The Future of Biomarkers for BC: Evidence, Efficacy and Expense

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How to improve BC outcomes

1. Prevention
2. Increasing awareness/education
3. Early identification of BC
4. Improved stratification
5. Aggressive treatment of high-risk BC
6. Improved surgical treatment

Can biomarkers help?
Bladder Cancer Prevention: Reduce tobacco usage

• 50% of all BC related to cigarette use
  – Smokers are over 3-4x as likely to develop BC than non-smokers
  – Cigars, pipe & marijuana: suggested associations
  – Second-hand smoke also risk factor

• Former smokers have decreased risk than current smokers

BC: Increase Awareness

- Population are unaware of risks of tobacco & BC
- Most are unaware of risks of tobacco & ED
Hypothesis:

• Knowledge regarding BC risk factors is limited

Methods:

• Surveyed 280 patients at a urology clinic regarding their knowledge of the risk factors for bladder and other cancers

Results

• 98% knew tobacco was a risk factor for lung CA vs. 36% who knew tobacco was a risk factor for BC
• Women & > Education were more likely to be aware of the association between smoking & BC

Conclusions:

• Need to increase education to help combat smoking related cancers

BC: tobacco cessation

- Surveyed pts with BC at time of surveillance cystoscopy
- Nearly 60% of patients continued to smoke after BC diagnosis

**Conclusion**: Patients who cont to smoke warrant smoking cessation intervention

Bladder Cancer Screening

- Not currently recommended by US Public Health Service

- Despite the fact that the main risk factor (tobacco) is *well-known & modifiable*

- Multiple studies have demonstrated a delay in diagnosis
  - In women (thought to have UTIs)
  - In men (thought to have BPH, stones)
Delay in Diagnosis

- Evaluated 212 consecutive pts with BC
- Hematuria presenting symptom in 80%
- Median onset of sx to treatment: 15 weeks
- Half delay secondary to PCP

Delay in Diagnosis

- Retrospective study of 340 pts
- Mean symptom delay (pt’s): 15 days
- Mean MDs delay: 62 days
  - MDs delay longer in women than men
  - Pts with irritative symptoms had sig longer delays

Are patients with hematuria appropriately referred to Urology? A multi-institutional questionnaire based survey

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- Is there a delay in diagnosis of BC?
- Anonymously surveyed 780 primary-care & GYNs in Miami & Dallas regarding their typical evaluation of hematuria

Improve early diagnosis of BC

Results:
• Primary-care MDs only automatically refer 14% and 64% of patients with microscopic & gross hematuria to GU

Conclusions:
• MDs may be treating patients for other problems (e.g., UTIs) when they really have BC

Statistics

<table>
<thead>
<tr>
<th>Test Score:</th>
<th>Has the disease</th>
<th>Does not have the disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>True Positives (TP)</td>
<td>False Positives (FP)</td>
</tr>
<tr>
<td></td>
<td><strong>a</strong></td>
<td><strong>b</strong></td>
</tr>
<tr>
<td>Negative</td>
<td>False Negatives (FN)</td>
<td>True Negatives (TN)</td>
</tr>
<tr>
<td></td>
<td><strong>c</strong></td>
<td><strong>d</strong></td>
</tr>
</tbody>
</table>

PPV = \(\frac{TP}{TP + FP}\)

NPV = \(\frac{TN}{TN + FN}\)

Sensitivity: \(\frac{TP}{TP + FN}\)

Specificity: \(\frac{TN}{TN + FP}\)

Or,

- Sensitivity: \(\frac{a}{a + c}\)
- Specificity: \(\frac{d}{d + b}\)
Statistics

• Sens: % of sick people are correctly identified (True Positives)
• Spec: % of healthy people are correctly identified (True Negatives)
• PPV: % of patients with + test have disease
• NPV: % of patients with – test don’t have disease
  – Important for screening tests
• Goal: 100% Sens & Spec
  – Neither are valuable alone
  – Bogus test that is always POS: 100% sensitive
  – Bogus test that is always NEG: 100% specific
Why Urine Biomarkers?

- Non-invasive
- Avoid cystoscopy
- Avoid expense/radiation with CTU
- Improve referrals to Urology
- Improve compliance with followup
Biomarkers

- Cytology
- FISH
- NMP-22
- BTA
- CertNDx
- Combined biomarkers
Utility of cytology in w/u of Asymtomatic Microscopic Hematuria (AMH)

- Retrospective study of 200 pts with AMH referred to GU
- All had cytology x 3, cysto, imaging
- Cytology: 11% atypical, 89% negative
- Cysto: 8 tumors (cytol: 4 atyp, 4 neg)

Conclusions:
- Should w/u AMH
- Cytology is not useful and adds sig expense

Cytology is not useful in hematuria evaluations

- Retrospective review of 2,700 pts w/u for hematuria
- Cytology: 45% sensitivity, 90% specificity
- Only 2 had + cytology as only finding

Conclusions:
- Cytology is costly and of limited clinical value as a first line test in w/u of AMH

