Prostate Cancer – Known 2011

- Screening of healthy, young, well-informed men with serum PSA reduces significantly the risk of dying of prostate cancer (21% – 53%)
- It does so at the risk of over detection – detecting disease which would not have become clinically apparent over a patient's lifetime if left untreated
- Detection and treatment are, currently, too tightly linked
- Many are misinformed and confused on these issues

The Good News:

But at what cost?
The Changing Face of Prostate Cancer

The Biggest Risk with Screening is?

- **Over Detection** Which is Compounded by **Over Treatment**

Possible solutions

- 1. Tailor treatment to biology; reduce treatment for minimal-risk tumors
- 2. Identify high-risk populations and target prevention and screening efforts
- 3. Identify new screening markers better able to identify high-risk cancer early
- 4. Develop clinical and patient tools to support informed decision-making about prevention, screening, biopsy, and treatment
Possible solutions – UCSF Active Surveillance Program

1. Tailor treatment to biology; reduce treatment for minimal-risk tumors
2. Identify high-risk populations and target prevention and screening efforts
3. Identify new screening markers better able to identify high-risk cancer early
4. Develop clinical and patient tools to support informed decision-making about prevention, screening, biopsy, and treatment

Esserman et al. JAMA 2009; 302:1685

Active Surveillance for Early Stage Prostate Cancer
UCSF Experience

Active Surveillance
Rationale and Hypotheses

- Screening results in the detection of very early stage/grade lesions - many indolent
- Current staging/grading techniques accurate
- Natural history prolonged and can be measured

- Surveillance in low risk patients is feasible and associated with a limited risk of progression
- Progression can be quantitated
- Predictors of progression and treatment can be identified

The UCSF Active Surveillance Cohort
UCSF Cohort

- Entry criteria
  - PSA < 10
  - Gleason sum ≤ 6, no pattern 4/5
  - Stage T1-T2
  - ≤ 33% cores positive, ≤ 50% any single core positive

UCSF COHORT

- > 750 patients, update on 532
- Mean PSA 6.2 ng/ml
- Mean number of cores 12.7
- Mean number cores positive 1.8
- 80% CAPRA 0 - 2

Table 1. Baseline clinical information (n=532)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age ± SD (years)</td>
<td>62.5 ± 8.2</td>
</tr>
<tr>
<td>Year of Diagnosis -- no. (%)</td>
<td></td>
</tr>
<tr>
<td>≤ 2000</td>
<td>74 (14)</td>
</tr>
<tr>
<td>2001-2005</td>
<td>283 (53)</td>
</tr>
<tr>
<td>≥2006</td>
<td>175 (32)</td>
</tr>
<tr>
<td>PSA at Diagnosis -- no. (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;6</td>
<td>175 (52)</td>
</tr>
<tr>
<td>6-10</td>
<td>164 (31)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>66 (12)</td>
</tr>
<tr>
<td>Clinical T Stage -- no. (%)</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>346 (66)</td>
</tr>
<tr>
<td>T2</td>
<td>180 (34)</td>
</tr>
<tr>
<td>Gleason Grade -- no. (%)</td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>484 (93)</td>
</tr>
<tr>
<td>7 (3+4)</td>
<td>31 (6)</td>
</tr>
<tr>
<td>7 (4+3)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>8-10</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Biopsy Cores Positive -- no. (%)</td>
<td></td>
</tr>
<tr>
<td>≤33%</td>
<td>411 (88)</td>
</tr>
<tr>
<td>&gt;33%</td>
<td>58 (13)</td>
</tr>
</tbody>
</table>

