Paul F. Schellhammer, MD
Professor of Urology
Eastern Virginia Medical School
Norfolk, Virginia
Changing Landscape

- Pre-Diagnosis  \(\rightarrow\) Screening + Prevention
- Diagnosis  \(\rightarrow\) Treatment Options
- Post-Surgery  \(\rightarrow\) Adjuvant Treatment
- PSA Failure  \(\rightarrow\) Treatment Options
- Castration Resistant  \(\rightarrow\) Treatment Options
  - \(M_0\)
  - \(M_1\)
The Prostate Cancer Pseudoepidemic in the U.S

(G. Welch, “Should I Be Tested for Cancer?”, 2004)

New Prostate Cancer Cases and Deaths (per 100,000 men)

- TURP era
- PSA era

Over one million men who would not have been diagnosed in 1973
PSA Taps a Large Reservoir of Disease Yields an Increasing Low Risk Cohort

Source: The Journal of Urology 2003; 170:S21-S27 (DOI:10.1097/01.ju.0000095025.03331.c6)
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My Proposition: Screening & Prevention
Interrelated Unified Strategy

- Screening (exercised with informed consent)
- Chemoprevention (chemoretardation / chemosuppression)
### Unique Platform For Discussion

4 LARGE RCT - NEJM

<table>
<thead>
<tr>
<th>Screening</th>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLCO (76,693)</td>
<td>PCPT (18,882)</td>
</tr>
<tr>
<td>ERSPC (162,394)</td>
<td>REDUCE (8,231)</td>
</tr>
</tbody>
</table>
PSA Taps a Large Reservoir of Disease Yields an Increasing Low Risk Cohort
**NCCN CaP Guidelines 2010**

*Address Overtreatment*

<table>
<thead>
<tr>
<th>RECOMMENDATIONS FOR ACTIVE SURVEILLANCE</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Very Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>LE ≤10 yrs</td>
<td>LE ≤20 yrs</td>
</tr>
<tr>
<td>T1-2a, GS 2-6, PSA &lt;10,</td>
<td>T1c, GS 2-6, PSA &lt;10, &lt;3 cores, &lt;50% in any core, PSAD &lt;0.15</td>
</tr>
</tbody>
</table>

*But Does Not Address Overdiagnosis*
Morbidity Associated w/Prostate Bx

J Urol 183(3): 963, 2010

- 75,190 TRUS bx
- 1% hospital admission 1999
- 4.1% hospital admission 2005
- → sepsis
- 30 day mortality = .09%
  \[
  0.09 \times 700,000 = 630
  \]
- PLCO Trial - 0.68% TRUS – Bx Complications
Immediate Risk for Cardiovascular Events and Suicide Following a CaP Diagnosis: Prospective Cohort Study

All men in Sweden 4,305,358
Prostate Cancer Dx 168,584
## M&M - After Prostate Cancer Diagnosis

*PLOS Medicine 6(12), 2009*

<table>
<thead>
<tr>
<th>CV Event</th>
<th>RR one week</th>
<th>RR one year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre 1987</td>
<td>11.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Post 1987</td>
<td>1.9</td>
<td>1.3</td>
</tr>
<tr>
<td>Suicide</td>
<td>8.4</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Risk greatest among men < 54 yrs
Public Knowledge of Screening Benefits

*NNS to avoid 1 mortality*

- **Fact:**
  - *Breast* — 540 - 3125
  - *Prostate* — 1410

- **Perception**
  - *Breast* 〉 10-20
  - *Prostate* 〈

- Only 1% of women and 10% of men made accurate estimate
**Pt Survival Expectations with Treatment for CaP**

*J Am Board of Fam Med 22: 247, 2009*

**Eastern Virginia Medical School Study**

184 men w/ localized CaP

<table>
<thead>
<tr>
<th></th>
<th>Without Treatment</th>
<th>With Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 yrs</td>
<td>15 % (65%)</td>
<td>0.6%</td>
</tr>
<tr>
<td>5-10 yrs</td>
<td>49.8%</td>
<td>6.1%</td>
</tr>
<tr>
<td>11-19 yrs</td>
<td>34.5%</td>
<td>30%</td>
</tr>
<tr>
<td>&gt; 20 yrs</td>
<td>2.5%</td>
<td>63%</td>
</tr>
</tbody>
</table>

