Nomograms--Do They Have a Role in Bladder Cancer?

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UCSF Bladder Cancer Post Graduate Course
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Risk Assessment

- What do patients want?
  - Will I live or die?
  - How much time do I have?
  - Will I need additional treatment?

- What do clinicians want?
  - Accurate risk stratification
  - Criteria for peri-operative therapy
  - Clinical trial eligibility
  - Will treatment work in my patient - Targeted therapy

Computing Probabilities of Outcome

- Physician judgment
- Overall average
- Risk group stratification
- Prediction models eg Cox multivariate or logistic regression
- Nomograms – graphical representation of prediction model
  - Individualized prediction of endpoint

Problems with Physician Judgment

- We do not recall all cases equally
- We are inconsistent when processing memory
- We predict preferred outcome rather than the one with the highest probability
- Can we integrate multiple prognostic factors without the aid of a computer?
Patient Centered Care

- Attending surgeon is the single most important factor in treatment choice\(^1\)
- Patient recall of testing procedures generally poor\(^1\)
- Regret over decision-making significant when complications arise\(^2\)
- Therefore, accurate estimates of risk are essential for physicians if they are to recommend a specific management.

Other Nomogram Advantages

- Bootstrapping allows internal validation without sample size limitations\(^1\)
  - External validation requires “substantial” sample sizes
- Graphical representation allows one to see direction and magnitude of the contribution of each variable

Other Nomogram Advantages

First Generation RRP
Biochemical Recurrence (PSA $\geq 0.4$)

Nomogram vs. Clinician Prediction

- Nomogram and clinician similar in predicting organ-confined disease (CI 0.79 vs. 0.78, resp.)
- Nomogram outperformed urologist predicting 5-year recurrence-free probability (CI 0.67 vs. 0.55, resp.)

\(^1\)Miles et al Urology 53:169, 1999
\(^2\)Clark, et al JCO 19:72, 2001


\(^2\)Ross, et al Semin Urol Oncol 20:82, 2002
Validation Kattan Nomogram
Predicting Recurrence after RRP
  - CAPSURE community-based
  - CI 0.68
  - International Data set (Hamburg)
  - AUC 0.83 for 5-year biochemical recurrence

Bladder Cancer Nomograms
Potential Uses
- Invasive (≥T1)
  - Predict pathology
  - Predict outcome after treatment
  - Determine recommendation for neo or adjuvant therapy
  - Select patients for clinical trials
- Non-muscle invasive
  - Recurrence and progression probability
  - Intravesical therapy response

Radical Cystectomy
Factors Affecting Outcome
- Optimizing surgery
- Peri-operative chemotherapy
- Pathologic stage (T and N)
- Pathologic variables
  - LVI, CIS, Small cell, Micropapillary, biomarkers
- Age
- Gender
- Co-morbidity

The Bladder Cancer Research Consortium (BCRC)
- Founded in 2003
- Collaboration among Baylor College of Medicine, UT Southwestern, Johns Hopkins and the University of Montreal
- Patients contributed by Baylor, UT Southwestern and Johns Hopkins
- Senior collaborators:
  Seth P. Lerner, M.D.
  Arthur I. Sagalowsky, M.D.
  Mark P. Schoenberg, M.D.
Study cohort, n=958

- 958 consecutive patients
- Radical cystectomy
- 1984 to 2003
- 3 institutions:
  - BCM: 290 (30%)
  - UTSW: 392 (41%)
  - JHU: 276 (29%)

Study population, n=958

Exclusions: n = 176 (18.4%)

- Pre-operative TCC cancer: (n=67, 7.0%)
- Pathologic TCC cancer: (n=68, 7.1%)
- Pathologic T stage: (n=78, 8.1%)
- Pathologic grade: (n=5, 0.5%)
- Pathologic N stage: (n=33, 3.4%)
- Neoadj chemo: (n=38, 4.0%)
- Adjuvant chemotherapy: (n=50, 5.2%)
- Adjuvant radiotherapy: (n=2, 0.2%)
- Lympho-vascular invasion: (n=16, 1.7%)
- Time to recurrence/censoring: (n=4, 0.4%)
- CIS: (n=85, 9.0%)
- Recurrence/cystectomy dates: (n=3, 0.3%)

