Prostate Cancer

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Every 2 Minutes an American is Diagnosed with Prostate Cancer

Every 18 Minutes an American Dies of Prostate Cancer
Prostate Cancer Basics

- Biology
- Incidence and mortality
- Early detection guidelines
- Treatment guidelines - guideline compliant staging, treatment, and follow-up
The Prostate

• Fluid producing walnut sized gland with multiple fluid producing sacs (acini)
• Produces 50% of seminal fluid, protects & nourishes the sperm
• Seminal fluid contains a protein, prostate-specific antigen (PSA), that liquefies coagulated semen
• Enlarges at puberty and grows slowly during adulthood in most men
Prostate Carcinogenesis

- HPC mutation (genetic predisposition)
- Oxidative damage
- Dietary & environmental factors
- Inflammation or infection?

- Prostatic Intraepithelial Neoplasia (PIN)
  - GSTP1 methylation
  - Bp21 loss (NOC11)
  - AMACR
  - Telomere length

- Proliferative Inflammatory Atrophy (PIA)
  - 10q loss (PTEN)
  - 13q loss (Rb/)
  - RASSF1A methylation
  - p27
  - Telomerase, PSCA

- Localized Cancer
  - 17p loss (p53)
  - E cadherin function
  - Gene methylation

- Metastatic Disease

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Prostate Cancer Biology

- Cause- unknown; androgens required
- Not causes- prostate enlargement, BPH
- Risk factors- race, family history, BRAC1 mutation, ?high fat diet, ?seared red meat
- Prevention- fish oils, leafy vegetables, ?finasteride, ?dutasteride, ?selenium
- CaP occurs in the peripheral zone (periphery) whereas BPH occurs in the transition zone (central)
- BPH produces voiding symptoms but CaP does not; symptomatic CaP is incurable
- Prostate → capsular penetration → seminal vesicle/bladder neck invasion → pelvic lymph nodes → distant metastases (bone > liver > lungs)
- Adenocarcinoma (98%); small cell (2%)
Prostate-Specific Antigen (PSA)

- Serine protease that liquefies the ejaculate
- BPH produces 10x more PSA per gm tissue than CaP
- CaP erodes prostate-blood barrier causing leakage of lower concentrations of PSA into circulation
- False elevations due to:
  - Enlarged prostate
  - Prostatitis (may be subclinical)
  - Lower urinary tract symptoms (LUTS)
  - Prostatic calculi
  - Recent ejaculation (<36 h)
  - Intraindividual variation
  - Laboratory error
- 2/3 of men with elevated PSA do not have CaP and 10% of men with CaP have normal PSA
The Prostate Cancer Challenge

- Complex disease
- Many controversial aspects of management
- Lack of sound data to support most recommendations
- Several variables must be considered to tailor prostate cancer therapy to an individual patient
- Guidelines provide a framework on which to base treatment decisions
Important Terms

- **Gleason Grading System**
  - Pattern/ Grade = 1-5
  - Score/ Sum = 2-10 (2-6, 3+4, 4+3, 8-10)

- **TNM Stage**

- **Incidental/ Autopsy vs Clinical**

- **Screening vs Early Detection**

- **PSA**
  - Absolute/ Snapshot (<2.5 or <4.0)
  - PSA Velocity (<0.75 ng/ml/yr)
  - PSA Doubling Time (<9m, 18m, 3y, >5y)

- **Expectant Management (NCCN preferred)/ Observation/ Watchful Waiting/ Active Surveillance (NCCN preferred 2009)**
Gleason Grading System
Gleason Grading System

Gleason Grade 1

Gleason Grade 2

Gleason Grade 3

Gleason Grade 4

Gleason Grade 5
Important Terms

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• PSA
  – Absolute/ Snapshot (<2.5 or <4.0)
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  – PSA Doubling Time (<9m, 18m, 3y, >5y)

• Expectant Management (NCCN preferred)/ Observation/ Watchful Waiting/ Active Surveillance (NCCN preferred 2009)
### TNM Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>Tumor found in prostate tissue removed for reasons other than cancer; less than 5 percent of specimen is malignant</td>
</tr>
<tr>
<td>T1b</td>
<td>Same as T1 but more than 5 percent of specimen contains cancer</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumor found through biopsy done in response to an elevated PSA test or to an abnormal ultrasound exam; may be less extensive than a T1b tumor</td>
</tr>
</tbody>
</table>
### TNM Staging System

<table>
<thead>
<tr>
<th>Stage T2</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpable tumor confined to prostate gland</td>
<td>T2a Tumor confined to less than half of one lobe</td>
<td><img src="image1.png" alt="Tumor Image" /></td>
</tr>
<tr>
<td>T2b Tumor affecting more than half of one lobe</td>
<td><img src="image2.png" alt="Tumor Image" /></td>
<td></td>
</tr>
<tr>
<td>T2c Tumor involving both lobes</td>
<td><img src="image3.png" alt="Tumor Image" /></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage T3</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor that has begun to expand beyond the prostate</td>
<td>T3a Tumor that protrudes beyond the prostate</td>
<td><img src="image4.png" alt="Tumor Image" /></td>
</tr>
<tr>
<td>T3b Tumor that has invaded the seminal vesicles</td>
<td><img src="image5.png" alt="Tumor Image" /></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage T4</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor that is fixed and has pushed well beyond the prostate into adjacent structures</td>
<td><img src="image6.png" alt="Tumor Image" /></td>
</tr>
</tbody>
</table>
Prostate Cancer Basics

- Biology
- Incidence and mortality
- Early detection guidelines
- Treatment guidelines - guideline compliant staging, treatment, and follow-up
Prostate Cancer:

#1 Incidence (238,590)

#2 Deaths (29,720)

Cancer Statistics, 2013
U.S. Annual Age-Adjusted Incidence Rates
1975 – 2009
Cancer Statistics, 2013
Prostate Cancer Basics

• Biology
• Incidence and mortality
• Early detection guidelines
• Treatment guidelines - guideline compliant staging, treatment, and follow-up
Since the discovery of PSA, the death rate from prostate cancer has:

a. Increased due to side effects from unnecessary treatments
b. Decreased 10%
c. Decreased 40%
d. Decreased 60%
Since the discovery of PSA, the death rate from prostate cancer has:

a. Increased due to side effects from unnecessary treatments
b. Decreased 10%
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d. Decreased 60%
Prostate Cancer

- Abnormal growth and invasion/metastasis
- Resistance to apoptosis (programmed cell death)
- Increased cellular proliferation

- 85% multifocal
- 90% peripheral zone
- 10% transition zone (less aggressive)
Prostate Biopsy

- Biopsies sample prostate
- Biopsy detection rate
  - First: 75% of existing cancers
  - Second: 91%
  - Third: 97%
  - Fourth: 99%
- Accuracy of Gleason grade compared to RP
  - 30% grade increases
  - 5% grade decreases
Prostate Ultrasound

Downloaded from: Campbell-Walsh Urology (on 29 January 2008 07:50 PM)
Templates for Diagnostic Prostate Biopsies

A B C D

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• 70% of men with elevated PSA have negative biopsies
• PSA can fluctuate by 36% day to day
• Rate of rise more accurate
  – PSA Velocity or PSA Doubling Time
  – Requires ≥ 3 PSAs over ≥ 18 mo
• PSAV ≥ 0.75 ng/ml or PSADT ≤ 3 yrs
CaP Early Detection Recommendations

• U.S. Preventive Services Task Force (August 2008)
  – Routine screening not advocated especially >75

• American Urological Association (August 2009)
  – Annual PSA & DRE
    - From age 50 until LE <10 yrs
    - From age 40 if high risk (AA or family history)

• American Cancer Society (March 2010)
  - Annual PSA ± DRE
    - From age 50 until LE <10 yrs
    - From age 45 if high risk (AA or family history)
    - From age 40 if multiple family members
CaP Early Detection Recommendations

- U.S. Preventive Services Task Force (draft; October 2011)
  - Routine screening not advocated for anyone
- NCCN (the best recommendation) (October 2011)
  - PSA and DRE at 40 (category 2B), if <1, at 45
  - PSA and DRE at 45, if <1, at 50
  - If high risk because AA, family history, taking 5ARI or PSA >1, annual PSA and DRE at 40 (category 2B)
  - Routine screening less frequent in older men (65-75) and not advocated especially >75
- American College of Physicians; American Academy of Family Physicians
  - Counsel men 50 to 65 regarding risk vs. benefit
PSA and Prostate Cancer Screening

• PSA increases the detection of organ confined CaP
• Serial PSA screening improves the ability to detect organ confined prostate cancer
• PSA detects 2x as many cancers as DRE
Cancer Screening Costs

- Total cost of CaP screening/treatment: $17.6 – $25.7 billion
- Cost per quality-adjusted life year gained
  - CABG: $7,300-$62,900
  - CaP screening: $14,200-$51,267
  - Breast cancer screening: $20,000-$50,000
  - Colon cancer screening: $35,054
  - Liver transplant: $225,900

