Prostate Cancer Overview and Recent Advances: How Can a Common Disease Be So Controversial?

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Memorial Sloan-Kettering Cancer Center

March 27, 2010

1. The statistics: The pendulum is swinging.

2. A framework:

3. Risk adapted diagnostics:

4. Risk adapted prognostics to guide treatment:
### 2009 Cancer Statistics

<table>
<thead>
<tr>
<th>Estimated New Cases</th>
<th>Estimated Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td><strong>Males</strong></td>
</tr>
<tr>
<td>Prostate</td>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td>192,280</td>
<td>88,900</td>
</tr>
<tr>
<td>26%</td>
<td>30%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>Prostate</td>
</tr>
<tr>
<td>116,090</td>
<td>27,360</td>
</tr>
<tr>
<td>15%</td>
<td>9%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>Colon &amp; rectum</td>
</tr>
<tr>
<td>75,590</td>
<td>25,240</td>
</tr>
<tr>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Pancreas</td>
</tr>
<tr>
<td>52,810</td>
<td>18,030</td>
</tr>
<tr>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>Leukemia</td>
</tr>
<tr>
<td>39,080</td>
<td>12,590</td>
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<tr>
<td>5%</td>
<td>4%</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>Liver &amp; intrahepatic bile duct</td>
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<tr>
<td>35,990</td>
<td>12,090</td>
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<tr>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>Esophagus</td>
</tr>
<tr>
<td>35,430</td>
<td>11,490</td>
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<tr>
<td>5%</td>
<td>4%</td>
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<tr>
<td>Leukemia</td>
<td>Urinary bladder</td>
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<tr>
<td>25,630</td>
<td>10,180</td>
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<tr>
<td>3%</td>
<td>3%</td>
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<tr>
<td>Oral cavity &amp; pharynx</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>25,240</td>
<td>9,830</td>
</tr>
<tr>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Kidney &amp; renal pelvis</td>
</tr>
<tr>
<td>21,050</td>
<td>8,160</td>
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<td>3%</td>
<td>3%</td>
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<tr>
<td>All Sites</td>
<td>All Sites</td>
</tr>
<tr>
<td>766,130</td>
<td>292,540</td>
</tr>
<tr>
<td>100%</td>
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</tbody>
</table>


#### Cancer Incidence and Mortality Rates

**age adjusted, standardized over time**

![Cancer Incidence and Mortality Rates](image)


Page 2
In an Aging Population, the Implications of “Detecting” And “Diagnosing” All Prostate Cancers Is Clear


The prostate produces seminal fluid that protects sperm.

The Disease Usually Starts in the Peripheral Zone and is Often Multifocal, That May Limit the Role for Therapies That Do Not Treat the Whole Gland


Screening, Early Detection and Diagnosis:
The Harder You Look, the More You Will Find

TNM Staging

1. Characterizes disease at the time of diagnosis:
   Localized disease: TNM (+PSA)

2. Applies only to the untreated patient.

3. Does not inform the prognosis of a patient who has failed.

4. What is the “STAGE” of a patient with a detectable PSA after a radical prostatectomy?

The Paradox of Prostate Cancer

1. A high prevalence in the general male population: overdiagnosis of clinically insignificant cancers a concern.

2. A natural history that often spans 10 years or more, for which treatment is “deferred” at diagnosis, at recurrence, or at relapse.

3. Can be less lethal to a patient than existing comorbidities, yet the second leading cause of cancer deaths in males.

4. A dynamic disease that can become more aggressive over time, and which is influenced by the specific therapies administered.
Prostate Cancer Overview and Recent Advances: How Can a Common Disease Be So Controversial?