Comorbidity adj life exp = 22.9 yrs
## Screening Dilemma

<table>
<thead>
<tr>
<th>Age</th>
<th>CaP</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 y.o.</td>
<td>1/1,000</td>
<td>Trauma 5x</td>
</tr>
<tr>
<td>75 y.o.</td>
<td>20/1,000</td>
<td>CV 7 x CV 20x</td>
</tr>
</tbody>
</table>
Paul Schellhammer, MD, EVMS”:
“I believe that the screening trials have provided hard data that supports the concern that many men are not well served by the diagnosis and treatment of prostate cancer. That is not to say however that a number of men do not derive benefit, and the healthcare community cannot ignore this benefit.”
PSA: Friend or Foe

Dr. H. Gilbert Welch, author of “Should I be tested for cancer? Maybe not and here’s why” and a physician whose opinion I respect, has noted that his analysis of the data convinces him that he would not have a PSA.
I also respect my opinion and I made the decision to have periodic PSA testing. As a result I was diagnosed with prostate cancer, have received in succession surgery, radiation, intermittent and continuous androgen deprivation, second line hormone therapy and participated in a phase 2 clinical trial. I have no regrets.
PSA:  Friend or Foe

• But it does not matter what Dr. Welch thinks or what I think. Each individual needs to calculate and calibrate his own situation. For some there will be intuitive conviction towards one direction or another, but for others there will be indecision, which, unfortunately, current data cannot entirely resolve.
Local Treatment Options

- **Surgery** – Open, RALP, (daVinci)
- **Radiation** – IMRT, Cyberknife, Protons
- **Brachytherapy** – I125, PD103
- **Cryotherapy** – Total / Focal
- **HIFU** – Total / Focal
- **Active Surveillance** – ?Triggers
Quality of Life - QOL

- No RCT completed to define oncologic superiority of any treatment modality for localized prostate cancer
- QOL impacted long after all treatment modalities
- Health related Quality of Life outcomes are important measures of prostate cancer treatment strategies
Exposing Physician Bias

CaPSURE - large, observational, primarily community based database

1,366 CaPSURE patients treated with RP, BT, EBRT

Patients and physicians completed HRQOL survey

Patient reported HRQOL domains consistently lower than physician reported
## Differences in Physician & Patient Perceptions

*Differences between patients and physicians reporting HRQOL domains*

<table>
<thead>
<tr>
<th></th>
<th>% Urinary Incontinence/Urinary Function (No.)</th>
<th>% Diarrhea/Bowel Function (No.)</th>
<th>% Decreased Sexual Desire/Sexual Function (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2001 – 2007:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td>33 (80)</td>
<td>4 (6)</td>
<td>44 (48)</td>
</tr>
<tr>
<td>Patient</td>
<td>55 (131)</td>
<td>35 (52)</td>
<td>94 (102)</td>
</tr>
<tr>
<td><strong>Early Follow up:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td>3 (243)</td>
<td>5 (28)</td>
<td>40 (155)</td>
</tr>
<tr>
<td>Patient</td>
<td>58 (358)</td>
<td>40 (208)</td>
<td>97 (385)</td>
</tr>
<tr>
<td><strong>Late Follow up:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td>22 (44)</td>
<td>4 (4)</td>
<td>33 (31)</td>
</tr>
<tr>
<td>Patient</td>
<td>42 (85)</td>
<td>18 (21)</td>
<td>95 (88)</td>
</tr>
</tbody>
</table>

Significant difference in > 2 yr follow up data
**HRQOL Study EVMS/Sentara**

- Prospective, patient-reported, longitudinal comparison of HRQOL parameters among patients with localized CAP undergoing:
  - *Open radical prostatectomy (ORP)*
  - *Robotic assisted radical prostatectomy (RAP)*
  - *Brachytherapy (BT)*
  - *Cryotherapy (CT)*
- Salvage, neoadjuvant, adjuvant therapies excluded
- Measured HRQOL impact and recovery profiles
Results