Target sample: 782 (81.6%) evaluable patients

Statistical analyses:
- Kaplan-Meier analyses and multivariate Cox regression models
- Outcome: bladder cancer recurrence and survival at 2, 5 and 8 years
- Predictors: gender, age, pathologic grade, pT, pN, LVI, CIS, neoadjuvant chemo, adjuvant chemo, adjuvant XRT
- Regression coefficient-based nomogram
- 200 bootstrap internal validation to reduce overfit bias

Results
Clinical and pathological characteristics n= 728

- Age (33.1-89.2 yrs) Mean: 64.5; Median: 66.0
- LVI 272 (37.4%)
- Pathologic T stage:
  - T0 56 (7.7%)
  - Tis 92 (12.6%)
  - Ta 23 (3.2%)
  - T1 94 (12.9%)
  - T2 163 (22.4%)
  - T3 215 (29.5%)
  - T4 85 (11.7%)
- Pathologic N stage:
  - 0 556 (76.4%)
  - 1 66 (9.1%)
  - 2 92 (12.6%)
  - 3 14 (1.9%)
- Pathologic grade:
  - absence of cancer 56 (7.7%)
  - 2 55 (5.5%)
  - 3 619 (84.8%)

Suite of Nomograms

- Radical cystectomy outcomes
  - Recurrence
  - Survival
- Pre-operative prediction of pathologic T3,T4 or N+
- Competing Risk Survival
Case 1

- A 50-year-old female with a pathologic stage P2bN0M0 bladder TCC after radical cystectomy and orthotopic continent diversion.
- Estimated 5-year recurrence probability is: **25%** (Yu, et al J Urology 2006)
Case 1 (cont.)

- Nomogram estimated probability of recurrence at 5 years is: 16%

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nomogram estimate</th>
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<tbody>
<tr>
<td>Age 60</td>
<td>17%</td>
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<tr>
<td>Age 70</td>
<td>18%</td>
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<tr>
<td>CIS +</td>
<td>19%</td>
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<tr>
<td>LVI +</td>
<td>21%</td>
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<tr>
<td>CIS+/LVI+</td>
<td>25%</td>
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Comparing Accuracy

- PCA biochemical recurrence CI
  - RRP recurrence (Baylor) (n=983) 0.79
  - RRP recurrence 2nd generation (n=1978) 0.79
  - Radiotherapy predicting metastases (n=1677) 0.81
- Renal Cell Ca recurrence (MSKCC)
  - Radical nephrectomy (n=601) 0.74
  - Clear cell post rad/partial nephrectomy (n=771) 0.82
- Bladder cancer recurrence
  - PBCR consortium (n=728) 0.78
  - International (MSKCC) (n=9064) 0.75

Biomarker Nomogram Predicting Recurrence: PTa-3N0

Predictive accuracy with markers improved 10.9% from 72.5% without markers (p<0.001)

Nomogram Limitations

Generalizability

- Patient population
- Time period
- Cell type
- Stage migration
- Single center vs. multi-center
- Tertiary care vs. community based
Should I Use This Nomogram?

**BJUI Comments**

- Is the nomogram treatment comparable?
- Is the time frame contemporary?
- Is the predicted endpoint relevant?
- Is the alternative prediction tool better or worse?

*BJU Int 102:421, 2008*

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**MSKCC Bladder Recurrence Nomogram:**

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**International Bladder Cancer Nomogram**

Recurrence after Radical Cystectomy

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<th>Points</th>
<th>0</th>
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<th>20</th>
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<th>80</th>
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Predictive accuracy:
- CI: .75
- Path stage: .62
- TNM: .68

*Borch, et al IJC 24:3967, 2006*

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**Validation**

  - 423 patients 2 centers in Germany, RC 1992 - 2007

<table>
<thead>
<tr>
<th>Variable</th>
<th>c-indices of</th>
<th>5-year recurrence</th>
<th>AUC/TNM</th>
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<tr>
<td>BCRC-nomogram</td>
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<td>0.84</td>
<td>0.96</td>
</tr>
<tr>
<td>BCRC-nomogram</td>
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<td>0.75</td>
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<tr>
<td>ACS</td>
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<td>0.85</td>
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<tr>
<td>CSS</td>
<td></td>
<td>0.85</td>
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"...widespread application of such nomograms can now be initially supported on a sound basis."
Does Nomogram Improve Decision Making for Adjuvant Chemotherapy?