Prospective study at 3 centers of pts presenting with hematuria
  – All had NMP-22 as part of workup
Evaluated results with and without NMP-22 and cytology
Enrolled 381 patients
NMP-22: FDA-approved point of care test

Bladder cancer found in 23 (6%)
- More likely in Whites (9% vs 3%), Age > 65 (11% vs 4%), Male (10% vs 2%), Gross Hematuria (10% vs 2%), + NMP22, + Cytology

NMP-22: NPV: 96%, PPV: 37%
- Neg in 13/23

Cytology: NPV: 96%, PPV: 83%

Conclusion: Need improved risk-stratification and referrals to GU

• Retrospective, multi-center trial evaluating 10 biomarkers in 125 pts with a h/o BC
  – Evaluating utility in Recurrent BC
• Compared results with Cytology and FISH
• 53/125 (42%) recurrences

Combo of Biomarkers

Table 2. Protein biomarker performance data for the detection of recurrent bladder cancer

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>AUC</th>
<th>95% CI</th>
<th>Correctly predicted events, n</th>
<th>Correctly predicted non-events, n</th>
<th>Non-events predicted as events, n</th>
<th>Events predicted as non-events, n</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
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<tbody>
<tr>
<td>IL8</td>
<td>0.774</td>
<td>0.685-0.862</td>
<td>29</td>
<td>69</td>
<td>3</td>
<td>24</td>
<td>55</td>
<td>96</td>
<td>91</td>
<td>74</td>
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<tr>
<td>MMP9</td>
<td>0.771</td>
<td>0.683-0.859</td>
<td>29</td>
<td>68</td>
<td>4</td>
<td>24</td>
<td>55</td>
<td>94</td>
<td>88</td>
<td>74</td>
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<tr>
<td>SERPINA1</td>
<td>0.864</td>
<td>0.799-0.929</td>
<td>46</td>
<td>52</td>
<td>20</td>
<td>7</td>
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<td>72</td>
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<tr>
<td>ANG</td>
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<td>0.726-0.882</td>
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<tr>
<td>VEGFA</td>
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<td>0.667-0.847</td>
<td>30</td>
<td>68</td>
<td>4</td>
<td>23</td>
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<td>0.737-0.891</td>
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<td>21</td>
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<td>76</td>
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<tr>
<td>MMP10</td>
<td>0.837</td>
<td>0.758-0.917</td>
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<td>13</td>
<td>12</td>
<td>77</td>
<td>82</td>
<td>76</td>
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<tr>
<td>APOE</td>
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<td>0.685-0.865</td>
<td>39</td>
<td>60</td>
<td>12</td>
<td>14</td>
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<td>83</td>
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<td>81</td>
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<tr>
<td>SERPINE1</td>
<td>0.778</td>
<td>0.693-0.863</td>
<td>29</td>
<td>68</td>
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<tr>
<td>SDC1</td>
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<td>0.741-0.895</td>
<td>32</td>
<td>67</td>
<td>5</td>
<td>21</td>
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<tr>
<td>All 10 biomarkers</td>
<td>0.904</td>
<td>0.853-0.956</td>
<td>42</td>
<td>63</td>
<td>9</td>
<td>11</td>
<td>79</td>
<td>88</td>
<td>82</td>
<td>85</td>
</tr>
</tbody>
</table>

- FISH: 42%/94% sens/spec
- Cytology: 33%/90% sens/spec
- Biomarkers: 79%/88% sens/spec

CertNDx (Predictive Biosciences)

- Novel urine test that combined 4 biomarkers

Methods:
- Retrospectively reviewed 130 patients who had a CertNDx test between 7/11 – 8/12
- Correlated CertNDx results with cystoscopy, imaging and cytology findings

Results:
- Mean age 65 years old
- 44% were smokers or former smokers
- 99% of patients considered “high-risk” for BC (age > 40 or tobacco history)
CertNDx Results

- 2 patients (2%) were found to have a BT
- NPV: 100%

<table>
<thead>
<tr>
<th></th>
<th>Negative</th>
<th>Intermediate</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>CertNDx Results</td>
<td>71 (55%)</td>
<td>57 (44%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Bladder Tumors</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**Conclusion:** By obviating a complete w/u, no patient would have had a “missed tumor”
Molecular Grading

MOLECULAR AND CLINICAL PATHWAYS OF BLADDER CANCER

FGFR3 mutation

Normal Urothelium

p53 ↑
Ki-67 ↑

Ta G1/2

Ta/1 G2/3 CIS

Progression

T2 G2/3

T2 G3

Metastasis

INCREASING NUMBER OF GENETIC EVENTS

Conclusions

Multiple different areas to improve BC outcomes
• Need to educate smokers & those at risk
• Need to educate patients and primary-care MDs regarding early signs and symptoms
  – Need early/timely GU evaluation
• Need improved urine/tissue biomarkers
  – Costly to bring to market (need long-term studies)
  – Negative predictive value most important?
Conclusions

• Need to improve TURBT quality
  – No hesitation to re-resect
• Need aggressive treatment of high-risk disease
  – Early cystectomy