Littrup et al, Cancer 1997
## Screening Performance

<table>
<thead>
<tr>
<th></th>
<th>Mammography</th>
<th>PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ Predictive Value</td>
<td>7-17%</td>
<td>33%</td>
</tr>
<tr>
<td>Organ Confined</td>
<td>50%</td>
<td>80%</td>
</tr>
<tr>
<td>+ Lymph Nodes</td>
<td>20%</td>
<td>2%</td>
</tr>
<tr>
<td>“Latent” Cancer</td>
<td>8%</td>
<td>7%</td>
</tr>
</tbody>
</table>
Screening Men with a Family History

- 2-3 fold increased risk if first-degree relative with CaP (Keetch, J Urol, 1995; Walsh, Cancer, 1997)
- Younger age at presentation
- Comparable results with RP (Beva, J Urol, 1998)
- Begin screening at age 40
Prostate Cancer Incidence and Death Rates by Race and Ethnicity, 2001 - 2005
*Cancer Statistics, 2009*

<table>
<thead>
<tr>
<th></th>
<th>Caucasian American</th>
<th>African American</th>
<th>Asian American and Pacific Islander</th>
<th>American Indian and Alaska Native</th>
<th>Hispanic Latino</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence</strong></td>
<td>156.7</td>
<td>248.5</td>
<td>93.8</td>
<td>73.3</td>
<td>138</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>24.6</td>
<td>59.4</td>
<td>11.0</td>
<td>21.1</td>
<td>20.6</td>
</tr>
</tbody>
</table>
Use of PSA for Early Detection is Most Appropriate for:

A) African Americans
B) Men with CaP in father or brother
C) Men with life expectancy $\geq 10$ yrs
D) Men with BRAC1 mutation
E) All of the above
Use of PSA for Early Detection is Most Appropriate for:

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PSA is:

A) Diagnostic for CaP when elevated
B) Expressed at higher levels in malignant than benign prostate
C) Expressed only by the prostate
D) Expressed only in humans
E) None of the above
PSA is:

A) Diagnostic for CaP when elevated
B) Expressed at higher levels in malignant than benign prostate
C) Expressed only by the prostate
D) Expressed only in humans
E) None of the above
Use of PSA: The Real World

• Men > 85 yo who have had PSA in last year
  – 25% in National Health Interview Study 2000 and 2005 (Drazer, JCO, 2011)
  – 36% in US Dept of Veteran Affairs in 2002-3 (Walter, JAMA, 2006)

• Interventions
  – Stop including PSA in routine annual labs (So, J Gen Intern Med, 2012)
  – Guidelines, pamphlets, internet, videos (Frosch, J Gen Intern Med, 2003)
“Don’t worry about not having any health insurance. I don’t have any malpractice insurance.”
Prostate Cancer Basics

- Biology
- Incidence and mortality
- Early detection guidelines
- Treatment guidelines - guideline compliant staging, treatment, and follow-up
NCCN Guidelines Version 1.2013
Prostate Cancer

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NCCN Guidelines Panel Disclosure

Continue

§ Radiotherapy/Radiation oncology
○ Urology
† Medical oncology
£ Supportive care, including palliative, pain management, pastoral care, and oncology social work
■ Pathology
*Writing committee member
PSA, Treatment and Mortality

- **Swedish RP vs Watchful Waiting**
  - 44, 35, 38% decline in CaP-specific mortality after 8.2, 10.8, 12.8 yrs follow-up
  - Enrolled 1989 – 1999 and almost no PSA use
  - Bill-Axelson, NEJM, 2005; JNCI, 2008; NEJM 2011

- **Tyrol, Austria PSA-based screening study**
  - 54% decline in CaP-specific mortality
  - 10 yr PSA lead-time
  - Enrolled 1988 – 2005 and PSA since 1993
  - Bartsch G, BJU Int, 2008
March 26, 2009 CaP Explosion

NEJM 360:1310-19 and 1320-28

Screening and Prostate-Cancer Mortality in a Randomized European Study

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D.,
Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D.,
Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D.,
Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D.,
Antonio Berenguer, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D.,
Gunnar Aus, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D.,
Theodorus van der Kwast, M.D., Bert G. Blijenberg, Ph.D., Sue M. Moss, Ph.D.,
Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators*

Mortality Results from a Randomized Prostate-Cancer Screening Trial

Gerald L. Andrieo, M.D., E. David Crawford, M.D., Robert L. Grubb III, M.D.,
Saundra S. Buys, M.D., David Chia, Ph.D., Timothy R. Church, Ph.D.,
Mona N. Fouad, M.D., Edward P. Gelmann, M.D., Paul A. Kwale, M.D.,
Douglas J. Reding, M.D., Joel L. Weissfeld, M.D., Lance A. Yokochi, M.D.,
Barbara O'Brien, M.P.H., Jonathan D. Clapp, B.S., Joshua M. Rathmell, M.S.,
Thomas L. Riley, B.S., Richard B. Hayes, Ph.D., Barnett S. Kramer, M.D.,
Grant Izmirlian, Ph.D., Anthony B. Miller, M.B., Paul F. Pinsky, Ph.D.,
Philip C. Prorok, Ph.D., John K. Gohagan, Ph.D., and Christine D. Berg, M.D.,
for the PLCO Project Team*
Need to Treat to Prevent 1 Death:

- 100 low risk CaP, Canadian (Klotz, J Clin Oncol, 2005)
- No survival benefit, American (NEJM, 2009)
- 48 PSA-detected CaP, European (NEJM, 2009)
- 12 PSA-detected CaP in Goteburg subset, Sweden (Hugosson, Lancet Oncol, 2010)
- 15 DRE-detected CaP; 7 if < 65 yo, Sweden (Bill-Axelson, NEJM, 2011)
NCCN Concerns

- High prevalence of CaP upon autopsy
  Sakr, In Vivo, 1994
- High frequency of CaP upon biopsy even when PSA and DRE normal
  Thompson, NEJM, 2004
- Mortality about 1/6 incidence
  Jemal, CA Cancer J Clin, 2010
- 29-50% of screen-detected CaP over-treated
  Etzioni, JNCI, 2002; Draisma, JNCI, 2003; Miller, JNCI, 2006
Active Surveillance or Immediate Active Treatment?

- The **risks** include
  - chance of missed opportunity for cure
  - nerve-sparing may be more difficult
  - anxiety

- The **benefits** include
  - avoidance of treatment-related side effects from a treatment that was unnecessary
2010 Guideline Updates

1. Very low risk CaP

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Very Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• T1-T2a</td>
<td>• T1c</td>
</tr>
<tr>
<td>• GS 2-6</td>
<td>• GS 2-6</td>
</tr>
<tr>
<td>• PSA&lt;10</td>
<td>• PSA&lt;10</td>
</tr>
<tr>
<td></td>
<td>• &lt;3 cores positive</td>
</tr>
<tr>
<td></td>
<td>• &lt;50% CaP in any core</td>
</tr>
<tr>
<td></td>
<td>• PSAD&lt;0.15</td>
</tr>
</tbody>
</table>
2010 Guideline Updates

2. Active surveillance only recommendation for men with:

a. Low risk CaP and L Exp < 10 yrs
b. Very low risk CaP and L Exp < 20 yrs
Prostate Cancer Spreads While Patients Thinking!

- 645 Canadians who underwent RP 1987-1997
- 10 yr biochemical progression-free survival
  - $RP < 3 \text{ mo}$ 75%
  - $RP \geq 3 \text{ mo}$ 61%
  - $p = 0.05$
- RP delay $\geq 3 \text{ mo}$ associated with 46% increased chance of PSA progression after adjusting for grade, stage, and PSA at diagnosis

Nam, Can J Urol, 2003
But Several Studies Show NO Harm from Treatment Delay

• BPFS not impacted by delay between diagnosis and RP
  – 2 yr- Shibato, Urology, 2005 (n=151, MCG)
  – 6 mo- Freedland, J Urol, 2006 (n= 895, JH)
  – 3 mo- Phillips, Urol Oncol, 2007 (n= 393, WFU)

• GS rarely changes between diagnosis and rebiopsy
  – 2.4% convert from low to high grade CaP at 7 yrs-Whittemore, JNCI, 1991 (SEER data)
  – 13% changed from <7 to some 4 or 5 after 1-6 yr-Epstein, J Urol, 2001 (n= 70, JH)
  – 2.5%- Choo, J Urol, 2002 (n= 206, Canadian)
  – 4%- Klotz, JNCCN, 2007 (n= 331, Canadian)

• Klotz- “Need to treat an estimated 200 men with low risk CaP in order to prevent 1 CaP death”
Concern in Toronto AS Series

• 3 deaths from CaP among 450 men
• PSADTs < 2 yrs
• Treated 6, 9 and 11 mo after diagnosis
• Bone metastases < 1 yr after treatment → ADT
• Died 3, 5 and 5 yrs after diagnosis
• Conclusion: Micrometastases at diagnosis and treatment would not have altered outcome

