Looking Ahead:
Advances in the Treatment of Non-Invasive Urothelial Cancer

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Disclosures

• Funding
  – AHRQ K08 grant
  – PCORI Engagement Award
Outline

• Biomarkers
• Technology
• Surgery
• New Trials
  – Lower Tract Urothelial Cancer
  – Upper Tract Urothelial Cancer
Biomarkers

• AUA & EAU only recommend cytology
• FISH (UroVysion) with some benefits, in very specific situations, but not incorporated into guidelines
# Summary of Urinary Markers

<table>
<thead>
<tr>
<th>Markers</th>
<th>For Symptom Evaluation</th>
<th>For Surveillance</th>
<th>Point-of-Care?</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall sensitivity (%)</td>
<td>Overall specificity (%)</td>
<td>Overall sensitivity (%)</td>
<td>Overall specificity (%)</td>
</tr>
<tr>
<td>UroVysion</td>
<td>73%</td>
<td>95%</td>
<td>55%</td>
<td>80%</td>
</tr>
<tr>
<td>Immunocytc/ uCyt+</td>
<td>85%</td>
<td>83%</td>
<td>75%</td>
<td>76%</td>
</tr>
<tr>
<td>CxBladder</td>
<td>82%</td>
<td>85%</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>NMP22 (qualitative)</td>
<td>58%</td>
<td>93%</td>
<td>70%</td>
<td>83%</td>
</tr>
<tr>
<td>NMP22 (quantitative)</td>
<td>67%</td>
<td>84%</td>
<td>61%</td>
<td>71%</td>
</tr>
<tr>
<td>BTA stat (qualitative)</td>
<td>76%</td>
<td>78%</td>
<td>60%</td>
<td>76%</td>
</tr>
<tr>
<td>BTA Trak (quantitative)</td>
<td>76%</td>
<td>53%</td>
<td>58</td>
<td>79%</td>
</tr>
</tbody>
</table>

AHRQ Review, Diagnosis & Treatment of NMIBC, 2015
Biomarker Comparisons

- No difference between quantitative or qualitative NMP22
- ImmunoCyt higher sensitivity than FISH
- Cytology + biomarkers more sensitive than biomarker alone (no difference in specificity)
- Variety of other studies too small to conclude performance
Biomarkers: Bottom Line

No study has evaluated effectiveness of urinary biomarkers to decrease mortality or improve outcomes compared with standard diagnostic methods.
<table>
<thead>
<tr>
<th>Study</th>
<th>Cytology</th>
<th>FISH</th>
<th>n=</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reynolds, Ca Cytopath (2014)</td>
<td>38%</td>
<td>89%</td>
<td>43%</td>
<td>84%</td>
</tr>
<tr>
<td>Xu, Urol (2011)</td>
<td>45%</td>
<td>100%</td>
<td>79%</td>
<td>98%</td>
</tr>
<tr>
<td>Mian, EU (2010)</td>
<td>21%</td>
<td>97%</td>
<td>100%</td>
<td>90%</td>
</tr>
<tr>
<td>Johannes, JU (2010)</td>
<td>18%</td>
<td>100%</td>
<td>54%</td>
<td>78%</td>
</tr>
<tr>
<td>Luo, Ca Gen Cyto (2009)</td>
<td>24%</td>
<td>--</td>
<td>86%</td>
<td>--</td>
</tr>
<tr>
<td>Marin-Aguilera, EU (2007)</td>
<td>36%</td>
<td>100%</td>
<td>77%</td>
<td>95%</td>
</tr>
</tbody>
</table>
Enhanced Cystoscopy

- Blue Light
  - 5-ALA
  - Cysview/Hexvix
- Narrow Band Imaging
5-Aminolevulinic Acid

- IV injection
- Accumulates in urothelial cancers
- Absorbs & emits light at specific wavelengths
- Side Effects: skin photosensitivity
- Topical applications attempted
  - Enhanced detection for initial TUR
  - Improved recurrence rates
  - Improved recurrence-free survival
Hexaminolevululinate (HAL)

