Conceptual basis for active surveillance

1. Screening results in overdiagnosis
2. Clinically insignificant disease can be identified
3. All treatments have significant side effects and cost.
4. Delayed radical treatment is still curative.
5. The psychological burden is acceptable (less than the effects of overtreatment).
The Screening Problem: U.S. Example
Welch JNCI 2005:97:1132-7

• Biopsy of all men with PSA > 2.5:
  ▶ Result in 775,000 diagnosed cases,
    3 x higher than current incidence

▶ This is 25 times the 30,350
  Prostate Cancer deaths per year in the US!
PSA testing in US men

- 75% of men and 87% of male MDs have had a PSA
- 50% tested regularly
- Lifetime risk of diagnosis 19% (from 10% in pre PSA era)
- >90% treated radically
Overtreatment is common

- Studies of non-screen detected men
  - Albertsen
  - Johannson
  - SPCGS-4

- PSA era studies
  - Cancer registries
  - PCPT
  - ESRPC
20-Year Outcomes Following Conservative Management of Clinically Localized Prostate Cancer
Albertsen P et al, JAMA. 2005;293:2095-2101

Lead Time effect 0 10 20 30

Years 0 10 20 25

Gleason score shift 10 20 30
**ESRPC: % of indolent cancer at surgery**

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<tr>
<th>PSA</th>
<th>1(^{st}) screen</th>
<th>2(^{nd}) screen</th>
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<tr>
<td>&lt;3</td>
<td>67</td>
<td>56</td>
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<td>3-4</td>
<td>45</td>
<td>31</td>
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<td>4-10</td>
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<td>&gt;10</td>
<td>13</td>
<td>36</td>
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<td>Total</td>
<td>33</td>
<td>43</td>
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### Estimates of overdiagnosis: Draisma 2007

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<tr>
<td>T1</td>
<td>69%</td>
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<td>T2</td>
<td>38%</td>
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<td>T3</td>
<td>30%</td>
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<tr>
<td>Gleason &lt; 7</td>
<td>62%</td>
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<td>7</td>
<td>40%</td>
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<td>&gt;7</td>
<td>8%</td>
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Candidates for active surveillance

- 60% of new cases are Gleason 5-6 (CapSure)
- 80% PSA ≤ 10
- 65% T1c, 25% T2a
- Thus 45-50% of newly diagnosed cases are favorable risk
- About 50% of these fulfill criteria for insignificant prostate cancer
- One third of patients (85,000/year in US and Canada)
The three challenges of surveillance

- Identifying the right patient
- Communicating safety (‘cancer hysteria’)
- Trigger for intervention
  - Timely treatment for patients reclassified as high risk
  - Avoid jumping the gun
Surveillance therapy with selective delayed intervention

- Favorable risk (D’Amico):
  - Gleason $\leq 6$
  - PSA $\leq 10$
  - T1c/T2a

- In younger patients
  - $\leq 1/3$ cores positive
  - $< 50\%$ involvement of all cores

- If available, PSA DT $> 3$ years or PSA velocity $< 2.0$ ng/ml/year

- Hypothesis:
  - Most can be observed
  - Delayed treatment effective in those whose disease appears to be higher risk over time
‘Animals in the barnyard’ and cancer natural history

Only the rabbits benefit from early diagnosis and treatment.
Identifying the rabbits: the controversies

- PSA kinetics
  - Reliability (too late)
  - Interpretation (Velocity vs doubling time)
  - How to calculate

- Biopsy
  - How often, how many cores
  - Trigger for intervention: extent/volume/grade shift
Identifying the rabbits: Toronto approach

- Rapid PSA doubling time
  - PSA every 3 months x 2 years then every 6 months
  - Usually decision to intervene at 2 years, 8-9 PSAs
  - PSA DT < 3 years (20% of patients)

- Gleason grade progression
  - Biopsy at 1 year (confirmatory)
  - Then every 4 years (progression)
  - Treat if Gleason 4+3 or worse (5% of patients)