Klotz, JNCCN, 2007
2011 Guideline Updates

3. Active surveillance program clarified
   a. PSA as often as every 3 mo but at least every 6 mo
   b. DRE as often as every 6 mo but at least every 12 mo
   c. Needle biopsy may be repeated within 6 mo of diagnosis if initial bx was < 10 cores; may be performed within 18 mo of initial biopsy >/= 10 cores
   d. Uncertain what the progression criteria should be to warrant treatment
3. Active surveillance program clarified

a. PSA as often as every 3 mo but at least every 6 mo

b. DRE as often as every 6 mo but at least every 12 mo

c. Needle biopsy may be repeated within 6 mo of diagnosis if initial bx was <10 cores; may be performed within 18 mo if initial biopsy >/= 10 cores

d. Uncertain what the progression criteria should be to warrant treatment

Buethe, JNCCN, 2012; Dall’Era, Eur Urol, 2012
Criteria for Progression:

- Toronto: clinical or PSADT < 3 yrs
  - Neither PSA > 10 nor > 20 or PSAV > 2 ng/ml/yr better
- Johns Hopkins: annual pbx GG 4-5 or cores > 2 or core > 50%
  - Neither PSADT nor PSAV assoc w/ pbx progression
- No harm to period of AS
  - RP after AS has better PSA cure rate than RP
- Need biomarker for CaP aggressiveness

Loblaw, J Urol, 2010; Ross, JCO, 2010; Cooperberg, JCO, 2010
## North American AS Experience

<table>
<thead>
<tr>
<th>Center</th>
<th>Toronto(^1)</th>
<th>Johns Hopkins(^2)</th>
<th>UCSF(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>450</td>
<td>603</td>
<td>531</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>70</td>
<td>66</td>
<td>63</td>
</tr>
<tr>
<td>F/U (mo, median)</td>
<td>82</td>
<td>31</td>
<td>43</td>
</tr>
<tr>
<td>OS</td>
<td>68%</td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td>CSS</td>
<td>97%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Treatment</td>
<td>30%</td>
<td>31%</td>
<td>24%</td>
</tr>
<tr>
<td>GS↑</td>
<td>8%</td>
<td>27%</td>
<td>38%</td>
</tr>
<tr>
<td>PSA</td>
<td>14% (DT&lt;3)</td>
<td>-</td>
<td>26%</td>
</tr>
<tr>
<td>Nodule</td>
<td>1%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3%</td>
<td>7%</td>
<td>8%</td>
</tr>
</tbody>
</table>

**NCCN Guidelines Version 1.2013**
Prostate Cancer

**RECURRENT RISK**
Clinically Localized:
Very Low:
- T1c
- Gleason score ≤6
- PSA <10 ng/mL
- Fewer than 3 prostate biopsy cores positive, ≤50% cancer in any core
- PSA density <0.15 ng/mL/g

Low:
- T1-2a
- Gleason score ≤6
- PSA <10 ng/mL

**EXPECTED PATIENT SURVIVAL**

![Diagram of expected patient survival and initial therapy options]

**INITIAL THERAPY**

- Active surveillance (category 2B)
  - PSA at least as often as every 6 mo
  - DRE at least as often as every 12 mo
  - Repeat prostate biopsy as often as every 12 mo

- Active surveillance
  - PSA at least as often as every 6 mo
  - DRE at least as often as every 12 mo

- Active surveillance
  - PSA at least as often as every 6 mo
  - DRE at least as often as every 12 mo
  - Repeat prostate biopsy as often as every 12 mo

- RT (Daily IGRT with IMRT/3D-CRT) or brachytherapy
  - Radical prostatectomy (RP)
    - ± pelvic lymph node dissection (PLND) if predicted probability of lymph node metastasis ≥2%

**ADJUVANT THERAPY**

- Progressive disease
  - See Initial Clinical Assessment (PROS-1)

- Adverse features
  - RT
  - Observation

- Lymph node metastasis:
  - Observation
  - ADT
  - ADT + RT (category 2B)

---

**Notes:**
- All recommendations are category 2A unless otherwise indicated.
- Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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**References:**
- See Principles of Life Expectancy Estimation (PROS-A).
- The Panel remains concerned about the problems of over-treatment related to the increased diagnosis of early prostate cancer from PSA testing. See NCCN Guidelines for Prostate Cancer Early Detection. Active surveillance is recommended for these subsets of patients.
- Active surveillance involves actively monitoring the course of disease with the expectation to intervene if the cancer progresses. See Principles of Active Surveillance (PROS-B).
- See Principles of Radiation Therapy (PROS-C).
- See Principles of Surgery (PROS-D).
- Criteria for progression are not well defined and require physician judgement; however, a change in risk group strongly implies disease progression.
- Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.
- See Principles of Androgen Deprivation Therapy (PROS-E).
When is active surveillance an appropriate option in men with clinically localized prostate cancer?

A. When CaP is poorly differentiated
B. When CaP is palpable
C. When PSA exceeds 20
D. When PSA doubling time exceeds 5 yrs
When is active surveillance an appropriate option in men with clinically localized prostate cancer?

A. When CaP is poorly differentiated
B. When CaP is palpable
C. When PSA exceeds 20
D. When PSA doubling time exceeds 5 yrs
HEY! Wait a Minute.....

Every 2 Minutes an American is Diagnosed with Prostate Cancer

Every 18 Minutes an American Dies of Prostate Cancer
Radical Prostatectomy
Radical Prostatectomy
Neurovascular Bundles
Open Surgery
Laparoscopic Surgery

Laparoscopic instruments allow surgeons to remove the gallbladder through 4 tiny openings, each less than ½ inch in diameter.
Benefits of Robotic Surgery

- Simplify laparoscopy
  - Wristed instruments
  - 3D vision
- Improved dexterity/precision
  - Scaling
  - 12x magnification
- Eliminate tremor
  - Filtering
- Improved stability and ergonomics
Vas and Seminal Vesicles
The New Look of the Surgical Urologic Oncology Patient
Radiation Therapy

- Brachytherapy (interstitial radiation, “seeds”)
  - Iodine
  - Palladium
  - Cesium
- External radiation therapy
  - Electron, proton, or neutron
  - Conformal
  - IMRT
  - IGRT
Transperineal Technique
Implant/Dose Distribution
Brachytherapy

- For low-risk CaP, use brachytherapy alone
- For intermediate-risk CaP, consider combining brachytherapy with EBRT (40-50 Gy) ± 4 or 6 mo neoadjuvant/concomittant/adjuvant androgen deprivation therapy
- Brachytherapy contraindicated for high-risk CaP

NCCN Guidelines, 2007 - 2009
Brachytherapy

• Brachytherapy has increased risk of side effects if
  – prostate large or small
  – lower urinary tract symptoms significant
  – prior TURP

• Perform post-implant dosimetry to document implant quality

NCCN Guidelines, 2007 - 2009
Radiation

- 3D conformal and IMRT (intensity modulated RT) and IGRT (image guided RT) techniques required
- For > 75 Gy, use daily prostate localization
- Patients with high-risk CaP require pelvic lymph node irradiation
- Neoadjuvant/adjuvant ADT
  - Consider 4-6 mo ADT for intermediate risk
  - Use 2-3 yrs ADT for high risk
- Indications for salvage radiation simplified and nomogram usage recommended

NCCN Guidelines, 2007 - 2009
Dose Distribution: Standard Therapy
Dose Distribution: 3D Conformal
Intensity Modulated Radiation Therapy (IMRT)

- Radiation oncologist selects the volume for irradiation and the volumes to be spared
- Computer selects the optimal way to deliver dose
What is IMRT?

IMRT is the ability to deliver many “beamlets” of varying radiation intensity, within one treatment field.

“Fluence” or Intensity Map

“Beam-lets”
Multileaf Collimator
Treat Everyone... But Treatment Has Risks

- **Mortality**
  - RP 0.5%
  - RT 0.1%

- **Urinary incontinence**
  - RP 3% [5-60%]
  - RT 8%

- **Impotence**
  - RP 30% (≤65 yrs); 50% (>65 yrs) [12-56%]
  - RT 63-70%

Treatment Discussion

• Estimate Life Expectancy
• Risk stratify using Stage, Gleason Sum and PSA
• AS should be the first option discussed against which the benefits (potential and need for cure) and risks (mortality, urinary incontinence and impotence) of treatment should be compared
• AS should be recommended for very low and low-risk CaP when L Exp is <20 and <10 yrs, respectively
How does one estimate life expectancy with enough accuracy to guide treatment decision?

A. Ask the patient
B. Use the Minnesota Metropolitan Life Insurance tables
C. Use the Social Security Administration tables
D. Adjust for overall health status
E. All of the above
How does one estimate life expectancy with enough accuracy to guide treatment decision

A. Ask the patient
B. Use the Minnesota Metropolitan Life Insurance tables
C. Use the Social Security Administration tables
D. Adjust for overall health status
E. All of the above
Life Expectancy Estimation

• LExp can be estimated using the Minnesota Metropolitan Life Insurance Tables or the Social Security Administration LExp Tables.

