PROSTATE CANCER:
HOW CAN SUCH A COMMON DISEASE BE SO CONTROVERSIAL

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Adjunct Professor of Urology, UT Southwestern, Dallas, Texas, USA
Disclosures

- **Patents**
  - Method to determine prognosis after therapy for prostate cancer
    Granted 2002-09-06
  - Methods to determine prognosis after therapy for bladder cancer
    Granted 2003-06-19
  - Prognostic methods for patients with prostatic disease
    Granted 2004-08-05
  - Soluble Fas urinary marker for the detection of bladder transitional cell carcinoma
    Granted 2010-07-20

- Advisory board of and/or speaker for Astellas, Jansen, Ipsen, Olympus, Wolff, Cepheid, Pierre Fabre
Dilemma

“Is cure possible when it is necessary?”

“How do we best achieve cure, when cure is necessary?”

The right therapy...
+ at the right time...
+ for the right patient

Willet Whitmore, Jr., MD
Chief of the Urology Service, 1952 - 1983
Memorial Sloan-Kettering Cancer Center
Professor of Urology, Cornell Medical College
### US Statistics, 2015

<table>
<thead>
<tr>
<th>Estimated Incidence</th>
<th>Estimated Death rate</th>
</tr>
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<tbody>
<tr>
<td><strong>Prostate</strong></td>
<td>220,800 26%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>115,610 14%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>69,090  8%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>56,320  7%</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>42,670  5%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>39,850  5%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>38,270  5%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>32,670  4%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>30,900  4%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>25,510  3%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td>848,200 100%</td>
</tr>
</tbody>
</table>

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>86,380 28%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>26,100 8%</td>
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<tr>
<td>Pancreas</td>
<td>20,710 7%</td>
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<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>17,030 5%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>14,210 5%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,600 4%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>11,510 4%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,480 4%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>9,070  3%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td>312,150 100%</td>
</tr>
</tbody>
</table>

Siegel et al. CA Cancer J Clin 2015
TNM staging not sufficient to assess disease: why states are needed

**TNM**

1. Characterizes disease at the time of diagnosis
2. Applies only to the untreated patient
3. Does not inform trial designs for the patient who has failed
4. Does not include PSA, Gleason

**States**

1. Describes patient(s) at any point in the disease continuum
2. Applies to treated and untreated patients
3. Provides the framework for specific issues and questions to be addressed
4. Includes PSA and Gleason grade
Prostate cancer clinical states: Milestones in the illness in practice and in research

Diagnoses
- No cancer diagnosis
- Clinically localized disease
- Rising PSA: No visible metastases
- Rising PSA: Castrate

Deaths
- Clinical metastases: Castrate 1st line
- Clinical metastases: Castrate 2nd line
- Clinical metastases: Non-castrate
- Detectable metastases

Death from cancer exceeds death from other causes

Diagnoses:
- 220,800 diagnoses
- ~65,000 diagnoses

Deaths:
- 27,540 deaths
Prostate cancer clinical states:

- Each encounter is “NEW ONE”: assess and reassess disease status
- INTERVENE IF manifestations are SIGNIFICANT
- If none, determine the probability (risk) a significant event might occur and when
- Intervene if HIGH, defer treatment if LOW

Diagnoses 220,800 ~65,000

Deaths 27,540
Prostate cancer clinical states
Objectives and unmet needs

**OBJECTIVES**
- No cancer diagnosis
- Clinically localized disease
- Rising PSA: No visible metastases
- Clinical metastases: Non-castrate
- Clinical metastases: Castrate 1st line
- Clinical metastases: Castrate 2nd line

**UNMET NEEDS**
- Detect clinically significant cancers
- Risk (lethality): Tailor approach
- Source (location): local +/- systemic
- Risk: Tailor approach
- Understanding prognosis
- Treatment effect (is the drug working?)
- Matching drug to tumor

**Prevention**
- Minimize morbidity
- Maximize cure

**Cure if local**
- ? Cure if systematic: prevent metastases

**Eliminate/relieve/control:**
- Manifestations present
- Symptoms/death from disease

**Detect**
- Clinically significant cancers
- Risk approach

**Risk:**
- Tailor approach

**Source:**
- Local +/- systemic

**Risk:**
- Tailor approach
Prostate cancer clinical states:
Each objective requires a different outcome

OBJECTIVES
- Prevention
- Early treatment

UNMET NEEDS
- 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
- Detect clinically significant cancers

