam
- pT3 subcategorization should be made with gross-histologic correlation.
Staging in the Setting of Cancer in a Bladder Diverticulum

- Tumors involving diverticulum comprise 0.8-10.8% of bladder tumors.
- Vast majority of bladder diverticulum in adults are acquired and lacks a consistent MP layer in its wall.
- Thus, diverticular cancer has no pT2.
- The 2017 AJCC now officially recognizes the approach of “skipping” pT2 in diverticular cancer staging.

In the study by Golijanin et al. of 39 diverticular tumors, significant differences were observed in 5-year CSS of pTis/pTa (83%), pT1 (67%) and pT3 (45%) tumors.
- It is thought that the lack of MP in diverticular wall may facilitate invasion and confers poor outcome.
- However, data so far on outcome is limited.
- Hu et al. compared bladder cancer patients with and without diverticular involvement and showed NS difference in OS and RFS on MVA.

Perivesical Lymph Nodes

- Perivesical LNs can be identified around the bladder (16%-47% of cystectomies) and involved in its primary lymphatic drainage.
- Usually not excised separately by the surgeons and identification in cystectomy specimens relies on the pathologists.
- Can be positive in 3%-16% of radical cystectomies and confers worse prognosis.
- Bella et al. showed that perivesical LN+ is an independent predictor of OS (p=0.016) and DSS (p=0.25).

Number of Lymph Nodes

- Total number of resected LNs is associated with improve outcomes in patient undergoing radical cystectomy.
- Total number of LN+ is an independent predictor of worse oncologic outcome.
- The 2017 AJCC recommends that total number of resected LNs and number of LN+ be reported (Level of Evidence II).
- Excision of primary nodal regions should result in an average of >12 LNs.
- Optimal number of LNs for diagnosis and therapeutic benefit has yet to be defined.
- Improved LN counts correlate with submission of separate LN packets or specimens for pathological assessment.

Limited vs. Extended Pelvic Lymphadenopathy

- Two current prospective randomized radical cystectomy trials:
  1. German Urologic Oncology Group (AUO)*
     - Observed a trend but no significant difference toward improved RFS and CSS with an extended pelvic lymphadenopathy.
  2. SWOG (NCT01224665)
     - ??? Almost finishing enrollment.

* Gschwend et al. ASCO 2016 (abstract)
Visceral or Bone Metastasis

- Presence of **visceral metastasis** independently predicts poorer outcome in patients with metastatic or unresectable bladder cancers, including in those treated with systemic chemotherapy (GC or MVAC).
- Patients with metastasis limited to LNs have significant better outcome than patients with visceral or bone metastasis.
- ~10% experience complete radiologic response after systemic chemotherapy.
- Undefined fraction may be long-term survivors with or without additional primary tumor therapy.

**References:**

**Visceral or Bone Metastasis**

- Large (n=405) prospective randomized trial of GC vs. MVAC for locally advanced (pT4a, N2, N3) or metastatic (M1) bladder cancer by Von der Maase et al.
  - Patients without visceral metastasis to bone, liver or lung had median survival of 18.4 months and 5-year survival rate of 20.9%.
  - Patients with visceral metastasis had median survival of 10.3 months and 5-year survival rate of 6.8%.
- The 2016 AJCC now classifies LN+ beyond the common iliac as M1a and all other metastasis as M1b.

**8th Edition AJCC TNM Staging for Urethral Cancer: Summary of Changes**

1. In urothelial carcinoma of the prostate: previous Tis pu and Tis pd) collapsed into Tis: CIS involving prostatic urethra, periurethral or prostatic ducts and acini without stromal invasion.
2. For urothelial carcinoma of the prostate: T1 category is defined as tumors invading subepithelial connective tissue of prostatic urethra.
3. Extension of urethral cancer to the bladder proper classified as T4

**8th Edition AJCC TNM Staging for Urethral Cancer: Summary of Changes**

4. N1: Single regional LN metastasis in the inguinal region or true pelvis [perivesical, obturator, internal (hypogastric) and external iliac], or presacral LN
5. N2: Multiple regional LN metastasis in the inguinal region or true pelvis [perivesical, obturator, internal (hypogastric) and external iliac], or presacral LN

**Thank you**