• LExp can be adjusted for individual patients by adding or subtracting 50% based upon whether one believes the patient is in the healthiest quartile or the unhealthiest quartile, respectively.
  – SSA LExp for 65-year old American man = 16 yrs
  – If upper quartile of health, LExp = 24 yrs
  – If lower quartile of health, LExp = 8 yrs

• 2007 NCCN Guidelines, for the first time, included “Principles of Life Expectancy Estimation.”
Time to CaP Death: Population-Based

- **Gleason score**
  - 2-6 favorable
  - 7-10 unfavorable

- **Tumor volume**
  - < 4 cc favorable
  - ≥ 4 cc unfavorable (nodule, PSA >12, >3 biopsies, >50% of biopsy)

- **Aggressiveness (Stanford criteria)**
  - Low if both favorable
  - High if both unfavorable
  - Intermediate if only 1 favorable

- **Time to symptomatic metastases (Sweden)**
  - Low 12 yrs
  - Intermediate 10 yrs
  - High 8 yrs

- **Time to death**
  - Time to symptoms + 3 yrs for ADT remission + 10 yr PSA early detection lead time [if applicable]
  
  McNeal, Human Pathol, 1992; Bartsch G, BJU Int, 2008
Time to CaP Death: PSADT-Based

- Calculate PSA doubling time
- Assume symptoms at PSA 100-200
- Add 5 yrs for ADT-induced remission
- Example
  - Average PSADT for clinically detected CaP = 4 yrs
  - Diagnosed at PSA = 6
  - PSA >100 after 4 doublings or 16 yrs
  - Death after 21 yrs
Time to Put into Practice!
Case 1

• A common presentation of clinically localized CaP
• Change patient’s health and use NCCN guidelines to estimate life expectancy
• Examine effect upon relationship between risk of death from CaP vs other causes
• Use NCCN guidelines to see how recommended treatment changes
Case 1 - excellent

65 yo man presents with PSA 7.2, clinical stage T1c, and Gleason score 3+3=6 prostate cancer in 10% of 1 of 12 biopsies. Health is excellent. The best choice for treatment is:

1. 3D Conformal Radiation
2. Interstitial Implant (seeds)
3. Prostatectomy
4. Cryotherapy
5. Active Surveillance
• CaP-limited LExp is 12 (low aggressiveness) + 3 (ADT) + 10 (PSA lead time) = 25 yrs
• LExp by age = 16.4 yrs
  - Excellent health = 24.6 yrs
  - Average health = 16.4 yrs
  - Poor health = 8.2 yrs
• Chance of CaP death
  - Excellent health = 50%
  - Average health = 10%
  - Poor health = 0%
• Chance of cure of CaP by Partin Tables 83%
• Chance of CaP death after RP
  - Excellent health = 7%
  - Average health = 2%
  - Poor health = 0%
Case 1 - excellent

65 yo man presents with PSA 7.2, clinical stage T1c, and Gleason score 3+3=6 prostate cancer in 10% of 1 of 12 biopsies. Health is excellent. The best choice for treatment is:

1. 3D Conformal Radiation
2. Interstitial Implant (seeds)
3. Prostatectomy
4. Cryotherapy
5. Active Surveillance
Case 1 - poor

65 yo man presents with PSA 7.2, clinical stage T1c, and Gleason score 3+3=6 prostate cancer in 10% of 1 of 12 biopsies. Health is poor. The best choice for treatment is:

1. 3D Conformal Radiation
2. Interstitial Implant (seeds)
3. Prostatectomy
4. Cryotherapy
5. Active Surveillance
• CaP-limited LExp is 12 (low aggressiveness) + 3 (ADT) + 10 (PSA lead time) = 25 yrs
• LExp by age = 16.4 yrs
  - Excellent health = 24.6 yrs
  - Average health = 16.4 yrs
  - Poor health = 8.2 yrs
• Chance of CaP death
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• Chance of cure of CaP by Partin Tables 83%
• Chance of CaP death after RP
  - Excellent health = 7%
  - Average health = 2%
  - Poor health = 0%
Case 1 - poor

65 yo man presents with PSA 7.2, clinical stage T1c, and Gleason score 3+3=6 prostate cancer in 10% of 1 of 12 biopsies. Health is poor. The best choice for treatment is:

1. 3D Conformal Radiation
2. Interstitial Implant (seeds)
3. Prostatectomy
4. Cryotherapy
5. Active Surveillance
Case 1 - average

65 yo man presents with PSA 7.2, clinical stage T1c, and Gleason score 3+3=6 prostate cancer in 10% of 1 of 12 biopsies. Health is average. The best choice for treatment is:

1. 3D Conformal Radiation
2. Interstitial Implant (seeds)
3. Prostatectomy
4. Cryotherapy
5. Active Surveillance
• CaP-limited LExp is 12 (low aggressiveness) + 3 (ADT) + 10 (PSA lead time) = 25 yrs
• LExp by age = 16.4 yrs
  - Excellent health = 24.6 yrs
  - Average health = 16.4 yrs
  - Poor health = 8.2 yrs
• Chance of CaP death
  - Excellent health = 50%
  - Average health = 10%
  - Poor health = 0%
• Chance of cure of CaP by Partin Tables 83%
• Chance of CaP death after RP
  - Excellent health = 7%
  - Average health = 2%
  - Poor health = 0%
Case 1 - average

65 yo man presents with PSA 7.2, clinical stage T1c, and Gleason score 3+3=6 prostate cancer in 10% of 1 of 12 biopsies. Health is **average**. The best choice for treatment **prior to 2010** was:

1. 3D Conformal Radiation
2. Interstitial Implant (seeds)
3. Prostatectomy
4. Cryotherapy
5. Active Surveillance
Case 1 - average

65 yo man presents with PSA 7.2, clinical stage T1c, and Gleason score 3+3=6 prostate cancer in 10% of 1 of 12 biopsies. Health is average. The only treatment recommendation beginning 2010 is:

1. 3D Conformal Radiation
2. Interstitial Implant (seeds)
3. Prostatectomy
4. Cryotherapy
5. Active Surveillance
When is active surveillance an appropriate option in men with clinically localized prostate cancer?

A. When CaP is poorly differentiated
B. When CaP is palpable
C. When PSA exceeds 20
D. When PSA doubling time exceeds 5 yrs
When is active surveillance an appropriate option in men with clinically localized prostate cancer?

A. When CaP is poorly differentiated
B. When CaP is palpable
C. When PSA exceeds 20
D. When PSA doubling time exceeds 5 yrs
Take Home Points

1. Optimal use of PSA should reduce CaP mortality by 50% while avoiding overtreatment.

2. Better treatment decisions will result from individualized estimation of:
   - threat-to-life posed by CaP
   - chance of cure by treatment
   - risks of treatment

3. Active surveillance monitoring needs to be
“... Or, if you elect not to have the surgery, the insurance company offers six days and seven nights in Barbados.”
Definitions and Principles

- Radiation benefit should exceed risk
- Radiation should not be administered when disease metastatic
- Adjuvant – radiation administered for adverse pathology or biochemical persistence
- Salvage – radiation administered for biochemical recurrence after apparent cure
Restaging Evaluation Change

NCCN Guidelines Version 1.2013
Prostate Cancer

POST-RADICAL PROSTATECTOMY RECURRENCE

- Failure of PSA to fall to undetectable levels
  - Undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more determinations

- Studies negative for distant metastases
  - RT ± neoadjuvant/concomitant/adjuvant ADT
  - or Observation

ADT ± RT to site of metastases, if in weight-bearing bones, or symptomatic
  - or Observation

Progression

See Advanced Disease (PROS-8) and (PROS-9)

See Principles of Radiation Therapy (PROS-C).
See Principles of Androgen Deprivation Therapy (PROS-E).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Restaging Evaluation Change

NCCN Guidelines Version 1.2013
Prostate Cancer

POST-RADIATION THERAPY RECURRENCE

Candidate for local therapy:
- Original clinical stage T1-T2, NX or N0
- Life expectancy >10 y
- PSA now <10 ng/mL

Prostate biopsy positive, studies negative for distant metastases
  Observation or RP or Cryosurgery or Brachytherapy

Prostate biopsy negative, studies negative for distant metastases
  Observation or ADT or Clinical trial or More aggressive workup for local recurrence (eg, repeat biopsy, MR spectroscopy, endorectal MRI)

Studies positive for distant metastases
  ADT or Observation

ADT or Observation

Progression

ADT or Observation

See Advanced Disease (PROS-8) and (PROS-9)

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Reason for Restaging Evaluation Change

- Hopkins criteria for local recurrence only
  - SV, LN negative
  - Gleason sum ≤ 7
  - PSA undetectable ≥ 1 yr
- Retraction in Trock, JAMA, 2008
- NCCN 2011 “Evidence supports offering adjuvant/salvage RT in all men with adverse pathologic features or detectable PSA and no evidence of disseminated disease.”
Definitions and Principles