- All prostate cancer specific domains affected
- Score trend back towards baseline over time
- Kaplan-Meier survival curve constructed for each domain reflecting >90% return to baseline function and bother
- Patients with <30 on 100 scale omitted (arbitrary)
- Cox proportional hazard ratios calculated
### Cox Proportional Hazards for 90% Return Baseline QOL

Similar hazard ratios grouped together

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Univariate Hazard Ratio</th>
<th>95% CI</th>
<th>Adjusted Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urinary Function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORP &amp; RAP CT &amp; BT</td>
<td>1.0</td>
<td>2.78</td>
<td>2.98</td>
<td>2.98</td>
</tr>
<tr>
<td><strong>Urinary Bother</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORP &amp; RAP CT &amp; BT</td>
<td>1.0</td>
<td>1.42</td>
<td>1.48</td>
<td>1.48</td>
</tr>
<tr>
<td><strong>Sexual Function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORP, RAP, &amp; CT BT</td>
<td>1.0</td>
<td>5.62</td>
<td>5.71</td>
<td>5.71</td>
</tr>
<tr>
<td><strong>Sexual Bother</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORP &amp; RAP BT &amp; CT</td>
<td>1.0</td>
<td>2.16</td>
<td>1.99</td>
<td>1.99</td>
</tr>
<tr>
<td><strong>Bowel Function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BT ORP, RAP, &amp; CT</td>
<td>1.0</td>
<td>1.25</td>
<td>1.25</td>
<td>1.25</td>
</tr>
<tr>
<td><strong>Bowel Bother</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORP, BT, &amp; CT RAP</td>
<td>1.0</td>
<td>1.31</td>
<td>1.28</td>
<td>1.28</td>
</tr>
</tbody>
</table>

*Age, Gleason, baseline score*

BT/CT-3X better urine fxn

BT-5X better sex fxn

No sig. Difference Bowel fxn
QOL Data

Interpret with caution!
Interpret With Caution

- Objective data not as optimistic as subjective impression
  - Patients likely to minimize symptoms
- ALL studies demonstrate a great degree of heterogeneity
  - Nearly all baseline parameters and demographics between groups statistically different
- Impacted by:
  - Patient interpretation of questionnaire
  - Patient outcome expectations
Summary

- Our large prospective, longitudinal study of HRQOL thru 36 mos, BT was associated with higher scores when compared to RP.

- This is demonstrated in several other studies.

- Informed decision making re: options for CaP rx will require and rely upon further understanding of the HRQOL + oncologic outcomes from studies of the future.
Unanticipated and Underanticipated Outcomes During Management of Local Stage CaP: A Prospective Survey

J Urol 184: 120, 2010

- Underestimated impact of treatment on usual daily activity
- Underestimated value of advice provided by others
- The value of support groups
## Biochemical (PSA) Relapse / Failure

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>New prostate cancer cases per year (09)</td>
<td>≈ 200,000</td>
</tr>
<tr>
<td>75% have treatment for localized disease</td>
<td>170,000</td>
</tr>
<tr>
<td>25-35% experience PSA-only recurrence</td>
<td>≈ 50-60,000</td>
</tr>
<tr>
<td>Men are younger and healthier at time of PSA-only recurrence</td>
<td></td>
</tr>
</tbody>
</table>
Characteristics of Rising PSA Cohort

- Healthy, excellent performance states immunocompetent
- Limited (microscopic/sub clinical) disease burden
- Marker(s) to assess progression and treatment effect
Case Study

60 year old healthy male, no comorbidities

T1c, Gleason 4+3, PSA = 10, bone scan-neg

RRP with bilateral LND performed (8 nodes/side)

Pathology: Gleason 4+4, focal ECE; margins, SV, and nodes are negative.
Overall survival was improved with radiation (p=0.046; HR 0.75, 95% CI 0.56, 1.00).

SWOG 8794 – AUA 2008
PSA Profile After R.P.