Diagram:
- No cancer diagnosis → Clinically localized disease
- Clinically localized disease → Rising PSA: No visible metastases
- Rising PSA: No visible metastases → Rising PSA: Castrate
- Rising PSA: Castrate → Clinical metastases: Castrate 1st line
- Clinical metastases: Castrate 1st line → Clinical metastases: Castrate 2nd line
- Clinical metastases: Castrate 2nd line → Clinical metastases: Non-castrate
- Clinical metastases: Non-castrate → Detect clinically significant cancers
Chemoprevention with 5ARI

• **Efficacy:** ~ 25% Relative Reduction in Prostate Cancer
  – Absolute Reduction 5.8% (PCPT) and 5.2% (REDUCE)
  – Limited to modified Gleason Score (mGS) ≤ 6 tumors

• **Safety:** Smaller, Absolute Increase in HG Tumors
  – PCPT- mGS 7-10 (1.3%) or mGS 8-10 (0.8%)
  – REDUCE- mGS 8-10 (0.5%)

• Risk-Benefit Analysis Considerations
Benefit to Risk Ratio

The Number of Men Needed to Treat For:

- Reduction of One Prostate Cancer
  - PCPT: 39 – 73*
  - REDUCE: 60

- Development of One GS 8-10 Prostate Cancer
  - PCPT: 150 – 268*
  - REDUCE: 200

*NNT range shown for “All Biopsied” and “ITT” populations
Cancer chemoprevention: a rapidly evolving field

- Successful strategy in cardiovascular medicine
- Steady increase in cancer incidence with its associated morbidity and mortality + spiraling healthcare costs ➔ disease prevention
- $30 billions spent on dietary supplements each year and yet no chemoprevention trials with these have yielded positive outcomes
- For chemoprevention to take an important role in reducing the risk of cancer, we need to identify
  1. ideal target population (biomarkers),
  2. time of intervention,
  3. appropriate dosage, and
  4. extent of intervention required.

➔ Stringent study design and thorough interpretation to accurately judge the necessity and feasibility of the preventive measures
Cancer incidence and mortality rates
Age-adjusted, standardized over time


39% Reduction in mortality;
Accounting for 20% of the overall reduction in cancer mortality in men

International Trends in Mortality:

Countries with increasing mortality

The Changing Face of Prostate Cancer in the US thanks to PSA-screening

Prostate Cancer Screening RCTs:

<table>
<thead>
<tr>
<th></th>
<th>PLCO</th>
<th>ERSPC</th>
<th>Göteborg trial</th>
</tr>
</thead>
<tbody>
<tr>
<td># men</td>
<td>76,693</td>
<td>182,000</td>
<td>20,000</td>
</tr>
<tr>
<td>Results</td>
<td>negative</td>
<td>NNS=1055</td>
<td>NNS=293</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NNT=37</td>
<td>NNT=12</td>
</tr>
<tr>
<td>Limitations</td>
<td>52% contamination</td>
<td>relaxed screening</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>30% dilution</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↠ underpowered</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

21% reduction in death due to prostate cancer

44% reduction in death due to prostate cancer

13 yrs

11 yrs

14 yrs

For each prevented PCa death

Less than one man becomes incontinent

4 men suffer from erectile dysfunction

Carlsson S., European Journal of Cancer, 47:545, 2011
PLCO SUBGROUPS: CUMULATIVE MORTALITY

At 10 years
NNS: 736
NNT: 5

After 10 years follow-up men in the screening group had 44% lower PCa mortality for men with no or minimal comorbidity

Crawford et al., J Clin Oncol:29, 2011
COMPARING SCREENING TOOLS

- **PSA testing:**
  - NNS: 293 – 1055
  - NNT: 5 – 37

- **Mammography:**
  - NNS: 377 (age 60-69)
  - NNS: 1339 (age 50-59)
  - NNT at 10 years: 10

- **Colorectal cancer:**
  - NNS: 1173 (fecal blood)
  - NNS: 489 (flex sig)

- **Hyperlipidemia**
  - NNS: ~400

- **Hypertension**
  - NNS: ~300-1300
The PSA Prostate Screening “controversy”

• Do the benefits of PSA screening (reduction in mortality) outweigh the harms (overdiagnosis and overtreatment)?