- Radiation benefit should exceed risk
- Radiation should not be administered when disease metastatic
- Adjuvant – radiation administered for adverse pathology or biochemical persistence
- Salvage – radiation administered for biochemical recurrence after apparent cure
Caveat: Biochemical Persistence after RP

- Prostate cancer remains
- Benign prostate tissue remains
- PSA from non-prostatic source
- Non-specific interaction of blood component with an assay reagent
# Adjuvant Radiation

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<th>ARO 96-02</th>
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<td>64% vs. 35%</td>
<td>72% vs. 54%</td>
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</table>

Bolla, Lancet, 2001

Thompson, JAMA, 2006; Thompson, J Urol, 2009

Wiegel, J Clin Oncol, 2009
Survival by Treatment Arm

Thompson, J Urol, 2009
Summary

Consider adjuvant XRT for:
• PSA persistence
• PSM
• SV invasion
• ECE

Strongly consider adjuvant XRT for:
• Diffusely PSM
• PSM + persistent PSA
Case #2

55 yo man undergoes radical prostatectomy for clinical Gleason grade 3+3=6 T1c prostate cancer diagnosed for PSA 7.2. Chance of cure was 90% at 5 years (MSKCC historical). Pathology revealed Gleason grade 4+3=7 with ECE and positive surgical margin. PSA is undetectable at 6 mo.

The chance of biochemical progression-free survival at 5 yrs is:

A. 28%
B. 58%
C. 78%
D. 88%
E. 98%
Predicting Cure after Radical Prostatectomy

Memorial Sloan-Kettering Cancer Center

Prostate Cancer Nomograms: Post-Radical Prostatectomy

This nomogram can be used to predict the probability that a patient’s cancer will recur after radical prostatectomy, that is, the probability at two, five, seven and 10 years that the patient’s serum PSA level will become detectable and begin to rise steadily. The nomogram should only be used for patients when radical prostatectomy is the sole, primary treatment. To learn more, visit our frequently asked questions.

Enter Your Information

- Pre-Treatment PSA
  - PSA value from the laboratory report before the radical prostatectomy was performed or any other therapy for prostate cancer begun.
  - (0.1 to 100 ng/ml)

- Age
  - (20 to 120 yrs)

Gleason Grade

- Primary Gleason Grade at Surgery
  - The primary Gleason grade from the radical prostatectomy pathology report.
  - Select primary Gleason

- Secondary Gleason Grade at Surgery
  - The secondary Gleason grade from the radical prostatectomy pathology report.
  - Select secondary Gleason

- Gleason Sum at Surgery
  - Gleason sum will be automatically calculated or can be added here if the primary and secondary Gleason grades are not known.
  - 

Year of Prostatectomy

- Year radical prostatectomy was performed.
  - (1997 to Present)

Months Free of Cancer

- Number of months without detectable cancer or a rising PSA following radical prostatectomy.
  - 

Your Results

- Learn more about your results below.

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<th>CURRENT MODEL</th>
<th>HISTORICAL MODEL</th>
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<tr>
<td></td>
<td>10 Year</td>
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</table>

Make an Appointment

- Call us to schedule an appointment or contact us online.
  - Contact Us
Case #2

55 yo man undergoes radical prostatectomy for clinical Gleason grade 3+3=6 T1c prostate cancer diagnosed for PSA 7.2. Chance of cure was 90% at 5 years (MSKCC historical). Pathology revealed Gleason grade 4+3=7 with ECE and positive surgical margin. PSA is undetectable at 6 mo.

The chance of biochemical progression-free survival at 5 yrs is:

A. 28%
B. 58%
C. 78%
D. 88%
E. 98%
Case #3

55 yo man undergoes radical prostatectomy for clinical Gleason grade 4+3=7 T1c prostate cancer diagnosed for PSA 7.2. Chance of cure was 81% at 5 years (MSKCC historical). Pathology revealed Gleason grade 5+4=9 with ECE, SV invasion, and PSM. PSA is undetectable at 6 mo.

The chance of biochemical progression-free survival at 5 yrs is:

A. 22%
B. 42%
C. 62%
D. 82%
E. 96%
Predicting Cure after Radical Prostatectomy

Prostate Cancer Nomograms: Post-Radical Prostatectomy

This nomogram can be used to predict the probability that a patient's cancer will recur after radical prostatectomy, that is, the probability at two, five, seven, and 10 years that the patient's serum PSA level will become detectable and begin to rise steadily. The nomogram should only be used for patients when radical prostatectomy is the sole, primary treatment. To learn more, visit our frequently asked questions.

Enter Your Information

- Pre-Treatment PSA: Value from the laboratory report before the radical prostatectomy was performed or any other therapy for prostate cancer begun.
- Age: (20 to 120 yrs)

Gleason Grade

- Primary Gleason Grade at Surgery: Select primary Gleason
- Secondary Gleason Grade at Surgery: Select secondary Gleason
- Gleason Sum at Surgery: Gleason sum will be automatically calculated or can be added here if the primary and secondary Gleason grades are not known.
- Year of Prostatectomy: Year radical prostatectomy was performed.
- Months Free of Cancer: Number of months without detectable cancer or a rising PSA following radical prostatectomy.

Your Results

- Progression-Free Probability After Surgery: 2 Year, 5 Year, 7 Year, 10 Year

Make an Appointment

Call us to schedule an appointment or contact us online.
Case #3

55 yo man undergoes radical prostatectomy for clinical Gleason grade 4+3=7 T1c prostate cancer diagnosed for PSA 7.2. Chance of cure was 81% at 5 years (MSKCC historical). Pathology revealed Gleason grade 5+4=9 with ECE, SV invasion, and PSM. PSA is undetectable at 6 mo.

The chance of biochemical progression-free survival at 5 yrs is:

A. 22%
B. 42%
C. 62%
D. 82%
E. 96%
Case #3 (cont)

Observe 6 more months and PSAs 0.2 at 9 mo and 0.4 at 12 mo. 5 year BPFS would change from 42% without salvage to what after 72 Gy?

A. 2%
B. 18%
C. 44%
D. 62%
E. 88%
Predicting Benefit of Salvage Radiation

Prostate Cancer Nomograms: Salvage Radiation Therapy

This nomogram is designed for men who have experienced a recurrence of their prostate cancer after treatment with radical prostatectomy. The tool predicts the probability the recurrence can be successfully treated with salvage radiation therapy (SRT), calculating the probability that the cancer will be controlled and the PSA will be undetectable six years after SRT. To learn more, visit our frequently asked questions.

Enter Your Information

To gather the information required below, download our PDF worksheet.

- Prostatectomy PSA
  PSA value before radical prostatectomy.

Gleason Grade

- Primary Gleason Grade at Surgery
  Primary Gleason grade from the radical prostatectomy pathology report.

- Secondary Gleason Grade at Surgery
  Secondary Gleason grade from the radical prostatectomy pathology report.

- Gleason Sum at Surgery
  Gleason Sum will be automatically calculated or can be added here if the primary and secondary Gleason grades are not known.

Prostatectomy Pathology Report Details

- Surgical Margins Positive
  Was cancer present at edges of removed prostate?

- Extra Capsular Extension
  Was there extra capsular extension?

Your Results

Your results will be displayed here.

Learn more about your results below.

Progression Free Probability after Salvage Radiation Therapy

6 Year

Print These Results

Make An Appointment

Call us to schedule an appointment or contact us online.
Case #3 (cont)

Observe 6 more months and PSAs 0.2 at 9 mo and 0.4 at 12 mo. 5 year BPFS would change from 42% without salvage to what after 72 Gy?

