UPDATES IN SUPERFICIAL BLADDER CANCER
Disclosures

- Research Grant Support
  - American Cancer Society
  - Urology Care Foundation / Astellas

- Consultant
  - American College of Physicians
    - High Value Care Task Force
  - Best Doctors
SURVEILLANCE FOR LOW-RISK BLADDER CANCER

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Departments of Urology, Epidemiology, Health Policy & Management
University of North Carolina at Chapel Hill
Bladder Cancer in the United States

- Incidence: >70,000 cases per year
  - Median age at dx: 74 (incidence peaks in >80yrs)
  - Heterogeneous risk / natural history
    - ~75% non-muscle-invasive (<T2)

- Prevalence: >600,000 cases
  - Intensive lifelong surveillance

- Direct Costs: ~$2.6-3.7B/year
  - Most expensive per-patient from diagnosis to death
  - Substantial indirect costs (?)

SEER Cancer Statistics; Botteman et al Pharmacoconomics, 2003
Bladder Cancer in the United States

- Incidence: >70,000 cases per year
  - Median age at dx: 74 (incidence peaks in >80yrs)
  - Heterogeneous risk / natural history
    - ~75% non-muscle-invasive (<T2)
    - ~40-50% low grade noninvasive (Ta)

- Prevalence: >600,000 cases
  - Intensive lifelong surveillance

- Direct Costs: ~$2.6-3.7B/year
  - Most expensive per-patient from diagnosis to death
  - Substantial indirect costs (?)

SEER Cancer Statistics; Botteman et al Pharmacoeconomics, 2003
Low-Risk Bladder Cancer
The Elephant in the Room?

- Current Guidelines Recommendations
- Epidemiology
- Prognosis
- Comparative Effectiveness
- Costs / Budget Impact
Low-Risk Bladder Cancer

- Current Guidelines Recommendations
- Epidemiology
- Prognosis
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- Costs / Budget Impact
Surveillance in NMIBC
Surveillance Guidelines: low risk disease

American Urological Association:

- q3mo x2y; q6mo x 3y, annually thereafter
  - No explicit risk stratification
  - “Reset” at recurrence (50-85% by 5 years); lifelong
  - Acknowledge possible acceptability of lower intensity in select cases (not specified)

https://www.auanet.org/education/guidelines/bladder-cancer.cfm
Surveillance Guidelines: low risk disease

- EAU: explicit risk stratification (calculator)
  - Low risk (LGTa <3cm, no CIS):
    - If negative @3mo: q9-12mo thereafter
  - High risk: same as AUA schedule

http://www.uroweb.org/gls/pdf/05_TaT1_Bladder_Cancer_LR.pdf
Surveillance Guidelines: low risk disease

- **EAU**: explicit risk stratification (calculator)
  - Low risk (LGTa <3cm, no CIS): if negative @3mo: q9-12mo thereafter
  - High risk: same as AUA schedule

- **NCCN**: Risk Stratified (LGTa vs other NMIBC)
  - LGTa: 3 months initially, then at increasing intervals as appropriate (not further specified)
  - Other NMIBC: q3-6mo x 2y, then increasing (unspecified) intervals as appropriate
  - age / comorbidity?

Surveillance of Low Risk Bladder Cancer

- Guidelines’ recommendations vary
  - Reflects uncertainty in this setting
Surveillance of Low Risk Bladder Cancer

- Guidelines’ recommendations vary
  - Reflects uncertainty in this setting
- BCAN Survey results:

![Pie chart showing 'Cystoscopy Every 3 Months'
- No
- Yes for all cases]
Surveillance of Low Risk Bladder Cancer

- Guidelines’ recommendations vary
  - Reflects uncertainty in this setting
- BCAN Survey: AUA schedule is effectively default for majority of US urologists
- Uncertainty in this area recognized as a priority research topic in the AUA’s National Urology Research Agenda (NURA)

http://www.urologyhealth.org/resourcecenter/pdfs/NuraMonograph.pdf
Low-Risk Bladder Cancer

- Current Guidelines Recommendations
- Epidemiology
- Prognosis
- Comparative Effectiveness
- Costs / Budget Impact
Epidemiology

- Burden of bladder cancer is rising: stable incidence of ~50k/yr in 1990s → >70k/yr
- Overall adjusted incidence rates (per 100k population) relatively stable
  - Growing, aging population
- Approximately half of incident cases = LGTa
  - Disproportionately rising?
Surveillance of Urothelial Carcinoma

Stage and Grade Migration, 1993-2005 and Survival Trends, 1993-2000

Kevin A. David, MD, Katherine Mallin, PhD, Matthew I. Milowsky, MD, Jamie Ritchey, MA, Peter R. Carroll, MD, and David M. Nanus, MD

FIGURE 3. Bladder cancer percentage stage distribution by diagnosis year.