- Hexyl ester derivative of 5-ALA
- Increased potency
  - Lipophilic
  - Tissue soluble
- Decreased instillation time
- Decreased recurrence for short, intermediate and long-term follow-up
- No difference in progression or mortality

AHRQ Review, Diagnosis & Treatment of NMIBC, 2015
Blue Light Cystoscopy: Benefits

• Decreased recurrence
• Cost savings $\rightarrow$ fewer TURs
• Estimated at $250$/patient over 7 year follow-up

Dansk, Fut Oncol 2016
Rose, BJUI 2016
Witjes, EU 2014
Blue Light Cystoscopy: Obstacles

• High false-positive rate\(^1\text{-}^3\)
  – 10-50%
  – Recent TUR
  – Prior BCG
  – Inflammation
  – Can depend on surgeon experience
• Inability to use with hematuria
• Access to technology

\(^1\)Stenzl, JU 2010
\(^2\)De Dominicis, Urol 2001
\(^3\)Geavlete, BJU 2012
Narrow Band Imaging

- Filtered white light into 2 wavelengths
  - 415 (blue)
  - 540 (green)
- Capitalizes on peak absorption of hemoglobin
- Accentuates vascular architecture of bladder tumors (compared to normal urothelium)
- Does not require instillation agent
- Avoids time delay and cost of agent
NBI: Detection & Recurrence

- Less evidence than blue light
- Better detection than WL (≈33%)
- Lower risk of recurrence at 3 and 12 months compared with WL
- False positives ≈33%
Enhanced Endoscopy: UTUC

- Hexvix
  - Minimal experience in upper tract
- SPIES (Storz)
  - No upper tract data
- NBI
  - WL and NBI in 27 patients (same urologist)
  - NBI improved visual accuracy
  - Increased detection by 23%

Traxer, Int Braz J Urol, 2011
Kamphuis, App J Endoruol 2016
High Frequency Endoluminal US

- May have a role for better staging of UTUC
  - Mechanically rotating transducer 5Fr
  - Passed over wire after initial ureteroscopy
  - 20 MHz frequency in B-mode; axial image
  - Depth range 1-6cm, best images at 2-3cm

- Prediction of invasive disease (n=7)
  - PPV = 66.7%
  - NPV = 100%

Matin, J US Med 29(9), 2010
Optical Coherence Tomography

- 1300nm near-infrared light
- Uses working channel of flexible, semi-rigid or rigid URS
- Excellent visualization of anatomic tissue layers
  - Helpful to assess stage, depth invasion

Hermes 2008, Optics express
OCT combined with ELUS
On the Horizon…

- Cysview Flex Trial (*Photocure*)
- Oncolytic vectors (CG0070) (*Cold Genesys, Inc.*)
- rAd-IFN (Instiladrin) (*FKD Therapies Oy*)
- HS-410 (*Heat Biologics*)
- Mitogel (*Urogen*)
Cysview Flex Trial

• Primary Objective
  – Compare BL and WL cysto in detection of bladder cancer during surveillance

• Secondary Objectives:
  – Assess efficacy and safety of BL with Cysview after repetitive use
  – Compare BL with WL in detection of CIS
Cysview Flex Trial: Patient Selection

- Patients with NMIBC in follow-up for tumor recurrence
  - Enroll at first surveillance cysto after a histologically confirmed tumor
- Intermediate to high risk NMIBC
  - History of multiple tumors
  - Recurrent tumors (low grade)
  - High grade tumors
Cysview Flex Trial: Trial Design

- Patient assessed with white light (WL), then randomized to blue light (BL) or nothing
- If suspicious for recurrence \( \rightarrow \) OR
  - Cysview administered
  - Lesions mapped by WL and BL
  - Biopsies performed
- Follow-up after pathology returned
  - Assess bladder function
  - Additional patient-reported outcomes
Cysview Flex Trial: Status Update