A. 2%
B. 18%
C. 44%
D. 62%
E. 88%
Definitions and Principles

- Radiation benefit should exceed risk
- Radiation should not be administered when disease metastatic
- Adjuvant – radiation administered for adverse pathology or biochemical persistence
- Salvage – radiation administered for biochemical recurrence after apparent cure
Salvage Radiation

• More complex situation
• Benefit depends on
  – Time to PSA recurrence
  – PSA doubling time
  – Absence of metastatic disease
Salvage Radiation

- PSA elevation after RP does not necessarily lead to clinical failure (Jhaveri, Urology, 1999)
- No benefit to salvage XRT for PSA recurrence w/ PSADT > 3 yrs after age 65
Actuarial Likelihood of Metastasis-Free Survival in 1,997 Men Treated with PSA Recurrence after Radical Prostatectomy

Pound, JAMA, 1999
Biochemical Recurrence after RP

Frequency: $\leq 40\%$

Definition: > 10 reported

NCCN: detectable PSA that increases on 2 subsequent measurements

AUA: > 0.2 confirmed upon repeat

Stephenson: $\geq 0.4$ that increases on a subsequent measurement

NCCN.org

AUA, PSA Best Practice Statement: 2009 Update

Stephenson, JCO, 2006
Case #4

65 yo Caucasian American who had RP at age 55 for clinical GG 3+3=6 T1c PSA 7.2 who was pathological GG 3+3=6, organ confined/-SM and PSA values were undetectable until:

0.04 age 63
0.06 age 64
0.08 age 65

His health is excellent. The best recommendation is:

A. Obtain PSA in 3 months
B. Obtain PSA in 1 year
C. Observation
D. Salvage radiation
E. Androgen deprivation therapy
LExp by age = 16 yrs
- Excellent health = 24 yrs
- Average health = 16 yrs
- Poor health = 8 yrs
CaP-limited LExp = 27 years
- PSADT = 2 years
- 22 yrs until PSA >100
- 5 yrs for ADT-induced remission
Chance of CaP death
- Excellent health = 40%
- Average health = 5%
- Poor health = <1%
Chance of cure by Salvage XRT = 71% at 6 yrs
Chance of CaP death after Salvage XRT
- Excellent health = 12%
- Average health = 1.5%
- Poor health = <<1%
Case #4

65 yo Caucasian American who had RP at age 55 for clinical GG 3+3=6 T1c PSA 7.2 who was pathological GG 3+3=6, organ confined/-SM and PSA values were undetectable until:

0.04  age 63
0.06  age 64
0.08  age 65

His health is excellent. The best recommendation is:

A. Obtain PSA in 3 months
B. Obtain PSA in 1 year
C. Observation
D. Salvage radiation
E. Androgen deprivation therapy
Case #4

65 yo Caucasian American who had RP at age 55 for clinical GG 3+3=6 T1c PSA 7.2 who was pathological GG 3+3=6, organ confined/-SM and PSA values were undetectable until:

0.04  age 63
0.06  age 64
0.08  age 65

His health is poor. The best recommendation is:

A. Obtain PSA in 3 months
B. Obtain PSA in 1 year
C. Observation
D. Salvage radiation
E. Androgen deprivation therapy
LExp by age = 16 yrs
- Excellent health = 24 yrs
- Average health = 16 yrs
- Poor health = 8 yrs
CaP-limited LExp = 27 years
- PSADT = 2 years
- 22 yrs until PSA >100
- 5 yrs for ADT-induced remission
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Chance of CaP death after Salvage XRT
- Excellent health = 12%
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0.04 age 63
0.06 age 64
0.08 age 65

His health is poor. The best recommendation is:

A. Obtain PSA in 3 months
B. Obtain PSA in 1 year
C. Observation
D. Salvage radiation
E. Androgen deprivation therapy
Case #4

65 yo Caucasian American who had RP at age 55 for clinical GG 3+3=6 T1c PSA 7.2 who was pathological GG 3+3=6, organ confined/-SM and PSA values were undetectable until:

0.04 age 63
0.06 age 64
0.08 age 65

His health is average. The best recommendation is:

A. Obtain PSA in 3 months
B. Obtain PSA in 1 year
C. Observation
D. Salvage radiation
E. Androgen deprivation therapy
LExp by age = 16 yrs
- Excellent health = 24 yrs
- Average health = 16 yrs
- Poor health = 8 yrs
CaP-limited LExp = 27 years
- PSADT = 2 years
- 22 yrs until PSA >100
- 5 yrs for ADT-induced remission
Chance of CaP death
- Excellent health = 40%
- Average health = 5%
- Poor health = <1%
Chance of cure by Salvage XRT = 71% at 6 yrs
Chance of CaP death after Salvage XRT
- Excellent health = 12%
- Average health = 1.5%
- Poor health = <<1%
Case #4

65 yo Caucasian American who had RP at age 55 for clinical GG 3+3=6 T1c PSA 7.2 who was pathological GG 3+3=6, organ confined/-SM and PSA values were undetectable until:

0.04  age 63
0.06  age 64
0.08  age 65

His health is average. The best recommendation is:

A. Obtain PSA in 3 months
B. Obtain PSA in 1 year
C. Observation
D. Salvage radiation
E. Androgen deprivation therapy
Case #5

60 yo African American who had RP at age 55 for clinical GG 3+3=6 T1c PSA 7.2 who was pathological GG 4+3=7, organ confined/-SM and PSA values were undetectable until:

0.04 age 59
0.06 age 59½
0.08 age 60

His health is excellent. The best recommendation is:

A. Obtain PSA in 3 months
B. Obtain PSA in 1 year
C. Observation
D. Salvage radiation
E. Androgen deprivation therapy
LExp by age = 17 yrs
- Excellent health = 25 yrs
- Average health = 17 yrs
- Poor health = 9 yrs
CaP-limited LExp = 16 years
- PSADT = 1 years
- 11 yrs until PSA >100
- 5 yrs for ADT-induced remission
Chance of CaP death
- Excellent health = 90%
- Average health = 50%
- Poor health = <10%
Chance of cure by Salvage XRT = 58% at 6 yrs
Chance of CaP death after Salvage XRT
- Excellent health = 36%
- Average health = 21%
- Poor health = <<4%
Case #5

60 yo African American who had RP at age 55 for clinical GG 3+3=6 T1c PSA 7.2 who was pathological GG 4+3=7, organ confined/-SM and PSA values were undetectable until:

0.04  age 59
0.06  age 59½
0.08  age 60

His health is excellent. The best recommendation is:

A. Obtain PSA in 3 months
B. Obtain PSA in 1 year
C. Observation
D. Salvage radiation
E. Androgen deprivation therapy
Case #5

60 yo African American who had RP at age 55 for clinical GG 3+3=6 T1c PSA 7.2 who was pathological GG 4+3=7, organ confined/-SM and PSA values were undetectable until:

0.04 age 59
0.06 age 59½
0.08 age 60

His health is poor. The best recommendation is:

A. Obtain PSA in 3 months
B. Obtain PSA in 1 year
C. Observation
D. Salvage radiation
E. Androgen deprivation therapy
LExp by age = 17 yrs
- Excellent health = 25 yrs
- Average health = 17 yrs
- Poor health = 9 yrs
CaP-limited LExp = 16 years
- PSADT = 1 years
- 11 yrs until PSA >100
- 5 yrs for ADT-induced remission
Chance of CaP death
- Excellent health = 90%
- Average health = 50%
- Poor health = <10%
Chance of cure by Salvage XRT = 58% at 6 yrs
Chance of CaP death after Salvage XRT
- Excellent health = 36%
- Average health = 21%
- Poor health = <<4%
Case #5

60 yo African American who had RP at age 55 for clinical GG 3+3=6 T1c PSA 7.2 who was pathological GG 4+3=7, organ confined/-SM and PSA values were undetectable until:

0.04 age 59
0.06 age 59½
0.08 age 60

His health is poor. The best recommendation is:

A. Obtain PSA in 3 months
B. Obtain PSA in 1 year
C. Observation
D. Salvage radiation
E. Androgen deprivation therapy
Case #5

60 yo African American who had RP at age 55 for clinical GG 3+3=6 T1c PSA 7.2 who was pathological GG 4+3=7, organ confined/-SM and PSA values were undetectable until:

0.04  age 59
0.06  age 59½
0.08  age 60

His health is average. The best recommendation is:

A. Obtain PSA in 3 months
B. Obtain PSA in 1 year
C. Observation
D. Salvage radiation
E. Androgen deprivation therapy
LExp by age = 17 yrs
- Excellent health = 25 yrs
- **Average health = 17 yrs**
- Poor health = 9 yrs
CaP-limited LExp = 16 years
- PSADT = 1 years
- 11 yrs until PSA >100
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Chance of CaP death
- Excellent health = 90%
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0.04 age 59
0.06 age 59½
0.08 age 60

His health is **average**. The best recommendation is:

A. Obtain PSA in 3 months
B. Obtain PSA in 1 year
C. Observation
D. Salvage radiation
E. Androgen deprivation therapy
ADVANCED DISEASE: ADDITIONAL SYSTEMIC THERAPY FOR CASTRATION-RECURRENT PROSTATE CANCER

Studies negative for metastases → Maintain castrate serum levels of testosterone → Clinical trial (preferred)
- Observation
- Secondary hormone therapy
  - Antiandrogen
  - Antiandrogen withdrawal
  - Ketoconazole
  - Steroids
  - DES or other estrogen

PSA relapse or metastases (M1) → Follow pathway below
- Abiraterone acetate\textsuperscript{1} or enzalutamide (category 1, post-docetaxel therapy)
- Cabazitaxel (category 1, post-docetaxel)\textsuperscript{1}
- Salvage chemotherapy
- Docetaxel rechallenge\textsuperscript{1}
- Mitoxantrone\textsuperscript{1}
- Other secondary hormone therapy
  - Antiandrogen
  - Antiandrogen withdrawal
  - Ketoconazole
  - Steroids
  - DES or other estrogen
  - Sipuleucel-T\textsuperscript{5}
  - Clinical trial

