The Quantum Theory of Prostate Cancer Screening
-or-
“How I Learned to Love Epistemic Ambivalence”

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Prostate Cancer Incidence (30 years)

Incidence per 100,000 men

Decline may be from a combination of reduced screening and under-reporting from increase in use of active surveillance. (AS cases not always captured in registries.)

U.S. Preventative Services Task Force Recommendation

The Task Force Recommendation on PSA-based Screening for Prostate Cancer

Population
This recommendation applies to men of all ages. It does not include the use of the PSA test for monitoring in men who have been diagnosed with or are being treated for prostate cancer.

Possible benefit of screening:
In an unselected population, about 5 out of every 1,000 men will die from prostate cancer after 10 years.

Results of several large trials have shown that, at best, PSA screening may help 1 in 1,000 avoid death from prostate cancer. After at least 10 years, most help, the number needed to screen, is even smaller. This means that with PSA screening, 4.5 out of every 1,000 men will die from prostate cancer after 10 years.
Natural History of Prostate Cancer

- 1 in 7 men* will be diagnosed with CAP
  - 1 in 6 of those will die of CAP
- Overall, 1 in 39* men will die of CAP
- The risk of death from most localized disease at 5 years without treatment = 0%
- The risk of death from most localized disease at 15 years without treatment = 15%

Shift in Management Strategy 2003 to 2015

<table>
<thead>
<tr>
<th>Year</th>
<th>Surg</th>
<th>Rad</th>
<th>AS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>45%</td>
<td>48%</td>
<td>7%</td>
</tr>
<tr>
<td>2015</td>
<td>35%</td>
<td>25%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Active Surveillance

- By 2 years
  - 20% off active surveillance
- By 5 years
  - 40% off active surveillance

Ref: Klotz, J of Clinical Oncology, 1/1/2010
Risks & Harms of Treatment

1. Cost *

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMRT (Radiation)</td>
<td>$31,574</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>$17,076</td>
</tr>
<tr>
<td>Brachy + IMRT</td>
<td>$36,795</td>
</tr>
<tr>
<td>Open Prostatectomy</td>
<td>$16,409</td>
</tr>
<tr>
<td>Robotic Prostatectomy</td>
<td>$16,762*</td>
</tr>
</tbody>
</table>

* Recently decreased 33% by CMS

JCO April 20, 2011 vol 29 no. 12:1517-1524 (Medicare 2005)

2. Quality of life
   a) Urinary incontinence
   b) Sexual dysfunction
   c) Psychosocial effects

3. Risk of secondary malignancy with radiation therapy

Relative Risk of Secondary Malignancy from Radiotherapy

<table>
<thead>
<tr>
<th>Secondary Cancer</th>
<th>No Radiotherapy</th>
<th>Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>Relative risk 0.76</td>
<td>1.42</td>
</tr>
<tr>
<td>Rectal</td>
<td>Relative risk 0.74</td>
<td>1.70</td>
</tr>
</tbody>
</table>

Data Source: SEER Database 1992-2010 (441,504 patients)

Ref: Cancer, Volume 120, Issue 17, pages 2735–2741, September 1, 2014

American Academy of Family Physicians

• Do not routinely screen for prostate cancer using a PSA test or digital rectal exam

• In men with a life expectancy ≤ 10 years,* it is recommended that general screening for prostate cancer with total PSA be discouraged, because harms appear to outweigh potential benefits.
  o Type and strength of recommendation: evidence-based, strong
Following Guidelines

- Defining population at risk
- Accurate actuarial assessment
- Confirming the need for evaluation

Population at Risk for Prostate Cancer

<table>
<thead>
<tr>
<th>Accepted Risks</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive family history</td>
<td></td>
</tr>
<tr>
<td>• African-American</td>
<td>1.6X</td>
</tr>
<tr>
<td>• 1 first-degree relative</td>
<td>2X</td>
</tr>
<tr>
<td>• 2 relatives</td>
<td>3X</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proposed Risks</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity (increased risk of advanced disease)</td>
<td>10%</td>
</tr>
<tr>
<td>Chronic prostate infections</td>
<td>?</td>
</tr>
<tr>
<td>Viral etiology</td>
<td>?</td>
</tr>
</tbody>
</table>

Actuarial Table of Life Expectancy

American Males

- e.g. 73 yo man has a 12 yr life expectancy
Confirming the PSA

- 37% of patients with elevated PSA normalize 4 weeks later with no treatment
- Empiric treatment with antibiotics in an asymptomatic patient is no longer recommended

Schemes for Improving the Prognostic Significance of PSA

- Age-specific reference ranges
- PSA velocity
  - Increase of 0.75 ng/mL in 1 year worrisome for CAP
  - Increase of 2.0 ng/mL in 1 year worrisome for aggressive CAP
- Free and total PSA
- PSA density
  - CAP can produce 10x more PSA per volume than BPH
  - 0.15 ng/mL/cm³
  - Requires TRUS measurement of prostate volume

Schemes for Improving the Prognostic Significance of PSA

<table>
<thead>
<tr>
<th>Age Range (Years)</th>
<th>Asian Americans</th>
<th>African Americans</th>
<th>Caucasians</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 to 49</td>
<td>0 to 2.0 ng/mL</td>
<td>0 to 2.0 ng/mL</td>
<td>0 to 2.5 ng/mL</td>
</tr>
<tr>
<td>50 to 59</td>
<td>0 to 3.0 ng/mL</td>
<td>0 to 4.0 ng/mL</td>
<td>0 to 3.5 ng/mL</td>
</tr>
<tr>
<td>60 to 69</td>
<td>0 to 4.0 ng/mL</td>
<td>0 to 4.5 ng/mL</td>
<td>0 to 4.5 ng/mL</td>
</tr>
<tr>
<td>70 to 79</td>
<td>0 to 5.0 ng/mL</td>
<td>0 to 5.5 ng/mL</td>
<td>0 to 6.5 ng/mL</td>
</tr>
</tbody>
</table>

