Prostate Cancer: Update on Screening and Management

NAAMA/Houston Convention

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Disclosures

- Grant Research/Support:
  - Bristol-Myers-Squibb (Consultant)
  - Exelixis (consultant)
  - Novartis (consultant)
  - Pfizer (consultant)
Outline

• Background
• PSA and Cancer Screening
• Staging and risk classification
• Local Therapeutic Options
• Metastatic Disease in 2015
Background
2013 US Prostate Cancer
Estimated New Cases and Estimated Deaths

~240,000 Cases

Estimated New Cases*

<table>
<thead>
<tr>
<th>Site</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>238,590</td>
<td>Breast</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>118,080</td>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td>Colorectum</td>
<td>73,680</td>
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</tr>
<tr>
<td>Urinary bladder</td>
<td>54,610</td>
<td>Uterine corpus</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>45,060</td>
<td>Thyroid</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>40,430</td>
<td>Non-Hodgkin lymphoma</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>37,600</td>
<td>Melanoma of the skin</td>
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<tr>
<td>Oral cavity &amp; pharynx</td>
<td>29,620</td>
<td>Kidney &amp; renal pelvis</td>
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<tr>
<td>Leukemia</td>
<td>27,880</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Pancreas</td>
<td>22,740</td>
<td>Ovary</td>
</tr>
<tr>
<td>All Sites</td>
<td>854,790</td>
<td>All Sites</td>
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</table>

~30,000 Deaths

Estimated Deaths

<table>
<thead>
<tr>
<th>Site</th>
<th>Males</th>
<th>Females</th>
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<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>87,260</td>
<td>Lung &amp; bronchus</td>
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<tr>
<td>Prostate</td>
<td>29,720</td>
<td>Breast</td>
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<tr>
<td>Colorectum</td>
<td>26,300</td>
<td>Colorectum</td>
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<tr>
<td>Pancreas</td>
<td>19,480</td>
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<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>14,890</td>
<td>Ovary</td>
</tr>
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<td>Leukemia</td>
<td>13,660</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,220</td>
<td>Non-Hodgkin lymphoma</td>
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<tr>
<td>Urinary bladder</td>
<td>10,820</td>
<td>Uterine corpus</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>10,590</td>
<td>Liver &amp; intrahepatic bile duct</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>8,780</td>
<td>Brain &amp; other nervous system</td>
</tr>
<tr>
<td>All Sites</td>
<td>306,920</td>
<td>All Sites</td>
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Siegel et al, CA Cancer J Clin 2013
Risk Factors

- Age

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<th>Age Interval</th>
<th>Relative Risk</th>
<th>Absolute Risk (%)</th>
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<tbody>
<tr>
<td>0-39</td>
<td>0.01%</td>
<td>1 in 8,499</td>
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<tr>
<td>40-59</td>
<td>2.63%</td>
<td>1 in 38</td>
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<tr>
<td>60-69</td>
<td>6.84%</td>
<td>1 in 15</td>
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<td>70 and older</td>
<td>12.54%</td>
<td>1 in 8</td>
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</table>

- Family History

<table>
<thead>
<tr>
<th>Family History</th>
<th>Relative Risk</th>
<th>Absolute Risk (%)</th>
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<tbody>
<tr>
<td>None</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Father or brother</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Father or brother affected at &lt; 60 years</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Father and brother</td>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td>Hereditary prostate cancer</td>
<td>5</td>
<td>35-45</td>
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</table>

Randomized Prevention Trials in Prostate Cancer

<table>
<thead>
<tr>
<th>Use of antioxidants to reduce damage to DNA</th>
<th>Suppression of androgen signaling (5α-reductase inhibitors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Selenium and Vitamin E Cancer Prevention Trial (SELECT)</td>
<td>– Prostate Cancer Prevention Trial (PCPT)</td>
</tr>
<tr>
<td></td>
<td>– Reduction by Dutasteride of Prostate Cancer Events (REDUCE) Trial</td>
</tr>
</tbody>
</table>