Studies positive for metastases → Denosumab (category 1) or zoledronic acid (category 1) if bone metastases
- Maintain castrate serum levels of testosterone and
- Symptomatic

Yes → Docetaxel\textsuperscript{q} (category 1)
- Mitoxantrone\textsuperscript{q,t}
- Abiraterone acetate\textsuperscript{1,t}
- Enzalutamide\textsuperscript{1,t}
- Palliative RT or radionuclide for symptomatic bone metastases
- Clinical trial

No → Sipuleucel-T (category 1)\textsuperscript{5}
- Secondary hormone therapy
  - Antiandrogen
  - Antiandrogen withdrawal
  - Abiraterone acetate\textsuperscript{1}
  - Enzalutamide\textsuperscript{1}
  - Ketoconazole
  - Steroids
  - DES or other estrogen
  - Docetaxel\textsuperscript{1,u}
  - Clinical trial

\textsuperscript{1}See Principles of Androgen Deprivation Therapy (PROS-E).
\textsuperscript{2}Frequency of imaging should be based on individual risk, age, PSA velocity, Gleason score, and overall health.
\textsuperscript{3}See Principles of Chemotherapy/immunotherapy (PROS-F).
\textsuperscript{5}Sipuleucel-T is appropriate for asymptomatic or minimally symptomatic patients with ECOG performance status 0-1. Sipuleucel-T is not indicated in patients with hepatic metastases or life expectancy <6 months.
\textsuperscript{1}For patients who are not candidates for docetaxel-based regimens.
\textsuperscript{u}Although most patients without symptoms are not treated with chemotherapy, the survival benefit reported for docetaxel applies to those with or without symptoms. Docetaxel may be considered for patients with signs of rapid progression or hepatic metastases despite lack of symptoms.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Androgen Receptor Expression in Castration-Recurrent Prostate Cancer

Mohler, Clin Cancer Res, 2004
New Theories for Prostate Cancer (CaP) Recurrence

- **Androgen Receptor (AR)** responds to castration with molecular and biochemical alterations that cause hypersensitivity to low levels of ligand.

- CaP responds to castration by synthesizing DHT from weaker androgens and/or cholesterol.
AR Hypersensitized

- AR 10,000 times more sensitive in androgen-independent than androgen-sensitive CaP cell lines
- AR coactivators change from SRC-1 to TIF-2 in cell lines, xenografts, and clinical specimens
- AR phosphorylated by SRC or Ack1 tyrosine kinases

Activated Ack1 Promotes Androgen-Independent Growth of LNCaP Xenografts

LNCaP cells (2 X 10^6 cells/injection) stably expressing caAck or vector control were injected subcutaneously into the flanks of castrated nude mice.

New Theories for CaP Recurrence

- AR responds to castration with molecular and biochemical alterations that cause hypersensitivity to low levels of ligand.

- CaP responds to castration by synthesizing DHT from weaker androgens and/or cholesterol.
Tissue Androgen Levels using RIA in Benign Prostate (n = 32; gray) vs Castration-Recurrent CaP (n = 23; white)

Mohler, Clin Cancer Res, 2004
LC-MS/MS of DHT and T in Benign Prostate Tissue

DHT
MW 291

T
MW 289

Titus, Clin Cancer Res, 2005
<table>
<thead>
<tr>
<th></th>
<th>Benign Prostate (n = 18)</th>
<th>Castration-Recurrent CaP (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T (nM)</td>
<td>DHT (nM)</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>3.4</td>
<td>23.6</td>
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</tr>
<tr>
<td>0</td>
<td>14.5</td>
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</tr>
<tr>
<td>1.2</td>
<td>16.8</td>
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</tr>
<tr>
<td>1.8</td>
<td>11.3</td>
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<tr>
<td>2.5</td>
<td>12</td>
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</tr>
<tr>
<td>2.9</td>
<td>20.5</td>
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<tr>
<td>13.0</td>
<td>17.1</td>
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<td>1.2</td>
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<td>1.6</td>
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<td>2.0</td>
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<td>2.7</td>
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<td>2.8</td>
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<tr>
<td>2.8</td>
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<tr>
<td>3.2</td>
<td>20.3</td>
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</tr>
</tbody>
</table>

**Titus, Clin Cancer Res, 2005**
# Testicular Androgen Levels in Castration-Recurrent CaP

<table>
<thead>
<tr>
<th>Mass Spec</th>
<th>Titus 2005</th>
<th>RIA</th>
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<tbody>
<tr>
<td></td>
<td>T</td>
<td>DHT</td>
</tr>
<tr>
<td>AS-BP (n=18)</td>
<td>2.75</td>
<td>13.7</td>
</tr>
<tr>
<td>CR-CaP (n=18)</td>
<td>3.75</td>
<td>1.25</td>
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<table>
<thead>
<tr>
<th>Montgomery 2008</th>
<th>Geller 1979</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>T</td>
</tr>
<tr>
<td>AS-BP (n=6)</td>
<td>0.04</td>
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<tr>
<td>AS-CaP (n=4)</td>
<td>0.23</td>
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<tr>
<td>CR-Met CaP (n=8)</td>
<td>0.74</td>
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<thead>
<tr>
<th>Labrie 1989</th>
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<tr>
<td></td>
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<tr>
<td>human CaP (n=?)</td>
</tr>
<tr>
<td>orch (n=5, 2-12m)</td>
</tr>
<tr>
<td>orch+fl (n=4, 2m)</td>
</tr>
</tbody>
</table>

Increased Levels of Enzymes that Make Testosterone

Stanbrough, Cancer Res, 2006
Testicular Androgen Production from Cholesterol

- $^{14}$C-cholesterol appears as $^{14}$C-DHT in LNCaP cells thru up-regulation of StAR, the rate-limiting enzyme in steroid synthesis
- DHT synthesis persists in spite of CYP17A1 (ketoconazole) and 5α-reductase-2 (finasteride) inhibition in A-I LNCaP cells and C-R LNCaP xenografts

Locke, *Prostate*, 2010
CaP that Recurs during ADT is:

1. Androgen independent
2. Hormone refractory
3. Castration resistant
4. Castration recurrent
5. Curable
CaP that Recurs during ADT is:

1. Androgen independent
2. Hormone refractory
3. Castration resistant
4. Castration recurrent
5. Curable
Origin of Tissue DHT in Castration-Recurrent CaP
Barriers to Understanding Androgen Metabolism

<table>
<thead>
<tr>
<th>Steroid conversion</th>
<th>Enzyme activity</th>
<th>Enzyme Acronym</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Androstenedione → T</td>
<td>Reductive 17β-HSD activity</td>
<td>17β-Hydroxysteroid dehydrogenase (RED)</td>
<td>17β-HSD3, 17β-HSD5, AKR1C3</td>
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<tr>
<td></td>
<td></td>
<td>3α-HSD aldo-keto reductase 1C3</td>
<td>25, 28</td>
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<tr>
<td>T → DHT</td>
<td>5α-reductase activity</td>
<td>steroid 5α-reductase type 1, 2</td>
<td>20, 26</td>
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<tr>
<td>Androstenedione →</td>
<td></td>
<td>steroid 5α-reductase type 1, 2</td>
<td></td>
</tr>
<tr>
<td>Androstaneolone</td>
<td></td>
<td>SRD5A1, SRD5A2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SRD5A1, SRD5A2</td>
<td></td>
</tr>
<tr>
<td>DHT → Androstaneolone</td>
<td>Reductive 3α-HSD activity</td>
<td>3α-Hydroxysteroid dehydrogenase (RED)</td>
<td>3α-HSD, AKR1C2</td>
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<tr>
<td></td>
<td>type 3 3α-HSD aldo-keto reductase 1C2</td>
<td></td>
<td>27, 19, 30</td>
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<tr>
<td>Androstaneolone → DHT</td>
<td>Oxidative 3α-HSD activity</td>
<td>17β-Hydroxysteroid dehydrogenase 6, retinol dehydrogenase 5</td>
<td>17β-HSD6, RDH5, 11-cis-retinol dehydrogenase, RODH5</td>
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<tr>
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<td></td>
<td>RODH-like 3α-HSD, RL-HSD</td>
<td>17β-HSD9, 17β-HSD10, RoDH, 19, 18</td>
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<tr>
<td></td>
<td></td>
<td>retinol dehydrogenase 4</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dehydrogenase short-chain reductase family member 9</td>
<td></td>
</tr>
<tr>
<td>Androstaneolone → Androsterone</td>
<td>Oxidative 17β-HSD activity</td>
<td>17β-Hydroxysteroid dehydrogenase 6, 17β-HSD6, 17β-HSD11</td>
<td>18, 19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17β-Hydroxysteroid dehydrogenase 11</td>
<td>18, 42</td>
</tr>
</tbody>
</table>
Pathways to DHT Synthesis