• Open to accrual at 12 sites
• Accrual
  – 16 at UNC
  – 114 overall
BOND2 (CG0070) Trial

• Adenovirus preferentially replicates, kills cancer cells
• Upregulated in Rb-pathway defective tumor cells (85% of cancers)
• Delivered with DDM agent
  – Dwell time 45-50 minutes with 4 positions
• Toxicities:
  – LUTS, arthralgia/myalgias, flu-like symptoms
Oncolytic Vector CG0070

- Single arm Phase II multicenter study
  - Safety & efficacy
- Patients with high grade NMIBC who have failed BCG and refuse cystectomy
- Given once/week for 6 weeks
  - If down-staged, down-graded or complete response, offered same regimen for 6 weeks every 6 months until month 18
Oncolytic Vector CG0070: Status Update

- Estimated primary collection 6/2017
- Estimated study completion in 6/2019
Instiladrin (rAd-IFN)

- Gene-based therapy to improve delivery of (and prolong exposure) of NMIBC cells to IFN-alfa2b
  - Patients with CIS, HGTa, HGT1
  - BCG unresponsive
- Phase I and II trials confirmed safety & efficacy
  - Well-tolerated with minimal AEs
  - 35% response rate in high grade refractory/relapsed BCG patients
Instiladrin (rAd-IFN) Phase III Trial

• Primary objective:
  – Evaluate incidence of recurrence-free survival at 12 months

• Secondary objectives:
  – Time to recurrence
  – Incidence/time to cystectomy
  – Overall survival
Instiladrin: Study Design

• Given as a single, one-hour intravesical administration
• May be repeated every 3 months up to maximum of 4 instillations
• Duration of study for each patients is up to 13 months but long-term survival data will be collected up to 3 years
Instiladrin: Status Update

• Approximately 40 study centers
• Plan to open at UNC in September
• Accrual target (overall) will be 135
HS-410

• Vaccine: vesigenurtacel-L (HS-410)
• Advantage is avoidance of intravesical delivery (intradermal injection)
• Since no treatment given in 6 weeks following BCG induction completion, may provide important window for continued immune stimulation
HS-410 Trial Design

- High risk NMIBC
- BCG-naïve (or prior BCG > 12 months)
- Induction:
  - 6 weeks of BCG + drug
  - 6 additional weekly injections of drug alone
  - Surveillance at week 13
- Subsequent maintenance:
  - 3 courses of 3 once/wk injection + BCG
HS-410 Phase II Trial

• Primary objective:
  – Evaluate 1-year recurrence free survival of vaccine and high-dose vaccine

• Secondary objectives:
  – Safety of combination with BCG
  – Recurrence & progression up to 24 months
  – Evaluate overall survival
  – Number of patients undergoing TURBT, fulguration or cystectomy
HS-410 Status Update

• Phase 2 complete
  – Last patient enrolled earlier this month
  – Long term follow-up for next 2-3 years
  – Monitor for recurrence

• Phase 3 may be on horizon
Mitogel

- Combines mitomycin C with TC-3 (a sterile hydrogel) allowing prolonged exposure to mitomycin C within upper urinary tract
- TC-3 turns into gel at room temperature, liquid when frozen
Mitogel Trial

• Primary objective
  – Evaluate tumor ablative effect of instillation of MitoGel in upper urinary tract of patients with UTUC

• Secondary objectives
  – Evaluate durability of tumor ablative effect
  – Evaluate safety & tolerability
MitoGel Preparation/Instillation

- Instillation performed in retrograde fashion (neph tube optional)
- MitoGel: 4mg MMC/mL TC-3 gel
- Injected volume individualized
  - Volumetric estimation using retrograde
MitoGel Trial Design

- Single-arm Phase III trial
- Confirmed LG non-invasive UTUC
- Treated with 6 week instillations of MitoGel
- Ureteroscopy 5 weeks after last instillation
MitoGel Status

• Performed compassionate use case at UNC
  – Some challenges but appeared to be effective
• Status: waiting for FDA approval; UNC plans to enroll