1. The statistics:


3. Risk adapted diagnostics:

4. Risk adapted prognostics to guide treatment:

TNM Staging is Not Sufficient to Assess Disease: Why States are Needed

<table>
<thead>
<tr>
<th>TNM</th>
<th>States</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Characterizes disease at the time of diagnosis</td>
<td>1. Describes patient(s) at any point in the disease continuum.</td>
</tr>
<tr>
<td>2. Applies only to the untreated patient.</td>
<td>2. Applicable to treated and untreated patients</td>
</tr>
<tr>
<td>3. Does not inform trial designs for the patient who has failed.</td>
<td>3. Provides the framework for specific issues and questions to be addressed</td>
</tr>
<tr>
<td>4. Does not include PSA.</td>
<td>4. Includes PSA.</td>
</tr>
</tbody>
</table>
Prostate Cancer Clinical States:
Milestones in the Illness In Practice and In Research

Diagnoses: 192, 280
Deaths: ~60,000

- No Cancer Diagnosis
- Clinically Localized Disease
- Rising PSA: No Visible Metastases
- Rising PSA: Castrate
- Clinical Metastases: Castrate 1st Line
- Clinical Metastases: Castrate 2nd Line
- Clinical Metastases: Non-Castrate

Death from Cancer Exceeds death from Other causes
Detectable Metastases

Prostate Cancer Clinical States:
Differentiating The Tortoise and the Hare

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- Clinical Metastases: Castrate 2nd Line
- Clinical Metastases: Non-Castrate

1. Each encounter is “new one”: assess and reassess disease status.
2. *Intervene if* manifestations are significant.
3. If none, determine the probability (risk) a significant event *might occur* and when.
4. Intervene if HIGH, defer treatment if low.
**Prostate Cancer Clinical States:**
Each Objective Requires a Different Outcome

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Minimize morbidity</th>
<th>Cure if local</th>
<th>Maximize cure</th>
<th>? Cure if systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OBJECTIVES</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>No Cancer Diagnosis</td>
<td>Clinically Localized Disease</td>
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<tr>
<td><strong>Rising PSA</strong></td>
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<tr>
<td>Prevent metastases</td>
<td>Rising PSA: Castrate</td>
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<tr>
<td>Clinical Metastases: Non-Castrate</td>
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<tr>
<td><strong>UNMET NEEDS</strong></td>
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<tr>
<td>Detect clinically Significant cancers</td>
<td>Risk (lethality): Tailor Approach</td>
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<tr>
<td>Source (Location): Local+/–Systemic</td>
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<tr>
<td>Risk Tailor approach</td>
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<tr>
<td><strong>Clinical Metastases: Castrate 1st Line</strong></td>
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<tr>
<td><strong>Clinical Metastases: Castrate 2nd Line</strong></td>
<td></td>
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</tbody>
</table>

**DEATH FROM DISEASE**

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**Prostate Cancer Overview and Recent Advances:**
How Can a Common Disease Be So Controversial?

1. The statistics:

2. A framework:

3. **Risk adapted diagnostics:** Identifying those who need them.

4. Risk adapted prognostics to guide treatment:
Risk Adapted Diagnostics and Treatment

Use the tools we HAVE to **identify patients** who are destined to **develop symptoms and die** of their cancers, and to **intervene while (early when)** it can make a **significant difference**.

**Prostate Cancer Clinical States:**
Each Objective Requires a Different Outcome

- **Prevention**
  - Early Treatment

- **OBJECTIVE**
  - No Cancer Diagnosis
  - Clinically Localized Disease
  - Rising PSA

- **UNMET NEEDS**
  - Detect clinically Significant cancers

- **Rising PSA:**
  - Castrate

- **Clinical Metastases:**
  - Castrate
  - 1st Line
  - 2nd Line

**DEATH FROM DISEASE**
Biomarkers for Clinically Significant Cancer

1. Biomarker: characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention.

2. Method (Analytical) validation: The process of assessing the assay and its measurement performance characteristics, and determining the range of conditions under which the assay will give reproducible and accurate data.

3. Qualification: The evidentiary process of linking a biomarker with biological processes and clinical endpoints.

4. Intended use: A qualified biomarker is one that can be useful in a specific clinical context for medical decision making.

The Regulatory Implications of Biomarker Qualification

• Definition:
  Qualification is a conclusion that within the stated context of use, the results of patient assessment with a biomarker can be relied upon to have a specific interpretation and application in drug development and regulatory decision-making.