→ DEPENDS ON THE TYPE OF SCREENING!
SMART Prostate Cancer Screening

4 golden rules to improve the ratio of harm to benefits of PSA-based PCa screening:

1. DON’T SCREEN MEN WHO WILL NOT BENEFIT
   – E.g.: screening elderly men >=70 years with co-morbidities

2. DON’T BIOPSY MEN WITHOUT A GOOD REASON

3. DON’T TREAT UNLESS YOU HAVE TO
   – Use of active surveillance to manage low-risk disease

4. IF YOU HAVE TO TREAT, DO SO AT A HIGH VOLUME CENTER
Risk Curve: PCa and metastasis within 30 years by PSA at age 45-50

Population distribution of PSA (Median: 1 ng/mL)

Vickers A et al, BMJ 2010
Don’t biopsy without a good reason: use PSA intelligently

- Most men with an increased PSA do not have PCa

- PSA levels vary considerably
  - Should be confirmed with a repeat test in 6-12 weeks before recommending a biopsy

- Don’t biopsy based on PSA velocity

---

Table 4. Predictive accuracy of models with and without prostate-specific antigen velocity (PSAV)*

<table>
<thead>
<tr>
<th>End point</th>
<th>No. of subjects</th>
<th>Area under the curve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer on biopsy</td>
<td>5519</td>
<td>Modell without PSAV</td>
</tr>
<tr>
<td>Clinically significant cancer†</td>
<td>5188</td>
<td>0.702</td>
</tr>
<tr>
<td>Gleason score 7–10</td>
<td>5509</td>
<td>0.767</td>
</tr>
</tbody>
</table>

We found no evidence to support the recommendation that men with high PSA velocity should be biopsied in the absence of other indications; this measure should not be included in practice guidelines.

Don’t treat unless you have to

...But we aggressively treat low risk disease
... and undertreat high risk disease
If you have to treat, do so at a high volume center

…but most treatment done by low volume providers

- National In-patient Sample: 2005
  - Similar data from SPARCS (NY)

- 933 identifiable sampled surgeons
  - 251 (27%) did only a single procedure
  - 615 (66%) did 5 or fewer
  - 773 (83%) did 10 or fewer

Savage and Vickers J Urol 2009
Objectives and unmet needs for clinically localized disease

**OBJECTIVES**
- Minimize morbidity: Overtreatment
- Maximize cure

**UNMET NEEDS**
- Risk or presence of symptoms, metastases, or death from disease → Tailored approach

- Rising PSA: Castrate
- Clinical metastases: Castrate 1st line
- Clinical metastases: Castrate 2nd line
- Clinically localized disease
- No cancer diagnosis
Risk adapted diagnostics & treatment

• We have to:

1. Identify patients who are destined to develop symptoms and die of their cancers
2. Intervene while (early when) it can make a significant difference
PCA3: A novel urine marker for prostate cancer

Likelihood ratios evaluated on a cohort of 521 U.S. men (not from the PCPT cohort) exceeded 1 for high values of PCA3, i.e. PCA3 provided independent predictive value to PSA and the other PCPT risk factors.

Likelihood Ratio =

\[
\frac{P(\text{PCA3} \mid \text{PCPT Risk Factors, Cancer})}{P(\text{PCA3} \mid \text{PCPT Risk Factors, No Cancer})}
\]

PCPT Risk Factors = PSA, DRE, Family History, Prior Biopsy
Techniques are now available to isolate and characterize circulating tumor cells

Detection, prognostication and molecular profiling

Gradient centrifugation
- Specific gravity
- Centrifugation
- Blood
- Ficoll
- Plasma
- Enriched lymphocyte

Immunomagnetic separation
- Surface antigen
- Ab-Magnetic beads
- Cell mixture

Immunoaaffinity ("CTC" Chip)\(^1\)
- Surface antigen

Filtration\(^2\)
- Cell mixture
- Size

“Pet” scan for PROSTATE CANCER

“...dogs can be trained to detect PCA by smelling urine with a significant success rate.”