- Stage 0a

Matthew E. Nielsen, MD, MS\textsuperscript{1,2,3}; Angela B. Smith, MD\textsuperscript{1,2}; Anne-Marie Meyer, PhD\textsuperscript{1,3}; Tzy-Mey Kuo, PhD\textsuperscript{1}; Seth Tyree, MS\textsuperscript{1}; William Y. Kim, MD\textsuperscript{1,4}; Matthew I. Milowsky, MD\textsuperscript{1,4}; Raj S. Pruthi, MD\textsuperscript{1,2}; and Robert C. Millikan, PhD\textsuperscript{1,5}.

Stage-specific, Age-adjusted Incidence Rate

- Ta
- Tis
- T1
- T2+

Cancer 2014;120:86-95.
Age Stratum-Specific Incidence Rates, By Stage
Figure 3. Race- and sex-adjusted stage-specific incidence rates for urothelial carcinoma of the bladder are shown by age strata, 1988 to 2006. Solid line with circles indicates Ta disease; solid line with tick marks, Tis disease; dotted line, T1 disease; solid line, \( \geq T2 \) disease.
Risk Stratification

- **GRADE**
  - Different microscopic appearances
  - Different **clinical behavior**
    - 50-70% Recurrence – lower or same stage / grade
    - Vs. **Progression** – higher stage / grade
  - Different **molecular biology**
    - FGFR3 pathway in low grade
    - p53/RB pathway, aneuploidy in high grade
  - Potentially different carcinogenesis?
Same organ, different phenotype?

- FGFR-3 mutations in 70-80% of low grade Ta, 10-20% of HG invasive tumors
  - Increased recurrence (LGTa), low progression
- Increased Ki-67, p53 mt associated with higher grade, poorer prognosis
- Commercially available biomarkers?
Low-Risk Bladder Cancer

- Current Guidelines Recommendations
- Epidemiology
- Prognosis
- Comparative Effectiveness
- Costs / Budget Impact
Bladder Cancer

Predicting Recurrence and Progression in Individual Patients with Stage Ta T1 Bladder Cancer Using EORTC Risk Tables: A Combined Analysis of 2596 Patients from Seven EORTC Trials

Richard J. Sylvester\textsuperscript{a,*}, Adrian P.M. van der Meijden\textsuperscript{b}, Willem Oosterlinck\textsuperscript{c}, J. Alfred Witjes\textsuperscript{d}, Christian Bouffioix\textsuperscript{e}, Louis Denis\textsuperscript{f,1}, Donald W.W. Newling\textsuperscript{g,2}, Karlheinz Kurth\textsuperscript{h,3}

Table 4 – Multivariate analysis of time to first recurrence and time to progression

<table>
<thead>
<tr>
<th></th>
<th>Recurrence</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Tumor status: primary, recurrent</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Prior recurrence rate: primary, recurrent ≤1 rec/yr, recurrent &gt;1 rec/yr</td>
<td>1.35 (1.24, 1.46)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Number of tumors: single, multiple</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Number of tumors: single, 2 to 7, 8 or more</td>
<td>1.56 (1.42, 1.71)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Tumor size: &lt;3 cm, ≥3 cm</td>
<td>1.54 (1.32, 1.80)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>T Category: Ta, T1</td>
<td>1.21 (1.07, 1.37)</td>
<td>0.003</td>
</tr>
<tr>
<td>Carcinoma in situ: no, yes</td>
<td>1.19 (0.924, 1.52)</td>
<td>0.180</td>
</tr>
<tr>
<td>Grade: G1, G2, G3</td>
<td>1.17 (1.07, 1.28)</td>
<td>0.001</td>
</tr>
<tr>
<td>Grade G3: no, yes</td>
<td>–</td>
<td>–</td>
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</table>
## Risk Stratification: Low vs. High GRADE

### Tumor Type

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>% Frequency</th>
<th>% Progression</th>
<th>% Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninvasive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papilloma</td>
<td>10</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>PUNLMP</td>
<td>20</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Low Grade Ta</td>
<td>20</td>
<td>5-10</td>
<td>1-5</td>
</tr>
<tr>
<td>High Grade Ta</td>
<td>30</td>
<td>15-40</td>
<td>10-25</td>
</tr>
<tr>
<td>Invasive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Grade T1</td>
<td>20</td>
<td>30-50</td>
<td>33</td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td>10</td>
<td>&gt;50</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>90</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Reference

Donat SM, Urol Clin N America 2003


Programmed by Richard Sylvester, EORTC Data Center, 83 avenue Mounier, 1200 Brussels, Belgium.