• Regulatory implication:
  Once qualified, drug developers will be able to use the biomarker in the qualified context in IND and NDA/BLA submissions without requesting that the relevant CDER review group reconsider and reconfirm the suitability of the biomarker.

Federico Goodsaid, CDER
Oncology Biomarker Qualification Initiative (OBQI) in the Context of Prostate Cancer

1. Intended uses:
   - **Detection**: probability of finding a cancer (that is significant)
   - **Prognosis**: predicting the probability of a clinical event: survival.
   - **Post-treatment response**: evaluating whether a systemic therapy is effective for tumor treatment.
   - **Treatment selection**: determining whether a patient’s tumor is likely to respond to a specific therapy.

2. The **Road MAP for INTENDED USES**:

3. **KEY**: An **analytically valid assay** linked to a clinical outcome.

4. Consider pre- and post-therapy changes in PSA.

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**PSA as a Biomarker in Castration Resistant Metastatic Prostate Cancer Only Goes So Far**

1. **Analytically valid**: Assays are reproducible and quantitative.

2. **Prognostic**: Rising values precede clinical indicators of disease progression and death from disease; higher baseline values portend a worse prognosis.

3. **Predictive**: While prognostic, PSA does not help select one **specific therapy** vs. another.

4. **Surrogate**: An early “**read out**” to help identify an active agent; but not a “**surrogate**” of clinical benefit.
Early Detection and Prostate Cancer Screening

Early Detection: the use of a test on *select populations* who seek an evaluation after being informed of the issues surrounding the assessment.

Screening: the application of a diagnostic procedure on a *general population*.

**PSA: the most common protein in seminal fluid**

How PSA leaks into the circulation:

- **Breakdown of basement membrane**
- **Elevated PSA level in blood**
- **Intact basement membrane = normal PSA level in blood**

- **4,000,000 ng/ml**
- **4 ng/ml**

PSA


• 1979 – Wang and Murphy (Invest Urol) purify and isolate PSA.

• 1987 – Stamey (NEJM ) shows that PSA accurately reflects the presence, volume, stage, prognosis and response to treatment of prostate cancer.

• 1991 – Catalona (NEJM) reports first large scale PSA screening trial for prostate cancer.


Trends in pathological stage and margin status (+SM)

From Swindle et al. MSKCC, AUA 2003

Logistic regression analysis

- Year of surgery (reflects change of surgical technique) \( p = 0.02 \)
- Organ confined disease (pathological stage) \( p = 0.001 \)

Both improved surgical technique and earlier treatment have contributed to improved outcomes.

PSA Limitations

1. Low specificity (~80% false positives)
2. Variable over time and between assays
3. Poorly distinguishes indolent from aggressive cancers
4. Has led to over detection of cancers that pose little threat to health or life
Embedding a Biomarker Question in a Phase III Trial: Multiple Trials Required for Qualification

1. Objective: Does PSA based screening impact survival?

2. Eligibility: Patient population.

3. Intervention: PSA and DRE at defined intervals.


5. Conclusion: ……………………………
Does PSA Screening Reduce Prostate Cancer Mortality?

PLCO: No

After 7 years of follow-up, no difference.

Mortality Results from a Randomized Prostate-Cancer Screening Trial

Gerald L. Andriole, M.D., E. David Crawford, M.D., Robert L. Grubb III, M.D., Saundra S. Buys, M.D., David Chia, Ph.D., Timothy R. Church, Ph.D.,

SCREENING

Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Trial
Trigger and follow-up

CONTROL ARM

Men (37,000)  Women (37,000)
Routine medical care

SCREENED ARM

Men (37,000)  Women (37,000)
Prostate: DRE, PSA
Lung: Chest x-ray
Colorectal: Flexible sigmoidoscopy
Ovarian: Pelvic exam, CA125, TV ultrasound
United States Prostate, Lung, Colorectal and Ovarian Screening Trial (PLCO)