Table 2. Follow-Up During Surveillance

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Follow-Up ± SD (months)</td>
<td>55 ± 38</td>
</tr>
<tr>
<td>Mean PSA's ± SD (no.)</td>
<td>13 ± 9</td>
</tr>
<tr>
<td>Number of Biopsies -- no. (%)</td>
<td></td>
</tr>
<tr>
<td>Diagnostic Only</td>
<td>112 (21)</td>
</tr>
<tr>
<td>1 Repeat</td>
<td>194 (37)</td>
</tr>
<tr>
<td>≥2 Repeats</td>
<td>226 (42)</td>
</tr>
<tr>
<td>Gleason Upgrade -- no. (%)</td>
<td>144 (27)</td>
</tr>
<tr>
<td>Treatment -- no. (%)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>369 (69)</td>
</tr>
<tr>
<td>Radical Prostatectomy</td>
<td>83 (16)</td>
</tr>
<tr>
<td>Radiation</td>
<td>58 (11)</td>
</tr>
<tr>
<td>Androgen Deprivation</td>
<td>22 (4)</td>
</tr>
<tr>
<td>Survival -- no (%)</td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>518 (97)</td>
</tr>
<tr>
<td>Died of Other Cause</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Died of Unknown Cause</td>
<td>6 (1)</td>
</tr>
</tbody>
</table>
Defining the Triggers for Intervention

- Change in PSA kinetics
- Progression on follow-up biopsy
- Patient preference
- Clinical/radiographic evidence of local/distant progression

1/3 of those treated do so without any evidence of progression!
Defining the Triggers for Intervention: PSA Kinetics

Whitson et al (in press JU)

Defining the Triggers for Intervention: Biopsy Progression

- Increase in Gleason grade
- Increase in tumor volume
  - Increase in absolute cores involved with cancer
  - Increase in percent of positive cores >33%
  - Increase in absolute tumor length (mm)
  - Increase in percent of tumor tissue >50% within a single core

Defining the Triggers for Intervention: Change in Gleason Grade on Serial Biopsy

Reproducibility of Tumor Location in Men who Experienced Upgrading

Degree of Site Match Upgrading <1 year

N (%)

<table>
<thead>
<tr>
<th>Upgrading &gt;1 year</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (&lt;25%)</td>
<td>28 (39)</td>
</tr>
<tr>
<td>Partial (25-75%)</td>
<td>25 (35)</td>
</tr>
<tr>
<td>Yes (&gt;75%)</td>
<td>19 (26)</td>
</tr>
</tbody>
</table>

In 102 men that experienced an upgrade who had a mapped diagnostic biopsy, 37% (38) did so at a sextant site that did not previously have cancer.

Median time between biopsies 13 months (9-20 IQR)
Defining the Triggers for Intervention: Change in Tumor Volume on Serial Biopsy

Volume change defined by:
1) increase in percent cores positive >33%
2) increase in % tumor in single core >50%

Defining the Triggers for Intervention: Association Gleason Grade and Cancer Volume on Serial Biopsies

<table>
<thead>
<tr>
<th>Upgrade on Biopsy</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-&gt;2</td>
<td>2.80</td>
<td>1.33-5.87</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>2-&gt;3</td>
<td>3.56</td>
<td>1.27-9.95</td>
<td>0.02</td>
</tr>
<tr>
<td>3-&gt;4</td>
<td>5.07</td>
<td>0.85-30.45</td>
<td>0.08</td>
</tr>
<tr>
<td>4-&gt;5</td>
<td>8.43</td>
<td>0.64-110.69</td>
<td>0.11</td>
</tr>
<tr>
<td>Upgrade Any Biopsy</td>
<td>2.11</td>
<td>1.20-3.72</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Adjusted for age, clinical stage, PSA at diagnosis, prostate volume, millimeters of tissue taken at diagnosis, and number of total biopsies

Can we determine the risk of untimely progression while on active surveillance (i.e. miss a window of opportunity)?
Risk of Under-staging and/or Grading

Primary vs Delayed RP for men meeting all criteria for AS

Radical Prostatectomy (n = 55)

Table 1: Binomial logistic regression results for low-risk patients only

Dall'era et al BJU Int 2010 (in press)
Does Young Age Exclude AS?

Remember it is about timing of treatment!

Active Surveillance

Best Candidates

- Based on Extended - Pattern Biopsy
  - Low grade (no pattern 4 or 5)
  - Low volume (< 33% of core); < 33% of total cores
  - Non-palpable (T1C)
- Serum PSA < 10 ng/ml; Stable, Free-Fraction Elevated, PSAD < 0.15
- Older Age and/or Significant Co-Morbidity
- Available for Follow-up

A well-performed biopsy essential

Cooperberg, Carroll, Klotz. J Clin Oncol, in press
Does Serial Biopsy Impact Erectile Function?

Estimated erectile dysfunction by BX Sequence, for a respondent diagnosed in 2007-2009 at 60 years of age, at a BX 12 months after diagnosis, and an ED evaluation 3 months after the BX.