Free:Total PSA ratio:

- 50-59 years
  - < or = 0.10: 49.2%
  - 0.11-0.18: 26.9%
  - 0.19-0.25: 18.3%
- 60-69 years
  - < or = 0.10: 57.0%
  - 0.11-0.18: 33.9%
  - 0.19-0.25: 23.9%
- 70 or >: 64.5%

Based on free:total PSA ratio: the percent probability of finding prostate cancer on a needle biopsy by age in years.
Case

- 55 y/o man
- PSA 5.0 ng/ml (repeated and confirmed)
- 1 cm prostate nodule

Discussion of Management

The Heisenberg Uncertainty Principle

The more precisely the position of a particle is known, the less precisely its momentum can be known.

- Sensitivity versus Specificity
- Werner Heisenberg 1901-1976

Epistemic Ambivalence
Schrödinger’s Cat
The Paradox of “Not Knowing”

Quantum superposition as applied to prostate cancer

Epistemic Ambivalence

The patient both has and does not have prostate cancer until he is evaluated.

The Many-Worlds Theory

PSA Screening

Harms and decreased quality of life

Significant disease found and cured

Best of all possible worlds

Died of other causes and never knew

Died of prostate cancer

No PSA Screening

Died of prostate cancer

Harms and decreased quality of life

Significant disease found and cured

Best of all possible worlds

Died of other causes and never knew

Died of prostate cancer
Prostate Cancer Management Paradox

Since 1987
• Early diagnosis improved
• Death rates declined

But

• Overdiagnosis / overtreatment
• Decreased quality of life

The Problem Is...

• What do I want to know?
• Why do I want to know it?

The Process of Knowing

One way

Prostate biopsy
The Fundamental Problem

Risks and Harms of Prostate Biopsy

• Bleeding 2%
• Infection (requiring hospitalization) 3%
• False-negative result
• Diagnosis of “insignificant” disease

“Significant” vs “Insignificant”

• Arbitrary and controversial
• Flawed definition based on
  o Sampling error
  o Multi-focality
  o 30% “insignificant” upgraded to “significant” at radical prostatectomy
Necessary vs Unnecessary Biopsy

- Current positive biopsy rate 50%
- A "negative" biopsy is not an unnecessary biopsy
- Men with "insignificant cancer" 11%

<table>
<thead>
<tr>
<th>11% Insufficient</th>
<th>39% Significant</th>
<th>28% False-negative</th>
<th>30% True-negative</th>
</tr>
</thead>
</table>

Biopsy positive for cancer

Biopsy negative for cancer

Making Biopsy Better

- Careful selection

- "Targeting" based on ultrasound or MRI
  - Reduce number of cores
  - Transperineal approach if appropriate

"Multiparametric" Ultrasound

- Gray Scale: Excellent for standard anatomic findings
- Color Doppler: Regions of increased blood flow
- Contrast-Enhanced: Micovascularity
- Elastography: Shear-wave elastography is quantifiable and reproducible
The Multiparametric Approach of MRI

T2-weighted  Diffusion weighted  Dynamic contrast-enhanced

Negative predictive value of 95%!

Decision Making Using New Technology

Pre-biopsy

Blood (variants of PSA) $80
[(4proPSA/free PSA) + 4PSA]

Probability of prostate cancer being present?

4Kscore®

Biopsy

Negative

Positive

If PSA levels stay high after negative bx is a repeat bx needed?

Blood (variants of PSA and a related protein) $400

Is the cancer aggressive or non-aggressive?

Biopsy $3,300

Prolaris®

Blood $4,400

Elevated PSA

How likely is it that “significant” cancer (≥ Gleason 7) is present?

4Kscore®, Prostate Health Index, PCA3
4Kscore®

The likelihood of metastatic disease within 20 years

- Before biopsy
- After negative biopsy

(Total PSA, free PSA, intact PSA, hK2)

AUC = 0.83

False Positive Rate (100 - Specificity)

True Positive Rate (Sensitivity)

Confirm MDx®

Is a negative biopsy truly negative?

Looks at DNA metabolism

“Halo” effect

Proteomic or epigenetic changes

Prolaris®

What is the risk of dying from untreated disease in < 10 years?

Looks at 46 gene expressions

Proteins

miRNA
**Oncotype® Diagnosis**

Likelihood of aggressive disease on radical prostatectomy

- Expression of cancer-related genes
- 4 different pathways

**Cancer Moonshot 2020**

- Liquid biopsy
- Cancer on a chip
- Designer drugs

**My Current Recommendations for Physicians**

- Annual PSA screening based on risk and life-expectancy
- Risk stratify PSA results (e.g. ASRR, free PSA)
- Repeat an abnormal PSA at 6 weeks
- Refer to urology if persistently elevated
My Current Recommendations for Patients

- Know your risk factors
  [http://www.yourdiseaserisk.wustl.edu (select Cancer, Prostate)]
- Control your diet and body weight
- Engage in a healthy lifestyle including exercise
- Make PSA and rectal exam part of your annual physical

Additional References

AUA University – Online Webcasts
[auanet.org (AUAU)]
Prostate Biopsy (Video)

Hyperechoic area

Traditional Biopsy

Systematic NOT blind
Incorporating Suspicious Areas into the Paradigm of Systematic Biopsy