- Study period: 1993 to 2001
- Randomized 76,693 men

- Annual Screen: 38,349
- Usual care: 38,350

Andriole et al. NEJM 2009; 360: 1310-19

PLCO: PC incidence and death at 7 years

Incidence
Screening: 2,820
Usual care: 2,322

22% more cancers in the screening group

Deaths
Screening: 50
Usual care: 44
US Prostate Cancer Screening Trial (PLCO)

1. No difference in stage and grade
2. No reduction in prostate cancer deaths
3. Issues:
   • Target population ages 55 to 74 years. Many men get screened starting at age 50 so eliminates these cancers from the study
   • About 40% of the usual care group had PSA testing

Andriole et al. NEJM 2009; 360: 1310-19

Does PSA Screening Reduce Prostate Cancer Mortality?
ERSPC: Yes, but at high cost

Screening and Prostate-Cancer Mortality in a Randomized European Study

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D.
European Randomized Study of Screening for Prostate Cancer Enrollment and Outcomes, According to Age Group

Schoder et al. NEJM 2009; 360:1320-8

SCREENING GROUP
8.2% Diagnosed with PC

CONTROL GROUP
4.8% Diagnosed with PC

Does PSA Screening Reduce Prostate Cancer Mortality?

326

0.80 (95% CI, 0.65 to 0.98; P=0.04).

YES
ERSPC: Screening Group Outcomes

1. More likely to be diagnosed with PC (8.2% versus 4.8%)

2. More likely to have low risk PC (72% vs 55%)

3. Less likely to die from PC (relative reduction of 20%)

4. PSA screening was associated with a significant absolute reduction of 0.71 prostate-cancer death per 1000 men after an average follow-up of 8.8 years (median, 9.0).

   To prevent one death from PC: 1410 screened \(\rightarrow\) 48 treated

PC Screening Guidelines: Evolving

<table>
<thead>
<tr>
<th></th>
<th>PSA Screening (life expectancy &gt;10 yrs)</th>
<th>PSA Screening (+risk factors)</th>
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<tbody>
<tr>
<td>American Cancer Society</td>
<td>Offer at age 50-70</td>
<td>Offer at age 45</td>
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<tr>
<td><a href="http://www.cancer.org">www.cancer.org</a></td>
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<tr>
<td>American Urologic Association</td>
<td>Baseline 40 years old</td>
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<td><a href="http://www.urolgyhealth.com">www.urolgyhealth.com</a></td>
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<tr>
<td>National Comprehensive Cancer</td>
<td>Baseline 40 years old:</td>
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<tr>
<td>Network</td>
<td>&gt;1 ng/mL annual follow-up</td>
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<tr>
<td><a href="http://www.nccn.org">www.nccn.org</a></td>
<td>&lt;1 ng/mL rescreen age 45</td>
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<tr>
<td>US Preventive Services Task</td>
<td>No screening for patients &gt;75</td>
<td></td>
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<tr>
<td>Force</td>
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<td><a href="http://www.annals.org">www.annals.org</a></td>
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</tbody>
</table>

Baseline PSA at age 40 is a stronger independent predictor of PC risk than ethnicity, family history, or DRE. (Loeb et al, AUA 2005)
Risk Factors for Prostate Cancer
Offering Detection to Those Who Need It

• **Age**
  - Less than 10% of prostate cancer cases are diagnosed in men < 54 years
  - 64% of prostate cancer is detected between 55 and 74 years

• **Race/Ethnicity**
  - 58% higher incidence for black men compared with white men
  - 143% greater mortality for black men compared with white men

• **Genetics/Family History**
  - Relatives of patients younger than 55 years have greater risk than those with older affected relatives
  - Strong familial clustering in families with early onset prostate cancer
  - Number of affected family members and age of onset are strong determinants of risk for other family members
  - At least 8 candidate susceptibility genes for prostate cancer have been reported


---

Risk of Prostate Cancer as a Function of PSA, DRE and Family History

![Graph showing risk of prostate cancer as a function of PSA and DRE](image_url)