@ 3 months after R.P. = <0.1
@ 6 months after R.P. = <0.1
@ 12 months after R.P. = <0.1
@ 15 months after R.P. = 0.25
@ 18 months after R.P. = 0.4
@ 21 months after R.P. = 0.8

Bone and CT scan – negative

PSA DT = 3 months
Critical Questions

- Is the rising PSA after local therapy secondary to:
  - *Persistent local disease*
  - *Distant metastasis* or
  - *Both*
Recurrence Free Survival - Time From RRP

KM analysis of PSA recurrence

\[ p = 0.01 \text{ (log rank)} \]
**PSA Outcomes after Salvage EBRT (level 4)**

1,540 patients from 17 centers (1987-2005)

- Outcome measure = PSA > 0.2 (confirmed)
- Overall 6 yr PSA free = 32% (CI 28-35%)

<table>
<thead>
<tr>
<th>PSA</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.5</td>
<td>48%</td>
</tr>
<tr>
<td>0.5-1.0</td>
<td>40%</td>
</tr>
<tr>
<td>1.0-1.5</td>
<td>28%</td>
</tr>
<tr>
<td>&gt;1.5</td>
<td>18%</td>
</tr>
<tr>
<td>PSA &lt; 0.5, PSADT &lt;10 mos, Gleason 8-10</td>
<td>41%</td>
</tr>
</tbody>
</table>
Failure after external beam (primary or salvage) occurs for 3 reasons

- *Cancer within the pelvis but outside the field (expand field)*
- *Distant micrometastases (systemic therapy)*
- *Radioresistant tumor within the field (dose/sensitizing agents/hyperthermia)*
Salvage Radiation
A Phase III Salvage Trial of Short Term AD w/Pelvic Lymph Node or Prostate Bed Only RT SUPPORT (Level 1)

- Arm I: PBRT Alone
  - *PBRT (64 – 70.2 Gy)*

- Arm II: PBRT + STAD

- Arm III: PLNRT + PBRT + STAD
  - *STAD for 4-6 mo, beginning 2 mo before RT*

1,700 pts
**UK – NCIC RADICALS trial**
**Adj vs Salvage – No AD vs L/S AD- Level 1**

- **RRP**
  - **Low risk**
    - Early salvage
    - “3”
  - **Int risk**
    - Observation
    - Early salvage
    - RT
    - “3”
  - **High risk**
    - Adjuvant RT
      - No ADT
      - Short ADT
      - Long ADT
      - “3”

- **Opened: Jan 2007**
- **Target – 4000 pts**
- **Endpoint = CSS & OS**
- **Early = 2 rises > 0.1 or any 3 rises**
Life After Traditional A.D. Failure

- Chemo Therapy
- Other Hormone Therapy
- Immuno Therapy
How Good Is A.D.?

- A.D. is the best therapy for any adult epithelial cancer
- 50% M+ alive at 24 months (median)
- Median for other advanced ca
  - colorectal 12-18 mos
  - breast 12-24 mos
  - lung 3-4 mos
  - gastric 3-4 mos

AND IT CAN BE EVEN BETTER
60 yr old – 5 yrs post R.P.

- pT3a, Gleason 4+4
- 1\textsuperscript{st} PSA Rise - Two yrs PO
  - \textit{Salvage EBRT + 6 mos A.D.}
- 2\textsuperscript{nd} PSA Rise
  - \textit{CAB X 2 yrs}
- 3\textsuperscript{rd} PSA Rise
  - Age 65 - PSA 3.0

\textit{What is Disease State?}
Definitions of Disease State

- Rising PSA after A.D.
  - Hormone refractory: - No
  - Androgen independent: - No
- Castrate resistant: - Maybe
  - If to med / surg cast and $T<50/20$ ng/dl: - Yes
  - If to all serum and tissue $T$: - ?? / No
What is Serum Castrate-T: Moving Target?

<table>
<thead>
<tr>
<th>Threshold</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 ng/dl</td>
<td>Traditional FDA cutpoint/LhRh assay limitation</td>
</tr>
<tr>
<td>&lt; 20 ng/dl</td>
<td>Orchietectomy cutpoint/sensitive assay</td>
</tr>
<tr>
<td>&lt; 1 ng/dl</td>
<td>Ultrasensitive assay</td>
</tr>
<tr>
<td>&lt; 0.1 ng/dl</td>
<td></td>
</tr>
</tbody>
</table>

Furthermore serum T ≠ tissue T
It is important not to let excessive pessimism replace excessive optimism. If CAB does produce an improvement of about 2% or 3% in overall survival, more effective hormonal regimens might produce greater benefits.

