Difficult Issues in NMIBC: Guidelines and Beyond

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Relevant Disclosure and Resolution

Under Accreditation Council for Continuing Medical Education guidelines disclosure must be made regarding relevant financial relationships with commercial interests within the last 12 months.

Michael S. Cookson

I have no relevant financial relationships with commercial interests to disclose.
Gap 1: Clinicians are unfamiliar with variant histology and risk stratification for patients with non-muscle invasive bladder cancer (NMIBC).

Gap 2: Understanding risk stratification is important not only for predicting that tumor recurrence and progression, but also for treatment recommendations that may alter the natural history of NMIBC.

Gap 3: Failure to describe and incorporate the AUA Guidelines for NMIBC into clinical practice may result in tumor under staging, delay in treatment, under treatment and potential for worse patient outcomes.
Learning Objectives

Upon completion of this session, participants will improve their competence and performance by being able to:

1. Identify the importance of variant histology and risk stratification in the management of patients with non-muscle invasive bladder cancer.

2. Defend the use and importance of a complete bladder tumor resection and repeat TUR for patients with high-risk non-muscle invasive bladder cancer.

3. Describe the benefits of perioperative, induction and maintenance intravesical therapies based on patient risk stratification.

4. Identify the diagnostic modalities that enhance detection of bladder cancer.
### Recurrence and Progression: NMIBC

- **Risk stratification after TURBT**

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Approximate probability of recurrence in 5 years (%)</th>
<th>Approximate probability of progression to muscle invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ta, low grade</td>
<td>50</td>
<td>Minimal</td>
</tr>
<tr>
<td>Ta, high grade</td>
<td>60</td>
<td>Moderate</td>
</tr>
<tr>
<td>T1, low grade (rare)</td>
<td>50</td>
<td>Moderate</td>
</tr>
<tr>
<td>T1, high grade</td>
<td>50-70</td>
<td>Moderate-High</td>
</tr>
<tr>
<td>CIS</td>
<td>50-90</td>
<td>High</td>
</tr>
</tbody>
</table>

EAU Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and CIS). European Association of Urology 2017
Guidelines: Risk Stratification

• 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

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

• AUA/SUO Additions → Lymphovascular invasion (LVI), prostatic urethral involvement, variant histology, poor response to BCG
<table>
<thead>
<tr>
<th><strong>Low Risk</strong></th>
<th><strong>Intermediate Risk</strong></th>
<th><strong>High Risk</strong></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(^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
Guidelines: Variant Histology

• An experienced GU pathologist should review pathology with regards to variant or suspected variant histology (micropapillary, nested, plasmacytoid, neuroendocrine, squamous or glandular differentiation) (Moderate Recommendation; Evidence Strength: Grade C)

• If a bladder sparing is considered with variant histology, then a restaging TURBT within four to six weeks of the initial TURBT (Expert Opinion)

• Due to the high rate of upstaging associated with variant histology, consider initial radical cystectomy. (Expert Opinion)
Variant Histology

- Variant histology: 7,500–18,000 cases/year
- 10%-25% of cases
- Discordance between TUR and Cystectomy (39-47%)
- ~ 44% of variants not recognized by community pathologists
- In decreasing order of frequency of missed diagnosis:
  - Lymphoepithelial > plasmacytoid > nested variant > micropapillary > small cell histology

Abd El-Latif et al, J Urol 2013
Shah RB et al, Urol Onc 2012
Why Histologic Variants Matters

• Many retrospective studies suggest that variant histology portends **worse outcomes**
• Higher propensity of **locally advanced** disease
• Greater degree of **lymph node metastasis**
• Upstaging at radical cystectomy: HR 2.77
• Different responses to therapy – BCG, chemotherapy or radiotherapy

Wasco et al, J Urol, 2007; Domanowska, Human Pathology, 2007; Turker et al, BJUI, 2012; Kassouf, Urology, 2009; Willis, J Urol, 2014
Early Radical Cystectomy Associated with Improved Disease-specific Survival

Upfront Cystectomy (n=36) versus Primary BCG (n=40)

$\begin{align*}
\text{Upfront Cystectomy vs. BCG} \\
\text{Disease Specific Survival} \\
\text{0.0} \quad \text{0.2} \quad \text{0.4} \quad \text{0.6} \quad \text{0.8} \quad \text{1.0} \\
\text{0} \quad \text{50} \quad \text{100} \quad \text{150} \quad \text{200} \\
\text{5y-DSS 100%} \\
\text{5y-DSS 60%} \\
\text{p=0.006}
\end{align*}$

Willis, ... Kamat et al, J Urol, 2015
MSKCC Series with MP Variant

- N = 36; F/U: 3 years
- All negative on reTUR
- 5-year DSS
  - BCG: 75% vs 83% with cystectomy, p = 0.8
- Metastatic rate at 5 years
  - BCG: 34% vs 21% with cystectomy, p = 0.9
- Authors concluded: Conservative mgt with BCG “acceptable”