*Pienta K. Urology. 2009;73(S5A):11-20.*

PSA: prostate specific antigen; DRE: digital rectal exam
Data Mining Continues to:

better define risk profiles,
PSA cutoffs,
and testing intervals

We can learn a lot from a single test.
Prostate cancer risk curve (MPP-cohort in Malmö): PSA at age 60

Lilja: Metastases from prostate cancer (p<0.001; AUC of 0.86; 95% C.I. 0.79, 0.92)

A Sample Algorithm
Baseline Screen at age 45

- **PSA ≥ 3§ ng/ml:** Consider biopsy
- **PSA > 1 but < 3 ng/ml:** Return for biennial PSA
- **PSA 0.65† – 1# ng/ml:** Return for PSA at age 50 (for men at age <50) or in 5 years (for men > 50)
- **PSA < 0.65 ng/ml:** Return for PSA at age 55 (for men at age 50 or less) or at age 60 (for men >50)

- † PSA 0.65 ng/ml equals population-based median at age <50
- # PSA 1 ng/ml equals top 80th centile at age <50
- § PSA 3 ng/ml above top 95th centile at age <50
For men aged 60 - 70

- PSA ≥ 3 ng/ml$: consider biopsy

- PSA > 1 but < 3 ng/ml. Return for biennial (yearly) PSA till age 70

- PSA ≤ 1 ng/ml$: no further screening

$: PSA ≈ 1 ng/ml equals population-based median at age <60
$: PSA ≈ 3 ng/ml corresponds to the top 10% PSA levels at age 60

Prostate Cancer Screening
Balancing the Benefits and Harms

- PSA screening detects cancers earlier

- Does screening reduce mortality due to prostate cancer?

- Overdiagnosis/Overtreatment
  - False positives lead to biopsies, pain, discomfort
  - Costs: screening, biopsy, treatment
  - Reduced quality of life, increased anxiety

- Non-invasive prostate cancer (“clinically insignificant”)
  - May never produce symptoms
  - May not progress to a life-threatening point before death due to other causes

- Issues associated with treatment for prostate cancer
  - Erectile dysfunction, Urinary incontinence, Bowel dysfunction, Death

Other Biomarkers for Prostate Cancer

- PCA3 (prostate cancer antigen 3) – molecular urine assay using transcription-mediated amplification

- EPCA-2 (early prostate cancer antigen) – ELISA assay for serum samples

- Circulating tumor cells

PCA3 Score vs Biopsy Results

Urine Collected at Biopsy

Mean PCA3 scores: 23.6 ± 40.5, 30.1 ± 20.8, 50.6 ± 23.5

Serum Analysis of EPCA-2
(a prostate cancer-associated nuclear protein)

N = 330 serum samples screened. ELISA cutoff: 30 ng/mL.


Prostate Cancer Overview and Recent Advances:
How Can a Common Disease Be So Controversial?

1. The statistics:

2. A framework:

3. Risk adapted diagnostics:

4. Risk adapted prognostics to guide treatment:
   Guiding treatment selection.
Objectives and Unmet Needs for Clinically Localized Disease

Minimize morbidity: Overtreatment.

Maximize cure

OBJECTIVES

No Cancer Diagnosis
Clinically Localized Disease
Rising PSA

UNMET NEEDS

Risk or presence of:
symptoms, metastases, or death from disease

Tailored Approach

Prostate Cancer Treatments for Localized Disease

- Active Surveillance (Watchful Waiting)
- Radical Prostatectomy
- Radiation
- Hormones
- Investigational: Chemotherapy, Cryoablation, HIFU, etc…
- Combinations of the above
Limitations of T stage for Prognostication:
“T1c” Disease Represents a Range of Prognoses:

T1: Clinically unapparent tumor not palpable nor visible by imaging
   T1a: Tumor incidental histologic finding in ≤ 5% of tissue resected
   T1b: Tumor incidental histologic finding in ≥ 5% of tissue resected
   T1c: Tumor identified by needle biopsy (e.g., because of elevated PSA)
T2: Tumor confined within prostate
   T2a: Tumor involves 1 lobe
   T2b: Tumor involves both lobes
T3: Tumor extends through the prostate capsule
   T3a: Extracapsular extension (unilateral or bilateral)
   T3b: Tumor invades seminal vesicle(s)
T4: Tumor is fixed or invades adjacent structures other than seminal vesicles:
    bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