No indication for antioxidants

Evidence that 5α-reductase inhibitors reduce risk of prostate cancer*

*FDA did not approve 5α-reductase inhibitors for the prevention of prostate cancer
Prostate Cancer Evaluation

- Prostate biopsy (Gleason score)
- Digital rectal examination
- Prostate-specific antigen
Anatomical Points (proximity):

1. Neurovascular Bundles
2. Urinary Sphincter
3. Bladder
4. Rectum
Morphology-What does it look like?

- **Gleason scoring**
- **First number** = primary (majority) pattern
- **Second number** = secondary (minority) pattern
- **Increasing order of significance**
  - \( 3+3 \ldots 3+4 \ldots 4+3 \ldots 4+4 \ldots 4+5 \ldots 5+4 \ldots 5+5 \)
- **Gleason 1+2 do not exist on biopsy**
- **Key point**—Morphology often more prognostic than staging

### Gleason Score and Percentage

<table>
<thead>
<tr>
<th>Gleason Score</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-5</td>
<td>2%</td>
</tr>
<tr>
<td>6</td>
<td>50%</td>
</tr>
<tr>
<td>7</td>
<td>30%</td>
</tr>
<tr>
<td>8-10</td>
<td>18%</td>
</tr>
</tbody>
</table>
Not all Prostate Cancers are the same….

Low risk vs high risk
(and those in between)

Factors to consider
- Age/Life expectancy
- Co-morbidities
- Prostate cancer risk stratification
Risk Stratification

D’Amico Risk

Low:
- T1c or T2 and ≤Gleason 6 and PSA <10

Intermediate:
- T2b or
- Gleason 7 or
- PSA 10-20

High:
- T2c/T3 or
- Gleason ≥8 or
- PSA ≥20
PSA and Screening
What is PSA?

• PSA is a serine protease made by malignant AND benign prostate epithelial cells

• Functions to liquefy semen

• 1986 FDA approved PSA to monitor progression in men diagnosed with prostate cancer

• 1994 FDA approved PSA in combo with DRE to screen asymptomatic men for prostate cancer
What is a normal PSA?

• There is no normal: 4.0ng/mL is traditional (although arbitrary) cut off

• Causes of elevated PSA
  • BPH
  • Prostatitis (acute and chronic subclinical)
  • UTI
  • Indwelling foley
  • Recent ejaculation
  • Bicycle riding, Horse back riding
  • Non-lethal forms of prostate cancer!!!
Traditional Strategy:
Early Detection and Treatment

• Routine annual screening at age 50
• Prostate biopsy if PSA greater then 4.0
• Cancer detected
  – Surgery
  – Radiation
  – Watchful waiting (life expectancy <10 years)
Prostate Cancer Mortality Declined in Association with Opportunistic PSA Screening in US

SEER Cancer Statistics
Screening Trials
NEJM 3/26/2009

- **PLCO**
  - 75,000 men
  - PSA annually x 6 years
  - DRE annually x 4 years
  - No impact on mortality
  - (1/2 screened anyway)

- **ERSPC**
  - 160,000 men
  - PSA every 4 years
  - 20% decrease in mortality
Harms

- **Harms of screening**
  - False elevation of PSA
    - Unnecessary biopsies
      - Infection
      - Bleeding (rectal/urinary)
      - Anxiety

- **Harms of over diagnosis/over treatment**
  - Side effects of surgery/radiation
    - Incontinence/Impotence
    - Urinary scarring
    - Anxiety

- **Harms of surveillance**
  - Additional biopsies to monitor on active surveillance
Mixed Data on Surgery for Localized Prostate Cancer

• **Scandinavian trial** (Axelson et al, NEJM, May 2011)
  – Observation vs. Radical Prostatectomy
  – Palpable or symptomatic disease
  – Positive trial

• **PIVOT Trial** (Wilt et al, NEJM, 2012)
  – Observation vs. Radical Prostatectomy
  – PSA screen detected
  – Negative trial
Where Does This Leave US?