Micropapillary Bladder Cancer clusters with Luminal Type Urothelial Carcinoma

Guidelines: Repeat TURBT

• With an incomplete initial resection, a repeat TUR of all remaining tumor should be done
  (Strong Recommendation; Evidence Strength: Grade B)

• In high-risk, high-grade Ta tumors, consider repeat TUR within six weeks of the initial TURBT
  (Moderate Recommendation; Evidence Strength: Grade C)

• In T1 disease, repeat TUR of the primary tumor site to include muscularis propria within six weeks of the initial TURBT
  (Strong Recommendation; Evidence Strength: Grade B)
Repeat TURBT in T1 Tumors: RCT

Number of pts recurring is HIGHER for NO Repeat TUR

NO Repeat TUR group with WORSE progression-free survival  \( p = 0.0001 \)

Randomized T1 cohort of 210 patients

Who Should Undergo Repeat TUR?

• Incomplete resection of tumor
  – any low or high grade NMIBC
• Should with *any* high grade Ta tumor
• Must with bladder conservation
  – T1 tumors
  – Variant histology
Guidelines: Single Instillation therapy

- With low or intermediate risk, consider a single post-op instillation of IVe chemotherapy (e.g., mitomycin C) within 24 hours of TURBT

- In case of suspected perforation or extensive resection, you should NOT use post-op chemotherapy
  (Moderate Recommendation; Evidence Strength: Grade B)
Guidelines: Single Instillation therapy

- With low or intermediate risk disease, should consider a single post-op instillation of IVe chemotherapy (e.g., mitomycin C or epirubicin) 24 hours of TURBT

- In case of suspected perforation or extensive resection, you should NOT use post-op chemotherapy (Moderate Recommendation; Evidence Strength: Grade B)
Caveats

• Best studied: Mitomycin C and Epirubicin

• Dwell Time: ~ 2 hours

• Administration: Within 24 hours

• Selection: single, small, low-grade tumors
Side Effects and Complications

• Most common:
  – LUTS: dysuria, frequency, urgency
  – Dystrophic calcifications

• Feared complication:
  – Frozen pelvis: several case reports

• If uncertainty regarding integrity of bladder, do not give
New Data: SWOG S0337

A Phase III Blinded Study of Immediate Post-TURBT Instillation of Gemcitabine vs. Saline in Patients with Newly Diagnosed or Occasionally Recurring Grade I/II Superficial Bladder Cancer

- 345 patients
- Gemcitabine (2 grams/100cc of saline) vs. saline
- Dwell time: 60 minutes
- Side effect profiles: no differences
- Only 62% had the correct pathology (low grade disease) for installation, noting the limits of cystoscopy in assessment by urologists of tumor grade

Messing EM, et al. JAMA. 2018;319(18):1880
Suspected LG NMIB UC

RANDOMIZE
To Blinded Treatment

Two Stratification Factors:
Disease status: 1st occurrence vs. recurrent
Tumor site: 1 vs. 2+

Treatment to start within 28 working days

TURBT + Gem
(2 gm/100 cc saline)

Follow for 4 yrs

TURBT + Saline (100 cc)

Follow for 4 yrs

Messing EM, et al. JAMA. 2018;319(18):1880
S0337 Results

Time to Recurrence, ITT
All Eligible, Randomized Patients

- **Gemcitabine**
  - At Risk: 201
  - Event: 67
  - 4-Year Estimate: 64%

- **Saline Only**
  - At Risk: 205
  - Event: 91
  - 4-Year Estimate: 52%

Patients at Risk
- **Gemcitabine**: 201
- **Saline Only**: 205

Years from Randomization
- 0
- 2
- 4
- 6
SWOG S0337 – Summary

- Gemcitibine reduces recurrence of LG NMIBC by 47%
  - HR = 0.53 (95% CIs 0.35 – 0.81) (p = 0.003)
    (54% [S] → 34% [G])
- Safe, well tolerated, readily available
- No adverse outcomes for HG NMI UC
- New standard for suspected LG NMI UC

- Personal Comment on Cost:
  - Gemcitabine is significantly more cost effective than Mitomycin-C
  - $36.90 vs. $1068.00

Messing EM, et al. JAMA. 2018;319(18):1880
Guidelines: Induction Intravesical Therapy

• In a low-risk, you should NOT administer induction intravesical therapy (Moderate Recommendation; Strength of Evidence Grade C)

• In intermediate-risk, you should consider a six week course of induction intravesical chemotherapy or BCG (Moderate Recommendation; Evidence Strength: Grade B)

• In a high-risk patient with CIS, HG T1, or HG Ta UCC, you should administer a six-week induction course of BCG (Strong Recommendation; Evidence Strength: Grade B)
Guidelines: Maintenance Intravesical Therapy

• In an **intermediate-risk** patient who completely responds to an induction course of IVe chemotherapy, *maintenance* therapy may be used (Conditional Recommendation; Evidence Strength: Grade C).

