Efficient and Effective Use of Exfoliative Markers

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San Francisco, CA

Overview

- URINARY TUMOR MARKERS
  - Potential Uses
    - Screening
    - Diagnosis
    - Monitoring
  - Cost-Effectiveness
  - Future Directions

Urinary Tumor Markers

- Hemoglobin Dipstick
- Urinary Cytology
- BTA-STAT / BTA-TRAK
- NMP-22
- ImmunoCyt
- UroVysion

Hemoglobin Dipstick

- Point-of-Care
- Detects hematuria, hemoglobinuria, myoglobinuria
- 25 cents
- False positives occur for any GU source not due to bladder cancer
- Follow-up with microscopic evaluation of urine
  - Positive test ≥2 RBC’s/HPF on 2/3 specimen
**Urinary Cytology**

- Send out to cytopathologist
- Cost around $60-$100
- Often “equivocal”, “atypical”, or “suspicious”
- “Equivocal” or “Atypical” frequent during BCG

**BTA-STAT / BTA-TRAK**

- Point-of-Care (BTA-STAT)
- Send out ELISA (BTA-TRAK)
  - $>14$ U/mL positive
- Detects Human Complement H related protein
- $10-$15 BTA-STAT / $175$ BTA-TRAK
- Patients already diagnosed with bladder cancer
- Used in conjunction with cystoscopy
- Not for screening, patients with signs of active infections, patients who have received BCG

**NMP-22**

- Point of Care (BladderCheck)
- Send out ELISA (NMP22)
  - $>10$ U/mL positive
- Nuclear Matrix Apparatus Protein
- $10-$30 (BladderCheck) / $125-$150 (NMP22)
- Both initial diagnosis patients risk factors or symptoms and monitoring
- Not for screening, or use in patients catheters or stents, or after cystectomy

**ImmuNoCyt**

- Send out conjunction cytology
- Carcinoembryonic Antigen (CEA) and 2 bladder cancer specific mucins
  - Single red or green cell positive
- $130-$385
- Monitoring patients known bladder cancer along with cystoscopy
**UroVysion**

- Send out to specialized lab
- Fluorescence in situ hybridization detects aneuploidy chromosomes 3, 7, and 17 and loss of 9p21 locus
  - ≥4 cells gains 3,7,17 or ≥12 cells loss 9p21
- $475-$700
- Diagnosis in patients with hematuria or monitoring in patients with known bladder cancer
- Not for use when patient has known untreated tumor

**Comparison of Markers (2006)**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Mean Sensitivity</th>
<th>(range)</th>
<th>Mean Specificity</th>
<th>(range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb Dipstick</td>
<td>71%</td>
<td>(47%-93%)</td>
<td>67%</td>
<td>(51%-84%)</td>
</tr>
<tr>
<td>Cytology</td>
<td>48%</td>
<td>(28%-76%)</td>
<td>96%</td>
<td>(81%-100%)</td>
</tr>
<tr>
<td>BTA-STAT</td>
<td>65%</td>
<td>(53%-89%)</td>
<td>74%</td>
<td>(54%-93%)</td>
</tr>
<tr>
<td>BTA-TRAK</td>
<td>62%</td>
<td>(17%-78%)</td>
<td>74%</td>
<td>(51%-95%)</td>
</tr>
<tr>
<td>NMP22</td>
<td>68%</td>
<td>(31%-92%)</td>
<td>74%</td>
<td>(5%-94%)</td>
</tr>
<tr>
<td>ImmunoCyt</td>
<td>58%</td>
<td>(39%-86%)</td>
<td>79%</td>
<td>(73%-84%)</td>
</tr>
<tr>
<td>UroVysion</td>
<td>77%</td>
<td>(73%-81%)</td>
<td>98%</td>
<td>(96%-100%)</td>
</tr>
</tbody>
</table>

**Comparison (2010)**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Patients</th>
<th>Sensitivity</th>
<th>(95% CI)</th>
<th>Specificity</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>22,260</td>
<td>44%</td>
<td>(38%-51%)</td>
<td>96%</td>
<td>(94%-98%)</td>
</tr>
<tr>
<td>NMP22</td>
<td>13,885</td>
<td>68%</td>
<td>(62%-74%)</td>
<td>79%</td>
<td>(74%-84%)</td>
</tr>
<tr>
<td>ImmunoCyt</td>
<td>4,199</td>
<td>84%</td>
<td>(77%-91%)</td>
<td>75%</td>
<td>(68%-83%)</td>
</tr>
<tr>
<td>UroVysion</td>
<td>3,321</td>
<td>76%</td>
<td>(65%-84%)</td>
<td>85%</td>
<td>(78%-92%)</td>
</tr>
</tbody>
</table>