Gleason Grading System

Image: Chris Pearson
Preoperative Nomogram for Prostate Cancer Recurrence

Instructions for Physician: Locate the patient’s PSA on the PSA axis. Draw a line straight upwards to the Points axis to determine how many points towards recurrence the patient receives for his PSA. Repeat this process for the Clinical Stage and Biopsy Gleason Sum axes, each time drawing straight upward to the Points axis. Sum the points achieved for each predictor and locate this sum on the Total Points axis. Draw a line straight down to find the patient’s probability of remaining recurrence free for 60 months assuming he does not die of another cause first.

Note: This nomogram is not applicable to a man who is not otherwise a candidate for radical prostatectomy. You can use this only on a man who has already selected radical prostatectomy as treatment for his prostate cancer.

Instruction to Patient: “Mr. X, if we had 100 men exactly like you, we would expect between <predicted percentage from nomogram - 10%> and <predicted percentage + 10%> to remain free of their disease at 5 years following radical prostatectomy, and recurrence after 5 years is very rare.”

A Recent Inventory of Prostate Cancer Prediction Tools

1. The literature search generated 111 prediction tools that may be applied to patients clinical stages of disease.

2. Nomograms provide evidence.

3. Allow individualized predictions.

4. Are more accurate than clinicians.

Shariat et al., Curr Opin Urol 18:279, 2008
Some Are Out of Date When Published Because of a Change in Practice Patterns: Models for the presence of prostate cancer on biopsy

1. Number: 12

2. Median number of cores: 6 (N/A in 4, only 1 had 11)

3. “Accuracy”: 76%

4. Validation: None in 7.

Shariat et al., Curr Urol Opin, 18:279, 2008

“T1c” Disease on DRE: A Data Dictionary That is Validated Prospectively Will be Required For Each Measurement

Koutcher et al., Radiology 246:480, 2008
These Models Require Prospective Validation

1. Validation involves more than adding cases to an existing model.

2. Requires testing on an independent data set.

3. Strength of association with outcome generally in the .75-79 range (right 3 out of 4 times).

4. Few are tested prospectively in the context of a trial.
On the other end of the spectrum --

It is important to remember that even supposedly “high risk” patients can achieve long term favorable outcomes, if they are definitively treated.

Models for A High Risk of PSA Recurrence Have Variable Performance

Kattan Nomogram

P. Scardino
Patients with “High Risk” Cancers Can Do Very Well Long Term: PSA Recurrence MAY NOT Mean Death From Disease

Risk Adapted Therapy for Localized Disease: We Need Better Models For Clinically Significant Outcomes

Factors Affecting Survival and/or Quality of survival

Factors and biological mechanisms affecting outcomes mediated through the model (nomogram)

Factors and biological mechanisms affecting outcomes not-mediated through the model (nomogram)
Risk Adapted Therapy Must Consider

1. Characteristics of the cancer
   - Stage (2002 TNM System)
   - Gleason grade, PSA
   - Systematic biopsy results
   - Predictive models: Staging tables - nomograms
   - Metastatic evaluation

2. The patient:
   - Age
   - Co-morbidity
   - Demographic factors
   - Personal concerns (utilities)

3. The environment:
   - Availability and quality of each treatment option

4. The expertise of the treating Physicians:
   - Surgeon / Radiotherapist / Imaging / Pathology / Diagnostics

Techniques Are Now Available to Isolate and Characterize Circulating Tumor Cells
Detection, Prognostication and Molecular Profiling

- Gradient Centrifugation
- Immunomagnetic Separation
- Immunoaffinity (“CTC” Chip)
- Filtration

†G. Vona, et al, American Journal Of Pathology, 2000

Courtesy of Dr. Richard Cote
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Acknowledgements

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Heiko Schoder  
Peter Smith Jones

Heddi Hricak