- Unequivocal clinical progression to T3 (3%)

- Guidelines, not rules
Distribution of PSA doubling times in 331 patients on surveillance. Choo, Klotz J Urol 2002
Overall and disease specific survival in Toronto surveillance cohort (adapted from Klotz L, J Clin Oncol. 2005 Nov 10;23(32):8165-9)

Overall Survival (n = 331)

Cause Specific Survival (n = 331)

P=0.51

P=0.05
The problem of calculating PSA DT

FLO: First and last months observation
BLF: Best line fit
General Linear Mixed Modeling

- Allows for individual predictors of intercept and slope to be integrated into model
- Aggregate estimate of variation used to reduce effect of individual PSA variation on PSA DT calculation
- For high risk line:
  \[
  \ln(PSA) = 1.003 \times \ln(baseline\ PSA) + 0.112 \times time + 0.041 \times time^2
  \]
- For low risk line:
  \[
  \ln(PSA) = 1.03 \times \ln(baseline\ PSA) - 0.0056 \times Age + 0.046 \times Gleason + 0.081 \times time + 0.0038 \times time^2
  \]
Zhang L, Loblaw DA, Klotz L. J Urol 2006
High risk—Intervene

Intermediate: continue close follow up

Low risk: relax follow up

GLMM approach to PSA DT during active surveillance

www.psakinetics/sunnybrook.ca
Baseline data for patient 3. Institution: TSRCC
Age: 79.0 years; Gleason: 6 (mean value used)

<table>
<thead>
<tr>
<th>Start YYYY-MM-DD</th>
<th>End YYYY-MM-DD</th>
<th>PSA (ng/ml)</th>
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<tbody>
<tr>
<td>1995-10-20</td>
<td></td>
<td>8.70</td>
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<td>1996-02-23</td>
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<td>1996-11-28</td>
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<td>7.30</td>
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<td>1997-02-27</td>
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<td>10.30</td>
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<tr>
<td>1997-03-27</td>
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<td>8.90</td>
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<td>1997-05-22</td>
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<td>9.20</td>
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<td>1997-09-04</td>
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<td>7.90</td>
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<tr>
<td>1997-11-20</td>
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<td>10.70</td>
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Select PSA metric:
- Velocity (lin.model)
- Doubl.Time (exp.model)

Summary: PSA doubling time = 6.4 years.

For the 3.5-year period PSA level was fluctuating between progression and non-progression lines therefore the patient should have ongoing close monitoring.

http://psakinetics.sunnybrook.ca
Effect of PSA triggers on stable patient cohort

<table>
<thead>
<tr>
<th>Trigger</th>
<th>Percentage</th>
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<tr>
<td>General linear mixed model of ln(PSA)</td>
<td>0%</td>
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<tr>
<td>PSA threshold &gt; 10</td>
<td>15%</td>
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<tr>
<td>Linear regression of ln(PSA) vs time &lt; 2yr</td>
<td>39%</td>
</tr>
<tr>
<td>ln(PSA) vs time &lt; 2 years using first and last PSA</td>
<td>29%</td>
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<tr>
<td>Actual PSA velocity &gt; 2.0</td>
<td>49%</td>
</tr>
<tr>
<td>Calculated PSA velocity &gt; 2.0</td>
<td>49%</td>
</tr>
</tbody>
</table>
PSA DT and surveillance:

- 270 active surveillance (from Swedish arm of ESRCP)
  - 39% treated
  - 70 RPs
    - 9 (12%) PSA relapse
    - 80% of these had PSA DT < 2 years
    - 0/37 with PSA DT > 4 years relapsed
  - 14 deaths (5%); 0 from PCa
  - No metastatic progression
175 favorable risk patients managed with ‘Toronto’ approach
99 with > 1 yr f/u, median 4 yrs
Mean age 66
Mean PSA 5.7
Intervention 8%: 2 RP, 3 XRT, 3 ADT
Mean PSA DT
  Untreated 13.1 yrs
  Treated 3.6 yrs
5 year PFS 85%
PCa survival 100%
Modelling the risk: A number needed to treat analysis
# The Scandinavian trial