Expanded Role for Imaging?
Randomized trial of RP v. Watchful Waiting

Surgical excision reduces the risk of metastases (HR 0.60) and death from prostate cancer (HR 0.56) significantly.

Distant metastasis

<table>
<thead>
<tr>
<th></th>
<th>Watchful waiting</th>
<th>Radical prostatectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years of Follow-up</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>4</td>
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</tr>
<tr>
<td></td>
<td>6</td>
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<tr>
<td></td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Distant metastasis: Watchful waiting 25.4%, Radical prostatectomy 15.2%

Cancer-specific mortality

<table>
<thead>
<tr>
<th></th>
<th>Watchful waiting</th>
<th>Radical prostatectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years of Follow-up</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
</tr>
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<td></td>
<td>4</td>
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<td>6</td>
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<td></td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Cancer-specific mortality: Watchful waiting 14.9%, Radical prostatectomy 9.6%

\[ p=0.01 \]

PIVOT Prostate cancer survival
Wilt T et al, NEJM 367;3, July 2012: 203-214

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Observation</th>
<th>Radical Prostatectomy</th>
<th>Hazard Ratio (95% CI)</th>
<th>PValue for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>31/367</td>
<td>21/364</td>
<td>0.63 (0.36–1.09)</td>
<td>0.63</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>12/131</td>
<td>6/122</td>
<td>0.52 (0.20–1.39)</td>
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</tr>
<tr>
<td>≥65 yr</td>
<td>19/236</td>
<td>15/242</td>
<td>0.68 (0.34–1.33)</td>
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</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>White</td>
<td>22/220</td>
<td>15/232</td>
<td>0.57 (0.30–1.10)</td>
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<tr>
<td>Black</td>
<td>7/121</td>
<td>5/111</td>
<td>0.80 (0.25–2.54)</td>
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</tr>
<tr>
<td>Other</td>
<td>2/26</td>
<td>1/21</td>
<td>0.56 (0.05–6.17)</td>
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<tr>
<td>Charlson score</td>
<td></td>
<td></td>
<td></td>
<td>0.63</td>
</tr>
<tr>
<td>0</td>
<td>19/220</td>
<td>14/224</td>
<td>0.69 (0.34–1.37)</td>
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<tr>
<td>≥1</td>
<td>12/147</td>
<td>7/140</td>
<td>0.54 (0.21–1.38)</td>
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<tr>
<td>Performance score</td>
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<td></td>
<td></td>
<td>0.57</td>
</tr>
<tr>
<td>0</td>
<td>25/310</td>
<td>18/312</td>
<td>0.67 (0.37–1.23)</td>
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</tr>
<tr>
<td>1–4</td>
<td>6/57</td>
<td>3/52</td>
<td>0.41 (0.10–1.71)</td>
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<tr>
<td>PSA</td>
<td></td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>≤10</td>
<td>15/241</td>
<td>14/238</td>
<td>0.92 (0.44–1.91)</td>
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</tr>
<tr>
<td>&gt;10</td>
<td>16/125</td>
<td>7/126</td>
<td>0.36 (0.15–0.89)</td>
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</tr>
<tr>
<td>Risk</td>
<td></td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>Low</td>
<td>4/148</td>
<td>6/148</td>
<td>1.48 (0.42–5.24)</td>
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<tr>
<td>Intermediate</td>
<td>13/120</td>
<td>6/129</td>
<td>0.50 (0.21–1.21)</td>
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<tr>
<td>High</td>
<td>15/261</td>
<td>11/254</td>
<td>0.40 (0.16–1.00)</td>
<td></td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
<td></td>
<td></td>
<td>0.57</td>
</tr>
<tr>
<td>&lt;7</td>
<td>15/86</td>
<td>10/98</td>
<td>0.68 (0.31–1.49)</td>
<td></td>
</tr>
<tr>
<td>≥7</td>
<td></td>
<td></td>
<td>0.51 (0.23–1.14)</td>
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</tr>
</tbody>
</table>
### Gleason 3 PCa is not a “real” cancer