**Overview**

- Public Health and Economic Impact
- Urinary Tumor Markers
- Potential Uses
  - SCREENING
    - Diagnosis
    - Monitoring
- Cost-Effectiveness
- Future Directions
### Screening

- Dipstick Hematuria studies from the late 1980’s

<table>
<thead>
<tr>
<th>Patients</th>
<th>Dipstick + Bladder Ca</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Study</td>
<td>~1500</td>
<td>13%</td>
</tr>
<tr>
<td>UK Study</td>
<td>~600</td>
<td>17%</td>
</tr>
</tbody>
</table>

### Modern studies investigating markers

- Attempt identify higher risk groups
  - Age, smoking, occupational exposure

### Modern Studies


<table>
<thead>
<tr>
<th></th>
<th>Steiner</th>
<th>Lotan</th>
<th>Greene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>Dipstick</td>
<td>NMP22</td>
<td>Cytology</td>
</tr>
<tr>
<td>Positive Test</td>
<td>31%</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Urothelial Ca</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>PPV</td>
<td>5%</td>
<td>9%</td>
<td>10%</td>
</tr>
</tbody>
</table>

### Overview

- Public Health and Economic Impact
- Urinary Tumor Markers
- Potential Uses
  - Screening
  - DIAGNOSIS
  - Monitoring
- Cost-Effectiveness
- Future Directions

### Diagnosis

- Sensitivity/Specificity applicable same dz spectrum
- PPV/NPV only applicable same dz prevalence
- Posterior Odds = Prior Odds X LR

\[ LR (+) = \frac{\text{sensitivity}}{1 - \text{specificity}} \]

\[ LR (-) = \frac{1 - \text{sensitivity}}{\text{specificity}} \]

\[ \text{Prob} = \frac{\text{odds}}{(1 + \text{odds})} \quad \text{Odds} = \frac{\text{prob}}{(1 - \text{prob})} \]
### Diagnosis

- **Microscopic Hematuria -- Risk Bladder Ca ~3%**
- **Eliminate cystoscopy with negative test?**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>LR (-)</th>
<th>Post-Test Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb Dipstick</td>
<td>71%</td>
<td>67%</td>
<td>0.43</td>
<td>1.3%</td>
</tr>
<tr>
<td>Cytology</td>
<td>44%</td>
<td>96%</td>
<td>0.58</td>
<td>1.8%</td>
</tr>
<tr>
<td>BTA-STAT</td>
<td>69%</td>
<td>74%</td>
<td>0.42</td>
<td>1.3%</td>
</tr>
<tr>
<td>BTA-TRAK</td>
<td>62%</td>
<td>74%</td>
<td>0.51</td>
<td>1.6%</td>
</tr>
<tr>
<td>NMP22</td>
<td>68%</td>
<td>79%</td>
<td>0.41</td>
<td>1.2%</td>
</tr>
<tr>
<td>ImmunoCyt</td>
<td>84%</td>
<td>75%</td>
<td>0.21</td>
<td>0.7%</td>
</tr>
<tr>
<td>UroVysion</td>
<td>76%</td>
<td>85%</td>
<td>0.28</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

### Diagnosis

- **Gross Hematuria -- Risk Bladder Ca ~20%**
- **Eliminate cystoscopy with negative test?**

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<thead>
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<td>10%</td>
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<tr>
<td>Cytology</td>
<td>44%</td>
<td>96%</td>
<td>0.58</td>
<td>13%</td>
</tr>
<tr>
<td>BTA-STAT</td>
<td>69%</td>
<td>74%</td>
<td>0.42</td>
<td>9%</td>
</tr>
<tr>
<td>BTA-TRAK</td>
<td>62%</td>
<td>74%</td>
<td>0.51</td>
<td>11%</td>
</tr>
<tr>
<td>NMP22</td>
<td>68%</td>
<td>79%</td>
<td>0.41</td>
<td>9%</td>
</tr>
<tr>
<td>ImmunoCyt</td>
<td>84%</td>
<td>75%</td>
<td>0.21</td>
<td>5%</td>
</tr>
<tr>
<td>UroVysion</td>
<td>76%</td>
<td>85%</td>
<td>0.28</td>
<td>7%</td>
</tr>
</tbody>
</table>

### Monitoring

- **LG Ta -- Recurrence 1st yr is 37% (~9%/eval)**
- **Eliminate cystoscopy with negative test?**