Version 1.0, January 2006
- 9167 patients with prior adenoma
  - Median follow-up 47.2 months
- Advanced CR neoplasia 11.8% (1082) (≥10mm, HG dysplasia, >25% villous)
  - ≥5 lesions: 24% risk; >20mm lesion 19.3%
- Invasive CRC (T2 disease): 0.6%
  - ≥5 lesions: 1.2% risk; >20mm lesion 0.8%
Low Grade Noninvasive Bladder Cancer

- 40-50% of incident cases—on the rise?
- Relatively indolent natural history
  - Risk = recurrence of low-grade lesions
  - Rare grade / stage progression
  - High vs. Low grade: distinct molecular biology
  - Majority of prevalent cases
- Lack of consensus in practice guidelines
- Paucity of data on outcomes, survivorship experience, decision making, patient perceptions of risk
Low-Risk Bladder Cancer

- Epidemiology
- Prognosis
- Current Guidelines Recommendations
- Comparative Effectiveness
- Costs / Budget Impact
Models in Research

“A model is a lie that helps you see the truth.”

Howard Skipper, PhD
(Sebring, FL native)
Simulation Modeling in CER

- National Research Council:
  - “A replicable, objective sequence of computations used for generating estimates of quantities of concern.”

- Synthesize evidence on health consequences and costs in a logical structure to inform health decisions—ISPOR

- Ruth Etzioni et al. {CISNET}
UNC-NCSU collaboration

- Brian Denton and Yuan Zhang
  - NCSU Industrial Engineering / Operations Research
- Developed cohort simulations (POMDP) of low grade noninvasive bladder cancer
  - Evaluate different guidelines for surveillance
  - Model age-specific and dynamic policies
  - Sensitivity analyses:
    - Age (competing risks)
    - Disutility of cystoscopy
Comparison of Surveillance Strategies for Low-Risk Bladder Cancer Patients

Yuan Zhang, PhD, Brian T. Denton, PhD, Matthew E. Nielsen, MD, MS

Objective. Low-grade noninvasive disease comprises approximately half of incident bladder cancer cases. These lesions have exceedingly low rates of progression to aggressive, muscle-invasive bladder cancer, and there is salient discordance with regard to management recommendations for these patients between the principal clinical practice guidelines. In this context, we compare the international guidelines with alternative surveillance strategies for low-risk bladder cancer patients. Methods. We used a partially observable Markov decision model based on states that defined patient risk levels associated with recurrence and progression of bladder cancer. The model also included states defining the effects of treatment, death from bladder cancer, and all other-cause mortality. Simulation was done to estimate quality-adjusted life years (QALYs), expected lifelong progression probability, and lifetime number of cystoscopies. Results. We compared current international guidelines and additional proposed surveillance strategies on the basis of QALYs. We conducted a bicriteria analysis to compare expected life-long progression rate vs. the number of cystoscopies. One-way sensitivity analysis was used to evaluate the influence of model parameters, including a patient’s disutility associated with cystoscopy, bladder cancer mortality, and all other-cause mortality. Conclusions. Age and comorbidity significantly affect the optimal surveillance strategy. Results suggest that younger patients should be screened more intensively than older patients, and patients having comorbidity should be screened less intensively. Key words: bladder cancer; surveillance; simulation; partially observable Markov model. (Mod Decis Making XXX;XX:xx-xx)

Unobservable States

Observables States

1. Low Risk Disease Free Following Treatment
2. Intermediate Risk Disease Free Following Treatment
3. High Risk Bladder Cancer
4. Muscle Invasive Bladder Cancer
5. Intermediate Risk Disease Free Following Treatment
6. High Risk Disease Free Following Treatment
7. Intermediate Risk Bladder Cancer
8. High Risk Bladder Cancer
9. Death
10. Death

The online version of this article can be found at: http://mdm.sagepub.com/content/33/2/198
Comparative Effectiveness (Prelim)

- Expected life-long T2 progression rate
  - AUA: 6.2% (15 cystoscopies)
  - EAU: 6.6% (8 cystoscopies)

- Sensitivity analyses:
  - Disutility of cystoscopy
  - Other-cause mortality / age at diagnosis

- Limitations \rightarrow future directions (ACS MRSG):
  - Microsimulation to reflect population age distribution
  - Costs, Empiric utility estimates
What Defines Quality Care?