<table>
<thead>
<tr>
<th>BX Sequence</th>
<th>ED Outcome = Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sexually Active</td>
</tr>
<tr>
<td>First (N = 270)</td>
<td>4.26 (4.04 – 4.49)</td>
</tr>
<tr>
<td>Second (N = 231)</td>
<td>4.09 (3.85 – 4.33)</td>
</tr>
<tr>
<td>Third (N = 119)</td>
<td>4.16 (3.86 – 4.46)</td>
</tr>
<tr>
<td>Fourth (N = 124)</td>
<td>4.36 (4.01 – 4.70)</td>
</tr>
<tr>
<td>Fifth (N = 67)</td>
<td>4.76 (4.37 – 5.14)</td>
</tr>
<tr>
<td>All</td>
<td>4.26 (4.06 – 4.46)</td>
</tr>
</tbody>
</table>

Initial Conclusions

- Active surveillance appears feasible
- 24% of men treated a median of 3 years after diagnosis
- Small percentage of men come off of surveillance despite no evidence of disease progression
- Overall median f/u remains short
- Change in Gleason grade is greatest driver of treatment

The Future

- Operational definitions of low risk changing
  - Grade assessment imprecise – low volume pattern 4
  - Volume cut - point of 0.5 may be re – set at 1.3 cc!
- Can we expand (or should we contract) the population of men eligible for AS?
- Can we identify new markers of risk?
- Can we identify low – risk interventions?
Outcomes of Surveillance

UCSF Studies
- Impact of lifestyle on gene expression profiling
  - Comprehensive
  - Lycopene, omega 3 fatty acid
- Value of imaging
  - TRUS
  - Multiparametric MR Imaging
- Biomarker assessment to assess risk
  - Expression profiling, etc.

New Markers of Risk/Progression
- Phenotypic and genotypic markers
  - DNA-based biomarkers (GEMCaP)
  - Comparative genomic hybridization (aCGH)
  - Gene expression (Prolaris - Myriad)
  - PCA3, MUC1, TMPRSS2-ERG
  - Non-coding microRNAs (miRNAs)
- Patient germline or lifestyle modifiers of risk
- Imaging


PASS
- 9 institution collaboration
- Prostate Active Surveillance Study (PASS)
  - 469/1000 enrolled

<table>
<thead>
<tr>
<th>Month</th>
<th>Entry</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>q 6 mo</th>
<th>q 12 mo</th>
<th>q 18 mo</th>
<th>Time of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
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<tr>
<td>DRE</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Tissue/Bx</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
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<tr>
<td>mHRQOL survey (prostate)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>DNA (from WBC)</td>
<td>x</td>
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</table>

Proc Natl Acad Sci U S A. 2008 Jun 17;105(24):8369-74
The Canary Study/DOD IMPACT award PC101769 UCSF / U Washington

- Aim 1: Upgrading / Upstaging from biopsy
- Aim 2: Progression on AS

- Serum: TGFβ1, IL6-SR
- Urine: PCA3, TMPRSS:ETS fusion
- Tissue: GEMCaP, Prolaris

- HRQOL

PO1 submitted (ENCOMPASS)

- Enhancing Cancer Outcomes in Men through the Prostate Cancer Active Surveillance Study
- Long-term infrastructure
- Longitudinal markers
- Imaging
- Effects of diet / lifestyle on progression

PCF grant submitted (PASSPORT)

- Prostate Active Surveillance Study: Predictors of Risk and Treatment

Also opening soon: MEAL study (UCSD/CALGB)

Active Surveillance

- Drivers of active treatment

Active Surveillance: Anxiety

- Treatment decision driven by PSA velocity and “anxiety velocity”

Dall’Era et al. Cancer 2008; 112:1650

Latini et al. J Urol 2007; 178:826

Change nomenclature?
PUNLUMP
IDLE or better
advise/counsel and support
Recurring Concerns/Myths

- You have to be treated very soon
- Your cancer is significant, aggressive, important
- What are you waiting for?
- There is only one way to treat
- Non-disclosure of significant conflicts
- Unverified claims
  - “I never had a recurrence!”
  - “90% of men will be potent!”
  - Promulgation of very poor research

Thank You

- UCSF
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