- Should we stop PSA screening?
  or
- Should we be more thoughtful and individualized in
  - how we screen
  - whom we biopsy and
  - how those with “cancer” are treated?
Consensus is to discuss benefits and harms of PSA screening with patients who have a minimum 10 year life expectancy.

- A shared and informed decision making process should occur between patient and physician.
- Individualized decision making to optimize the benefit to harm ratio.
Screening for prostate cancer. Recommendation statement date, May 2012:

• Recommendation:
  – Against prostate-specific antigen (PSA)-based screening for prostate cancer.
    Grade: D recommendation
  – Applies to men in the U.S population regardless of age, race, or family history
Prostate Cancer Screening

For
- AUA
- ASCO
- ACP
- EUA
- NCCN

Against
- AAFP
- USPSTF

Shared Decision-Making Process
(Discussion of the risks and benefits of PSA screening)

Abbreviations: AUA, American Urological Association; ASCO, American Society of Clinical Oncology; ACP, American College of Pathologists; EUA, European Urology Association; NCCN, National Comprehensive Cancer Network; AAFP, American Association of Family Physicians; USPSTF, U.S. Preventive Services Task Force.
Treatment
Patient Counseling Approach

3 key points:

1) Active surveillance versus active therapy

2) Active therapy—comparing the standards
   - Radical Prostatectomy vs Radiation Therapy
   - vs possible alternatives

3) Nuances of treatment technique and logistics
Low risk = active surveillance or one treatment option

Intermediate risk = one treatment option with high chance of durable cure

High risk* = 1-2 treatment options, more use of novel treatments, clinical trials, combinations, higher risk of repeat treatments and later progression to metastatic disease
Active Surveillance

- An approach to reduce the harms of prostate cancer screening
  - Unnecessary testing
  - Over-diagnosis
  - Over-treatment
1. **Selection** of men at low risk of harm from prostate cancer without treatment

2. Careful **monitoring** of those who select surveillance
   - Don’t want to miss the 20-30% who harbor worse disease.

3. Curative intervention for men who no longer meet criteria for surveillance
Active Treatment

Standard Therapies

• Radical Prostatectomy
  – Nerve sparing
  – Partial nerve sparing
  – Wide resection
  – Lymph node dissection (standard vs. extended)

• Radiation Therapy
  – Brachytherapy seed placement
  – External Beam with or without Androgen Deprivation:
    1) IMRT
    2) Proton therapy
Active Treatment

Newer and Sub-total Therapy

• Cryotherapy
• High frequency Ultrasound (HIFU)
• Cyberknife
• Photoablative therapy
Logistics

- 2-4 hour operation
- 1-2 day hospitalization
- Foley catheter x 7-10 days
- Return to work 4 weeks
- Urinary control:
  - Majority of return by 3 months
  - 10% risk of stress incontinence at 1 year
  - 2-3% secondary continence procedure
  - <1% risk of overt incontinence
- Erectile function: ~20-30% decline from baseline
- PSA should be undetectable forever (<0.2)
Radical Prostatectomy

Visual Comparison of current techniques

Open Incision  da Vinci port sites
Logistics

- 8 weeks for therapy: 1 hour a day, 5 days a week
- Continue work during therapy
- Side Effects:
  - 5-7% stress incontinence at 2 years
  - 3-4% risk of bowel complaints
  - 3-4% risk of urinary irritability
  - Slight increased risk in secondary malignancies, particularly after 12 yrs
  - Erectile function: ~30% decline from baseline
- New PSA baseline established
Red is prescription isodose. Beige is 20 Gy
Adjuvant Radiation Therapy

- Should be offered to patients with adverse pathology at prostatectomy (Level 1 evidence):
  - SVI
  - Positive surgical margins
  - Extraprostatic extension

- Should be offered to patients with adverse pathology at prostatectomy with a persistent detectable postprostatectomy PSA (Level 1 evidence)

AUA/ASTRO Guideline, J Urol 2013
Metastatic Disease
Contemporary Prostate Cancer Time Course

- Asymptomatic → Symptomatic
- Non-metastatic → Metastatic
- Androgen dependent → Androgen independent