- Adj ctx criteria pT3-4, TanyN+
- Risk recur 10%, 25%, 70%
- Nomogram use: better outcomes using 25% risk threshold then using only T and N stage


Adjuvantonline.com
Breast Cancer Chemotherapy

Accessed March 28, 2010

Alternative Models for Predicting Outcome

- Artificial Neural Networks
- Artificial Intelligence – Neurofuzzy Modeling

Artificial Neural Network

- 1133 patients 1996-2002
  - 70% used for reference series
  - 30% for validation
- Histology
  - TCC (54%)
  - SCCa (35%)
  - Other (11%)
- Mean follow up 3.7-3.8 years
- Endpoint: 5 year disease-free survival

Artificial Neural Network

Fuzzy Logic (Artificial Intelligence)
- BCRC dataset - recurrence nomogram
- 609 patients with no peri-operative chemotherapy and no LN metastases
- 2 models constructed
  - Classifier: Accuracy: 0.84, CI: 0.92
  - Predictive (timing of recur)
    - Median error of 8.15 months

Risk Assessment and Predicting Outcome in Non-muscle Invasive Disease
Risk Stratification

- Low - TaG1 solitary, primary - 50% patients
- Moderate - Multifocal, recurrent TaT1, G1-2, 35% patients
- High - CIS, any G3(Ta or T1) - 15% of patients
- Progression probability at 5 years
  - Low/Moderate - < 10%
  - High risk - 50%

EORTC: SOTS meeting 2000

Factors Affecting Recurrence

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary vs. Recurrent ≤ 1y vs. &gt; 1y</td>
<td>1.35</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Number tumors: single, 2-7, 8</td>
<td>1.56</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Size &lt; 3cm vs. ≥ 3cm</td>
<td>1.54</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Ta vs. T1</td>
<td>1.21</td>
<td>0.003</td>
</tr>
<tr>
<td>CIS</td>
<td>1.19</td>
<td>0.18</td>
</tr>
<tr>
<td>Grade 1, 2, 3</td>
<td>1.17</td>
<td>0.001</td>
</tr>
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</table>

Sylvester et al Eur Urol 49:466, 2006

Nomogram and NMIBC

- 2681 patients – international data set
- 957 recurred
- All with urine cytology and NMP-22

Sylvester et al Eur Urol 49:466, 2006
NMIBC Nomograms - Japan

- 800 patients 1991-2001
- No prior treatment

Recurrence

Progression


T1G3

- 73yo healthy WM
- 1997 RRP pT2 Gleason 3 + 3
- Undetectable PSA 2/06
- Gross hematuria
- Office cystoscopy with multifocal tumors right lateral wall
- Cytology positive

T1G3 (cont)

- Initial TURBT – right lateral wall tumors T1aG3
- Multifocal CIS
- Small papillary tumor anterior bladder neck also T1aG3
- Re-resection – complete into deep muscularis propria – TaG3 (suspicion of T1)

Case 1 – Risk Assessment and Treatment Options

<table>
<thead>
<tr>
<th>EORTC Risk Table</th>
<th>NMP22 Nomo</th>
<th>Yamada Nomo</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 year risk recurrence?</td>
<td>51% 89% 82%</td>
<td></td>
</tr>
<tr>
<td>2 year risk progression?</td>
<td>26% 27%</td>
<td></td>
</tr>
</tbody>
</table>

- Treatment options:
  - BCG induction
  - BCG + Interferon induction
  - Radical cystectomy