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<thead>
<tr>
<th>Marker</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>LR (-)</th>
<th>Post-Test Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb Dipstick</td>
<td>8%</td>
<td>67%</td>
<td>1.37</td>
<td>12%</td>
</tr>
<tr>
<td>Cytology</td>
<td>12%</td>
<td>96%</td>
<td>0.92</td>
<td>8%</td>
</tr>
<tr>
<td>BTA-STAT</td>
<td>47%</td>
<td>74%</td>
<td>0.72</td>
<td>7%</td>
</tr>
<tr>
<td>BTA-TRAK</td>
<td>63%</td>
<td>74%</td>
<td>0.50</td>
<td>5%</td>
</tr>
<tr>
<td>NMP22</td>
<td>61%</td>
<td>79%</td>
<td>0.49</td>
<td>5%</td>
</tr>
<tr>
<td>ImmunoCyt</td>
<td>80%</td>
<td>75%</td>
<td>0.27</td>
<td>3%</td>
</tr>
<tr>
<td>UroVysion</td>
<td>45%</td>
<td>85%</td>
<td>0.05</td>
<td>0%</td>
</tr>
</tbody>
</table>

### Monitoring

- **HG Ta,T1,CIS -- Recurrence 1st yr is 55% (~14%/eval)**
- **With negative cysto positive marker require biopsy?**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>LR (+)</th>
<th>Post-Test Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb Dipstick</td>
<td>76%</td>
<td>67%</td>
<td>2.3</td>
<td>7%</td>
</tr>
<tr>
<td>Cytology</td>
<td>64%</td>
<td>96%</td>
<td>15.0</td>
<td>35%</td>
</tr>
<tr>
<td>NMP22</td>
<td>75%</td>
<td>75%</td>
<td>3.8</td>
<td>11%</td>
</tr>
<tr>
<td>ImmunoCyt</td>
<td>80%</td>
<td>75%</td>
<td>3.4</td>
<td>10%</td>
</tr>
<tr>
<td>UroVysion</td>
<td>91%</td>
<td>85%</td>
<td>6.1</td>
<td>17%</td>
</tr>
</tbody>
</table>

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*adapted from Lotan Urol 2003 and Lokeshwar Urol 2005*
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  - Screening
  - Diagnosis
  - Monitoring

COST-EFFECTIVENESS

- Future Directions

Cost-Effectiveness

- Closer to a “true” cost-effectiveness analysis – 2010
  - Cytology and cystoscopy least effective strategy
    - 11.59 year life expectancy
    - ~$30k per year of life saved
  - Cysto+ImmunoCyt followed PDD TURBT dx and cysto follow-up most effective strategy
    - 11.66 year life expectancy
    - ~$400k per year of life saved
- However, this still doesn’t involve patient perspective

Cost-Effectiveness

- Patient Perspective on Urinary Markers to Replace Cystoscopy
  - 102 patients UMC, The Netherlands
    - 89% prefer cysto over marker if sensitivity <90%
    - Males, older patients, fewer prior cystos, fewer recurrences associated lower accepted sensitivity
  - 200 patients MSKCC
    - 75% required accuracy of >95%
    - Males and >pain during procedure associated lower accepted accuracy

Lotan J Urol 2002

Mowatt Health Tech Asscn 2010

Overview

• Public Health and Economic Impact
• Urinary Tumor Markers
• Potential Uses
  • Screening
  • Diagnosis
  • Monitoring
• Cost-Effectiveness
• FUTURE DIRECTIONS

REFLEX TESTING

Lotan J Urol 2008

PROGNOSIS

Whitson BJUI 2009

EARLY DETECTION IVT FAILURE

Whitson Int Braz J Urol 2009

Table 2 – Ability of an immediate UroVysion™ to predict 6 week biopsy findings.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology (n = 35)</td>
<td>56%</td>
<td>83%</td>
<td>82%</td>
<td>68%</td>
</tr>
<tr>
<td>UroVysion™ (n = 35)</td>
<td>85%</td>
<td>61%</td>
<td>64%</td>
<td>85%</td>
</tr>
<tr>
<td>UroVysion™ (n = 35)</td>
<td>83%</td>
<td>73%</td>
<td>78%</td>
<td>85%</td>
</tr>
</tbody>
</table>

* adjusting for detection of upper tract and metastatic disease. PPV = positive predictive value. NPV = negative predictive value.
Conclusions

• Screening
  • Hard to find “high risk” group; Low PPV
  • No prospective study survival benefit

• Diagnosis
  • Microhematuria – marker negative no cysto?
  • Gross Hematuria – little role for markers

• Monitoring
  • Low Risk – ImmunoCyt?
  • High Risk – not significantly better cytology

• Cost-Effectiveness
  • Lack of data particularly re: patient preferences

References (cont.)