Sir Richard Peto
Ketoconazole, Hydrocortisone, & Dutasteride in Asymptomatic Castration-Resistant CaP

CONCLUSION: The response proportion to ketoconazole, hydrocortisone, and dutasteride was at least comparable with previous studies of ketoconazole alone, whereas time to progression was substantially longer. Combination therapies targeting multiple steps in androgen synthesis warrant further investigation.

**Abiraterone**

- Androgen biosynthesis suppression
- Testosterone $< 0.1$ ng/ml
Phase III Trial in Post - Docetaxel Chemotherapy (N=1158)

CRPC – M1 Randomization 2:1

Abiraterone 1000 mg daily
Prednisone 10 mg daily

Placebo daily
Prednisone 10 mg daily

Overall Survival

Completed 2009 - Results 2010
Phase III Trial in Chemotherapy Naïve Pts

CRPC
Metastatic / Non-Metastatic 2:1

Abiraterone 1000 mg daily
Prednisone 10 mg daily

Placebo daily
Prednisone 10 mg daily

Progression Free & Survival
MDV 3100  (Medivation)

- Blocks androgen receptor with greater affinity than bicalutamide
- Impairs nuclear translocation and DNA binding of the androgen receptor
- Disables co-activators
Affirm – Phase III Post Docetaxal
1200 patients

CRPC – M1 Randomized 2:1

- MDV 3100 (160 mgm)
- Pcb or Prednisone

Results 2011-13
**Patch Trial**

2009 GU Symposium #173

- Transdermal estradiol patch vs Lh/Rh as first line therapy

- Primary endpoint: CV morbidity / mortality

- Secondary endpoint: T + PSA level
  QOL
**Sipuleucel-T: Patient-Specific Therapy**

**Day 1**
Leukapheresis

**Day 2-3**
sipuleucel-T is manufactured

**Day 3-4**
Patient is infused

**Apheresis Center**  **Dendreon**  **Doctor’s Office**

**COMPLETE COURSE OF THERAPY:**
Weeks 0, 2, 4
Randomized Phase 3 IMPACT Trial
(IMmunotherapy Prostate AdenoCarcinoma Treatment)

Asymptomatic or Minimally Symptomatic Metastatic Castrate Resistant Prostate Cancer (N=512)

- Sipuleucel-T Q 2 weeks x 3
  - Treated at Physician discretion
- Placebo Q 2 weeks x 3
  - Treated at Physician discretion and/or Salvage Protocol

Primary endpoint: Overall Survival
Secondary endpoint: Time to Objective Disease Progression
IMPACT Overall Survival: Primary Endpoint Intent-to-Treat Population

P = 0.032 (Cox model)
HR = 0.775 [95% CI: 0.614, 0.979]
Median Survival Benefit = 4.1 Mos.

Sipuleucel-T (n = 341)
Median Survival: 25.8 Mos.

Placebo (n = 171)
Median Survival: 21.7 Mos.
**Most Common Adverse Events (≥ 5%)**

**Higher Rate in Sipuleucel-T (p ≤ 0.05)**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Sipuleucel-T N = 338</th>
<th>Placebo N = 168</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chills</td>
<td>54.1</td>
<td>12.5</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>29.3</td>
<td>13.7</td>
</tr>
<tr>
<td>Headache</td>
<td>16.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>9.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7.4</td>
<td>3.0</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>5.3</td>
<td>0.6</td>
</tr>
</tbody>
</table>
PSA-TRICom Randomized Phase II Study

Asymptomatic or Minimally Symptomatic Metastatic Castrate Resistant Prostate Cancer (N=125)

2:1

PROSTVAC-VF Tricom + GM

Empty Vector + placebo

Primary endpoint: Progression Free Survival
Secondary endpoint: Overall Survival

Treated at physician discretion
Treated at physician discretion and/or Salvage Protocol
PSA-TRICom Progression-Free Survival

Hazard Ratio = 0.88 (95% CI 0.57 to 1.38)
P = 0.60 (stratified logrank)

PSA-TRICom Overall Survival

Hazard Ratio = 0.56 (95% CI 0.37 to 0.85)
P = 0.006 (stratified logrank)

- Control: N = 40, Events = 30, Median = 3.7
- PROSTVAC: N = 82, Events = 58, Median = 3.3