Cancer

- Castration
- Local Therapy
- CYP 17 inhibitors
- Chemotherapy
- Death

Volume/Activity vs. Time

- Tumor

Contemporary Prostate Cancer Time Course
FIRST LINE SYSTEMIC THERAPY: SURGICAL OR CHEMICAL CASTRATION

HYPOthalamus

LHRH

HYPOPHYSIS

LH

ACTH

TESTICLES

ADRENAL GLANDS

T

T

T

T

T

AR

AR

AR

AR

AR
FIRST LINE SYSTEMIC THERAPY: SURGICAL OR CHEMICAL CASTRATION

- HYPOPHYSIS
  - LH
  - ACTH
  - TESTICLES
  - ADRENAL GLANDS
- LHRH
  - LHRH AGONIST
  - LHRH ANTAGONIST

- HYPOTHALAMUS
  - LH
  - ACTH

AR

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Metastatic Prostate Cancer 2015

- Androgen Deprivation Therapy
- Abiraterone
- Enzalutamide
- Docetaxel
- Cabazitaxel
- Radium-223
- Sipuleucel-T
- Abiraterone
## Metastatic Prostate Cancer

### Androgen Deprivation Therapy

- **SIPULEUCEL-T**

### Secondary Hormone Treatments

- **Chemotherapy**
  - Radium-223

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Experimental Arm</th>
<th>Median OS</th>
<th>Control Arm</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tannock, 2004</td>
<td>Docetaxel + Prednisone</td>
<td>18.9mo</td>
<td>Mitoxantrone + Prednisone</td>
<td>16.5mo</td>
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<td>Petrylak, 2004</td>
<td>Docetaxel + Estramustine</td>
<td>17.5mo</td>
<td>Mitoxantrone + Prednisone</td>
<td>15.6mo</td>
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<tr>
<td>De Bono, 2010</td>
<td>Cabazitaxel + Prednisone</td>
<td>15.1mo</td>
<td>Mitoxantrone + Prednisone</td>
<td>12.7mo</td>
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</tbody>
</table>
Metastatic Prostate Cancer

- Androgen deprivation therapy
- Secondary hormone treatments
- Chemotherapy

SIPULEUCEL-T

Radium-223

PAP/GM-CSF

Metastatic Prostate Cancer

**Androgen Deprivation Therapy**
- **SIPULEUCEL-T**

**Secondary Hormone Treatments**

**Chemotherapy**
- **Radium-223**

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</tr>
</thead>
<tbody>
<tr>
<td>De Bono, 2011</td>
<td>Abiraterone + Prednisone</td>
<td>14.8mo</td>
<td>Placebo + Prednisone</td>
<td>10.9mo</td>
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<tr>
<td>Scher, 2012</td>
<td>Enzalutamide</td>
<td>18.4mo</td>
<td>Placebo</td>
<td>13.6mo</td>
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Metastatic Prostate Cancer

**ANDROGEN DEPRIVATION THERAPY**

- **SIPULEUCEL-T**
- **SECONDARY HORMONE TREATMENTS**
- **CHEMOTHERAPY**

<table>
<thead>
<tr>
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<th>Control Arm</th>
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Metastatic Prostate Cancer

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Experimental Arm (n=546)</th>
<th>Median OS</th>
<th>Control Arm (n=542)</th>
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<tr>
<td>Ryan, 2015</td>
<td>Abiraterone + Prednisone</td>
<td>34.7mo</td>
<td>Placebo + Prednisone</td>
<td>30.3mo</td>
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Metastatic Prostate Cancer

**ANDROGEN DEPRIVATION THERAPY**

**DOCETAXEL**

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<td>Beer, 2014</td>
<td>Enzalutamide</td>
<td>32.4</td>
<td>Placebo + Prednisone</td>
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</table>
Metastatic Prostate Cancer

- **Androgen Deprivation Therapy**
  - Sipuleucel-T
- **Secondary Hormone Treatments**
  - Radium-223
- **Chemotherapy**
Thank you