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<th>Mortality reduction at 10 years</th>
<th>NNT</th>
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<td><strong>Bill-Axelson</strong></td>
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<tr>
<td>2005</td>
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<td>&lt;65</td>
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<td></td>
<td>➤65</td>
<td>0.3%</td>
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A 50% risk reduction may yield little clinical benefit

- Clinically insignificant Disease
- Cured by therapy
- Death from disease
Swedish cohort differed from patients diagnosed in 2006

Swedish trial

- Mean age 64.7
- Mean PSA 12.8
- 5% screen detected
- 75% T2
- 40% Gleason 7 or higher

Typical screen diagnosed patient

- Mean age 62
- Mean PSA 6
- 95% screen detected
- 70% T1c
- 60% Gleason ≤ 6
- Volume migration
Unanswered question:

- NNT for:
  - Low grade
  - Small volume
  - Screen detected
  - Option of selective delayed therapy
NNT for each cancer death avoided at 20 years for favorable risk prostate cancer: RP vs surveillance

- Swedish trial 10 years
- Swedish trial 20 years (estimate)
- Lead time in screened population 20 years
- Corrected for grade difference

Include salvage opportunity
Predicted survival - conservative management of screen-detected prostate cancer

Parker et al. BJC (2006) 1361-8
Why Men Don’t Want to Wait
Cancer Hysteria: Who benefits?

- Fundraising Cancer Societies
- Cancer Research organizations
- Physicians
- Researchers
- Other health care workers in the cancer field
- Media
- Environmental activists
Who is Disadvantaged by Cancer Hysteria?

The patient
Fear is a Danger to Your Health

‘Cancer’ and sense of doom

“The dread expands and solidifies into such a major obstacle that I simply can’t get past it.”

Patients may feel so hopeless that they can’t absorb the medical facts
Communicating Risk

“The first step in positive thinking is to be able to understand what’s actually going on. Positive thinking begins with clear thinking.”

- a Patient
“I will remember that there is an art to medicine as well as science in that warmth, sympathy and understanding may outweigh the surgeon’s knife or the chemist’s drug”.

-Louis Lasagna, Academic Dean of the School of Medicine at Tufts University, 1964
The Crucial Question:

“What do you want from the rest of your life?”
Our Responsibility

- Reassure and offer hope
- Put the risk in perspective
- De-mystify the word ‘Cancer’
- Provide accurate data (use facts)
- Help the patient think clearly about the risks and benefits
- Avoid exploiting the patient’s fears
- Primum non nocere
Risk Assessment

The scientific community is divided. Some say this stuff is dangerous, some say it isn't.
A Phase III Study of Surveillance Therapy Against Radical Treatment (START) in patients Diagnosed with Favourable Risk Prostate Cancer

NCIC CTG Protocol Number: PR.11
SWOG/ECOG/CALGB/RTOG/UKCCCR

Study to open 2Q 2007 (any day now!)
START Trial Schema

Randomize (within 6 months of initial diagnosis)

**ARM 1:**
Radical intervention (radical prostatectomy or radiotherapy based on patient and physician preference)

**ARM 2:**
Active surveillance with radical intervention for either
- Biochemical progression
- Grade progression
- Clinical progression

Prostate cancer death
Biomarker Discovery

Serum Bank

Serial Biopsy Bank

Validation of Nomograms

START Trial

Global Study 2100 pts

Natural History Data Base

Correlative Sciences

Figure 4:

Prostate Cancer Specific Survival

- PSADT ≥15.6 months
- PSADT 9.0 - 14.9 months
- PSADT 3.8 - 8.9 months
- PSADT <3.0 months

Years after Biochemical Recurrence

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84-Month Rec. Free Prob.

0.01 0.1 0.3 0.5 0.7 0.8 0.9 0.95 0.98 0.99
Thank You