<table>
<thead>
<tr>
<th>Characteristic/Pathway</th>
<th>Gleason 3</th>
<th>Gleason 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expression of pro-proliferation embryonic, neuronal, hematopoietic stem cell genes, EGF, EGFR</td>
<td>No</td>
<td>Overexpressed</td>
</tr>
<tr>
<td>AKT pathway: MAP2K4, RALA, PHLPP, PML</td>
<td>No</td>
<td>Aberrant</td>
</tr>
<tr>
<td>HER2/neu</td>
<td>No</td>
<td>Amplified</td>
</tr>
<tr>
<td>Insensitivity to Antigrowth signals (Cyclin D2 methylation,CKDN1β)</td>
<td>Expressed</td>
<td>Absent</td>
</tr>
<tr>
<td>Resisting apoptosis: DAD1</td>
<td>Negative</td>
<td>Strong Exp</td>
</tr>
<tr>
<td>BCL2</td>
<td>Mostly Neg.</td>
<td>Upregulated</td>
</tr>
<tr>
<td>Absence of senescence: TMPRSS2-ERG</td>
<td>ERG normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Sustained angiogenesis: VEGF</td>
<td>Expression low</td>
<td>Increased</td>
</tr>
<tr>
<td>Expression of other pro-angiogenic factors, microvessel density</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Tissue invasion/metastasis markers (CXCR4, others)</td>
<td>Normal</td>
<td>Overexpressed</td>
</tr>
<tr>
<td>Clinical evidence of metastasis/mortality</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>
20 year PCa-specific mortality after radical prostatectomy

- N=23,910
- 12,000 Gleason 2-6
- Risk of PCa death after RP in men age 60-69: **0.2% at 20 years** (although significant PSA failure rate)

Eggener et al., J Urol 2011
Focal Therapy with High Intensity Focused Ultrasound

Right lobe 0 J
Left lobe 2000 J

Right lobe 2500 J
Left lobe 1600 J

Urethra

October 14th, 2010

Day 7 MRI

4.2 x 3 mm
4.9 x 3 mm

October 23th, 2010

Day 7 MRI

56.0 cc
11.6 cc

MEDIZINISCHE UNIVERSITÄT WIEN
Universitätsklinik für Urologie
MEDINAT
COMPREHENSIVE CANCER CENTER VIENNA
PCa – a multifocal disease

- Three patients, 12 tumour samples, 3 adjacent normals, 3 bloods
  - How are the regions related?
  - Is there anything going on in the adjacent normals? Field effect/developmental clones
  - Does convergent phenotypic evolution occur?

**ERG Split FISH Key:**
- **Es**plit (1,1,1)
- Normal (2,0,0)
- **Ed**el (1,1,0)
Radical Prostatectomy

- The concept that “one operation fits all” is wrong!
- Just because a surgeon removes the prostate and the patient goes home alive is not an appropriate measure of success.
- “Every job is a self-portrait of the person who did it. Autograph your work with excellence.”
Radical Prostatectomy:
Millimeters make a difference
Experience lowers rate of complications and increases cure rate and functional outcomes

Complications

Positive Margins

Recurrence

Begg et al., NEJM 2002, Shariat et al., Eur Urol 2010
NODAL METASTASES DISTRIBUTION IN PCA

- 9-15%
- 16-40%
- 19-25%
- 49-58%
- 60-70%

Godoy, Shariat et al, J Urol, 2012;187:2082-6
Metastasis After Radical Prostatectomy or External Beam Radiotherapy for Patients With Clinically Localized Prostate Cancer: A Comparison of Clinical Cohorts Adjusted for Case Mix

Michael J. Zelefsky, James A. Eastham, Angel M. Cronin, Zvi Fuks, Zhigang Zhang, Yoshiya Yamada, Andrew Vickers, and Peter T. Scardino

Table 2. Multivariable Cox Regression Model for the Outcome of Distant Metastases From Prostate Cancer

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at treatment*</td>
<td>0.98</td>
<td>0.95 to 1.02</td>
<td>.3</td>
</tr>
<tr>
<td>Year of treatment*</td>
<td>0.97</td>
<td>0.87 to 1.07</td>
<td>.5</td>
</tr>
<tr>
<td>NCCN risk (high v intermediate/low)</td>
<td>6.37</td>
<td>3.89 to 10.5</td>
<td>&lt; .0005</td>
</tr>
<tr>
<td>Treatment (surgery v radiotherapy)</td>
<td>0.35</td>
<td>0.19 to 0.63</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Abbreviation: NCCN, National Comprehensive Cancer Network.
*Hazard ratio estimates are given for a 1-year increase.
PCa-specific Mortality after Radical Prostatectomy, Radiation, and primary Hormone Therapy

Cooperberg et al., Cancer 2010
Patients with “high risk” cancers can do very well long term. PSA recurrence MAY NOT mean death from disease.