- “The extent to which health services for individuals and populations increases the likelihood of desired health outcomes and is consistent with current professional knowledge” - Institute of Medicine

What is the appropriate intensity of care?

- Risk of harm/mortality from malignancy?
  - Differential risks by cancer site
  - Differential risks within a given cancer site

- Potential harm from competing risks?
REMEMBER THE TWENTY EXTRA YEARS YOU ADDED TO YOUR LIFE THROUGH CLEAN, HEALTHY LIVING? - WELL, THESE ARE THEM.
Low-Risk Bladder Cancer

- Epidemiology
- Prognosis
- Current Guidelines Recommendations
- Comparative Effectiveness
- Costs / Budget Impact
Provider Treatment Intensity and Outcomes for Patients With Early-Stage Bladder Cancer

Brent K. Hollenbeck, Zaojun Ye, Rodney L. Dunn, James E. Montie, John D. Birkmeyer

Background
Bladder cancer is among the most prevalent and expensive to treat cancers in the United States. In the absence of high-level evidence to guide the optimal management of bladder cancer, urologists may vary widely in how aggressively they treat early-stage disease. We examined associations between initial treatment intensity and subsequent outcomes.

Methods
We used the Surveillance, Epidemiology, and End Results–Medicare database to identify patients who were diagnosed with early-stage bladder cancer from January 1, 1992, through December 31, 2002 (n = 20,713), and the physician primarily responsible for providing care to each patient (n = 940). We ranked the providers according to the intensity of treatment they delivered to their patients (as measured by their average bladder cancer expenditures reported to Medicare in the first 2 years after a diagnosis) and then

Results
The average Medicare expenditure per patient for providers in the highest quartile of treatment intensity was more than twice that for providers in the lowest quartile of treatment intensity ($7131 vs $2830, respectively). High-intensity providers more commonly performed endoscopic surveillance and used more intravesical therapy and imaging studies than low-intensity providers. However, the intensity of initial treatment was not associated with a lower risk of mortality (adjusted hazard ratio of death from any cause for patients of low- vs high-treatment intensity providers = 1.03, 95% confidence interval 0.97 to 1.09). Initial intensive management did not obviate the need for later interventions. In fact, a higher proportion of patients treated by high-treatment intensity providers than by low-treatment intensity providers subsequently underwent a major medical intervention (11.0% vs 6.4%, P = .02).

Conclusions
Providers vary widely in how aggressively they manage early-stage bladder cancer. Patients treated by high-treatment intensity providers do not appear to benefit in terms of survival or in avoidance of subsequent major medical interventions.
AUA/EAU Surveillance Cost Comparison
= Budget Impact Analysis

Low Grade Ta SURVEILLANCE COSTS

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Five-Year Per Patient Total Surveillance Cost</th>
<th>Five-Year Total Cohort Surveillance Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAU Guidelines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Low-risk</td>
<td>$2,228</td>
<td>$1,114</td>
<td>$1,114</td>
<td>$1,114</td>
<td>$6,684</td>
<td>$235,711,260</td>
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<tr>
<td>AUA Guidelines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Patients</td>
<td>$4,456</td>
<td>$4,456</td>
<td>$2,228</td>
<td>$2,228</td>
<td>$1,114</td>
<td>$14,482</td>
</tr>
</tbody>
</table>

- 54% total savings over 5 years
  - $7,798 per patient; $274,966,470 total population
  - [For one year’s worth of incident cases]
Future Directions

- Granular population-based data needed for model validation
- Risk stratification: tailoring interventions to maximize effectiveness
  - Integration of molecular markers in practice
    - Refine classification (molecular grading)—validation
    - Possible substitute for surveillance cystoscopy
- Pragmatic trial of different surveillance regimens
  - A role for emerging AUA-led registries?
Thank You

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: @m_e_nielsen