• In an **intermediate-risk** patient who completely responds to induction BCG, you should consider maintenance BCG for **one year** (Moderate Recommendation; Evidence Strength: Grade C).

• In a **high-risk** patient who completely responds to induction BCG, you should continue maintenance BCG for **three years** (Moderate Recommendation; Evidence Strength: Grade B).
Enhanced Technologies to Detect Bladder Cancer

- Narrow Band Imaging
- Fluorescence Cystoscopy

- Others not discussed today:
  - Optical Coherence Tomography
  - Confocal Laser Scanning Microscopy
Narrow Band Imaging™ (NBI)

- Olympus Optical imaging technology enhances visibility of vessels on mucosa.
- Filters white light into wavelengths that penetrate only surface and are absorbed by hemoglobin.
- Bluish light enhances superficial capillary network (brown)
- Greenish light enhances deeper vessel visibility: vessels are greenish-blue (cyan)

Cauberg EC et al. Urol 76: 658, 2010
Detection and Recurrence with NBI

- Results indicated that NBI increased NMIBC detection by 9.9% at the per-patient and 18.6% at the per-lesion

How Blue Light Works

• After instillation, Hexvix bypasses cellular regulation mechanisms for heme synthesis

• Leads to selective accumulation of Protoporphyrin IX (PpIX) in neoplastic cells due to increased mitotic rate

• Levels up to 10X greater in tumors than in normal tissue

Blue Light Cystoscopy with Cysview

Cysview Components & KARL STORZ D-Light C PDD System

Cysview Kit Includes:
- One 100 mg vial of Cysview powder (hexaminolevulinate HCL)
- One 50 mL diluent for Cysview
- One Luer Lock catheter adapter

KARL STORZ D-Light C PDD System:
- Tricam SLII Camera Head
- PDD Telescopes
- Fluid Light Cable
- PDD Camera Control Unit
- PDD Light Source
U.S. Pivotal Study – Recurrence Results

- Tumor recurrence rates over 9 months were
  - 47% with Cysview
  - 56% with white light (p=0.026)

- Relative reduction in recurrence rate was 16%

Stenzl A et al. J Urol 2010
Burger M et al. EAU 2012
## Blue Light Cysto: Impact on Recurrence

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients treated with BL, n (%)</th>
<th>Patients treated with WL, n (%)</th>
<th>Total</th>
<th>Follow-up period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herman et al.</td>
<td>27/68 (39.7%)</td>
<td>38/77 (49.4%)</td>
<td>145</td>
<td>12 months</td>
</tr>
<tr>
<td>Stenzl et al.</td>
<td>72/200 (36.0%)</td>
<td>92/202 (45.5%)</td>
<td>402</td>
<td>9 months</td>
</tr>
<tr>
<td>Dragoescu et al.</td>
<td>8/42 (19.0%)</td>
<td>17/45 (37.8%)</td>
<td>87</td>
<td>12 months</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>107/310 (34.5%)</strong></td>
<td><strong>147/324 (45.4%)</strong></td>
<td><strong>634</strong>*</td>
<td><strong>p=0.006; RR=0.761 (0.627-0.924)</strong></td>
</tr>
</tbody>
</table>

- **At least on T1 or CIS**
  - Herman et al.: 26/74 (35.1%) vs. 48/87 (51.7%)
  - Stenzl et al.: 72/200 (36.0%) vs. 92/202 (45.5%)
  - Total: 161*; p=0.052; RR=0.696 (0.482-1.003)

- **At least one Ta**
  - Herman et al.: 46/126 (36.5%) vs. 70/144 (48.6%)
  - Total: 524*; p=0.040; RR=0.804 (0.653-0.991)

- **High-risk subgroup**
  - Herman et al.: 43/95 (45.3%) vs. 40/74 (54.1%)
  - Total: 524*; p=0.029; RR=0.561 (0.334-0.944)

- **Inter.-risk subgroup**
  - Herman et al.: 14/78 (17.9%) vs. 34/98 (34.7%)

- **Low-risk subgroup**

**Rate of recurrence is reduced by 10.9% p= <0.006**

Guidelines: Enhanced Cystoscopy

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

- In a patient with NMIBC, you may consider use of NBI to increase detection and decrease recurrence
  (Conditional Recommendation; Evidence Strength: Grade C)
Take Home Messages

• Importance of Risk Stratification/Recognition of Variant Histology
• Value of repeat TUR
  – High Grade Ta, any T1, Variant Histology
• Single Postop Dose of Chemotherapy
  – Low Grade Ta (consider Gemcitabine)
• Use of Maintenance BCG
  – 1-yr for int. risk, 3-yrs for high risk
• Judicious Use of Technology: Blue Light, NBI