Shariat et al. J Urol 2008
Shifting the paradigm from palliation to cure

Combined modality treatment for newly diagnosed metastatic disease: hormones, surgery and new biologics

Newly diagnosed: Incurable with standard therapy

- T3b, Gleason 8 disease
- Pelvic bone metastases

End of Therapy

<table>
<thead>
<tr>
<th>Follow up w/ scans &amp; labs every 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 52: Interim endpoint: 0 PSA at 12mos</td>
</tr>
<tr>
<td>Week 84: Primary endpoint: Confirmed 0 PSA at 20mos</td>
</tr>
</tbody>
</table>
Lymph node imaging with gastrin-releasing peptide receptor PET scan with 64Cu-CBC-AR-06
The clonal origin of lethal prostate cancer
Haffner M, Yegasubramanian et al, JCI, epub Oct 29 2013
The Genomic Landscape of Prostate Cancer

The Mutational Landscape of Prostate Cancer

Christopher E. Barbieri\textsuperscript{a,b,*}, Chris H. Bangma\textsuperscript{c}, Anders Bjartell\textsuperscript{d}, James W.F. Catto\textsuperscript{e}, Zoran Culig\textsuperscript{f}, Henrik Grönberg\textsuperscript{g}, Jun Luo\textsuperscript{h}, Tapio Visakorpi\textsuperscript{i}, Mark A. Rubin\textsuperscript{a,b}
Molecularly-Driven Diagnostics & Therapeutics

• Therapies will increasingly target the key molecular hubs that drive cancer growth - not just individual mutations

• Treatments more personalized taking into account
  – when and how to intervene to hit the right targets
  – how treatments are likely to affect each patient

OLD MODEL: Treatment determined by a tumor’s location

NEW MODEL: Treatment determined by key molecular “hubs” targeted within cells
Develop More Relevant Models

Ex Vivo Tumor Cell Culture

Transplant the metastatic TME intact
Retain cellular heterogeneity
Often multiply drug resistant

Petri-dish

Cloned lines from 2-D plastic cultures
No TME or heterogeneity
Drug sensitive
FLEXIBLE CLINICAL RESEARCH SYSTEMS

• Criteria for entry in a trial based on molecular characteristics
  → Inclusion only of the participants most likely to respond
  → Faster & more conclusively answers
• Need to screen larger numbers of pts to identify participants
  → increased international collaboration

OLD MODEL: Large numbers of patients, not selected by molecular characteristics
  → lower chance of effectiveness

NEW MODEL: Small patient populations with relevant molecular defects
  → all participants potential to respond
CONCLUSIONS

- PCa incidence is increasing worldwide, mainly due to PSA
- Smart Screening can help reduce overdiagnosis and overtreatment
- PCa has a natural history that often spans 10 years or more
  → dynamic disease that can become more aggressive over time
- Biomarkers & predictive tools can help risk-stratify patients
- Treatment must be and can be tailored to tumor biology & patient wishes
Whitmore’s dilemma

“Is cure possible when it is necessary?”

“Is cure necessary when it is possible?”

à With modern strategies - cure is often possible when necessary

à With smart screening & active surveillance, we can avoid unnecessary tests & therapy - cure is possible but not necessary

YES - (TODAY) WE CAN
give the RIGHT THERAPY
for the RIGHT CANCER
in the RIGHT PATIENT
at the RIGHT TIME
Dealing with prostate cancer

Requires a balancing act

TEAMWORK = MULTIDICIPLINARY CANCER TEAMS

TOGETHER WE ARE STRONGER
QUESTIONS?

THANK YOU