Intact pathway

Adrenal androgen pathway

Cholesterol pathway

Backdoor pathway

Modified from Locke, Cancer Res, 2008
CYP17A1 Inhibition

- Abiraterone
  - Cougar/Johnson & Johnson
- TAK-700
  - Millenium/Takeda
- VN124-1
  - Tokai Pharmaceuticals
Abiraterone Improves Overall Survival

HR = 0.646 (0.54-0.77)  P < 0.0001

Abiraterone: 14.8 months
(95% CI: 14.1, 15.4)

Placebo: 10.9 months
(95% CI: 10.2, 12.0)

1 Prior Chemo OS:
15.4 months abiraterone vs 11.5 months placebo

DeBono, *NEJM*, 2011
Inactivate AR Using Antiandrogens

• Old and relatively ineffective
  – Flutamide
  – Bicalutamide
  – Nilutamide

• New and perhaps more effective
  – Small molecule AR antagonist (MDV3100)
    • Tran, *Science*, 2009
    • Scher, *NEJM*, 2012
    • Medivation, Inc.
  – AR-specific histone deacetylase inhibitors
    • Vorinostat, panobinostat, romidepsin
    • ie, Welsbie, *Cancer Res*, 2009
MVD3100

- 1199 men with CRPC after docetaxel
- 2:1 MDV3100 160 mg qd vs placebo
- Stopped at interim analysis after 520 deaths
- Overall survival (primary endpoint)
  - MDV3100 18.4 mo
  - Placebo 13.6 mo
- All secondary endpoints met, ie time to PSA progression
  - MDV3100 8.3 mo
  - Placebo 3.0 mo
- Side effects
  - 0.6% seizures
  - Fatigue, diarrhea, hot flashes

Scher, *NEJM*, 2012
SYSTEMIC SALVAGE THERAPY FOR CASTRATION-RECURRENT PROSTATE CANCER

Studies negative for metastases
- Clinical trial (preferred)
- Observation
- Antiandrogen withdrawal (if on combination androgen blockade)
- Secondary ADT
  - Antiandrogen
  - Adrenal enzyme inhibitor
  - Estrogen therapy

PSA relapse or metastases (M1) → Follow pathway below

Studies positive for metastases
- Sipuleucel-T (category 1)\(^{\circ}\)
- Docetaxel every 3 weeks and steroids (category 1)
- Other docetaxel regimen
- Secondary ADT
  - Antiandrogen
  - Adrenal enzyme inhibitor
  - Estrogen therapy
  - Mitoxantrone + steroids (category 1, for quality of life but not survival)\(^{\circ}\)
  - Palliative RT or radionuclide for symptomatic bone metastases
  - Bisphosphonates for patients with bone metastases

Clinical trial
- Salvage chemotherapy
  - Cabazitaxel + steroids (category 1)
  - Mitoxantrone + steroids
- Best supportive care

\(^{\circ}\)Sipuleucel-T is appropriate for asymptomatic or minimally symptomatic patients with ECOG performance status 0-1. It is not recommended for patients with visceral disease and a life expectancy less than 6 months.

\(^{\circ}\)For patients who cannot tolerate docetaxel-based regimens.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**ADDITIONAL SYSTEMIC THERAPY FOR CASTRATION-RECURRENT PROSTATE CANCER**

**Studies negative for metastases**
- Maintain castrate serum levels of testosterone
  - Clinical trial (preferred)
  - Observation
  - Antiandrogen withdrawal (if on combination androgen blockade)
- Secondary hormone therapy
  - Antiandrogen
  - Antiandrogen withdrawal
  - Ketoconazole
  - Steroids
  - DES or other estrogen

- PSA relapse or metastases (M1)
  - Follow pathway below

**Studies positive for metastases**
- Maintain castrate serum levels of testosterone and Denosumab (category 1) or zoledronic acid (category 1) if bone metastases

- Symptomatic
  - Clinical trial

- Visceral
  - Sipuleucel-T (category 1)p
  - Secondary hormone therapy
    - Antiandrogen
    - Antiandrogen withdrawal
    - Ketoconazole
    - Steroids
    - DES or other estrogen
  - Clinical trial

- No
- Yes

---

p Sipuleucel-T is appropriate for asymptomatic or minimally symptomatic patients with ECOG performance status 0-1. Sipuleucel-T is not recommended for patients with visceral disease and life expectancy < than 6 months.

o See Principles of Chemotherapy/Immunotherapy (PROS-F).

For patients who cannot tolerate docetaxel-based regimens.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
CRPC

1. Immunotherapy for asymptomatic or minimally symptomatic castration-recurrent metastatic prostate cancer
2. Cabazitaxel for docetaxel failure
3. Denosumab to prevent skeletal-related events
Sipuleucil-T: Mechanism of Action

Antigen (PAP-GMCSF) is exposed to an Antigen Presenting Cell (APC)

APC takes up the antigen

Antigen is processed and presented on surface of the APC

Fully activated, the APC is now sipuleucil-T and is collected

T-cells proliferate and attack cancer cells

sipuleucil-T activates T-cells in the body
**Sipuleucel-T: Logistics of Therapy**

- **Day 1**
  - Leukapheresis
  - Apheresis Center

- **Day 2-3**
  - Sipuleucel-T is manufactured
  - Central Processing

- **Day 3-4**
  - Patient is infused
  - Doctor’s Office

**COMPLETE COURSE OF THERAPY:**
Weeks 0, 2, 4
Randomized Phase III Trial of Sip-T in CRPC (D9901)

Asymptomatic metastatic CRPC (N=127)

- Placebo q2wks x 3 (N=45)
- Sip-T q2wks x 3 (N=82)

Progression

- APC8015F q2wks x 3
- Long-term follow-up

Small et al. JCO 2006
Results: Time to Objective Progression

- APC8015 (n=82)
- Placebo (n=45)

\[ P = 0.061 \text{ (log-rank)} \]
\[ HR = 1.43 \]
(95% CI: 0.98, 2.09)

Small et al. JCO 2006
Results: Overall Survival

- APC8015 (N=82)
- Placebo (N=45)

$P=0.01$ (log-rank)
$HR=1.7$
($95\%$ CI: 1.126, 2.563)

Small et al. JCO 2006
Randomized Phase 3 IMPACT Trial
(IMmunotherapy Prostate AdenoCarcinoma Treatment)

Asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer (N = 512)

2:1

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: Objective disease progression

Kantoff et al NEJM 2010
IMPACT Overall Survival
Final Analysis (349 events)

36.5 mo median f/u
HR = 0.759 (95% CI, 0.606, 0.951)
P = 0.017 (Cox model)
Median survival benefit = 4.1 months

Sipuleucel-T (n = 341)
Median survival: 25.8 mo.
36 mo. survival: 32.1%

Placebo (n = 171)
Median survival: 21.7 mo.
36 mo. survival: 23.0%

Kantoff et al NEJM 2010
Which is true about Sipuleucel-T?

1. Indicated for patients with asymptomatic or minimally symptomatic metastatic castration-recurrent CaP
2. Prolongs time to disease progression
3. Should be given with low dose steroids
4. Uses PSA as an antigen
Which is true about Sipuleucel-T?

1. Indicated for patients with asymptomatic or minimally symptomatic metastatic castration-recurrent CaP
2. Prolongs time to disease progression
3. Should be given with low dose steroids
4. Uses PSA as an antigen
New semi-synthetic taxane
  – Selected to overcome the emergence of taxane resistance
Clinical data
  – In Phase I trials, DLT was neutropenia
  – Antitumor activity in mCRPC in Phase I trials including docetaxel-resistant disease
TROPIC: Phase III Study

Primary endpoint: Overall Survival

Secondary endpoints: Progression-free survival (PFS), response rate, and safety

DeBono, Lancet, 2010
Primary Endpoint: Overall Survival

Median OS (months) MP 12.7 CBZ 15.1
Hazard Ratio 0.70
95% CI 0.59–0.83
P-value < 0.0001

DeBono et al. Lancet 2010
Conclusions

Cabazitaxel
  – 30% risk reduction of death (HR = 0.70, \( P < 0.0001 \))
  – Median OS improvement in favor of CBZP: 15.1 months vs 12.7 months
  – OS benefit was consistent across subgroups

Secondary endpoints (PFS, RR, and TTP) also improved significantly

Consider growth factor support for significant granulocytopenia

DeBono et al al Lancet 2010
CRPC

1. Immunotherapy for asymptomatic or minimally symptomatic castration-recurrent metastatic prostate cancer
2. Cabazitaxel for docetaxel failure
3. Denosumab to prevent skeletal-related events
Prevention of skeletal-related events (SREs) in patients with metastatic CRPC

- Zoledronic acid reduces SREs by 20%
- Zoledronic acid (Z) versus denosumab (D)
  - 1,901 patients with mCRPC
  - Patients randomized to D (120 mg SC q 4 weeks) or Z (4 mg IV q 4 weeks)
  - D delayed the time to the first on-study SRE (a fracture, need for bone radiation, need for bone surgery, or spinal cord compression) compared with Z (hazard ratio = 0.82)
  - D reduced the rate of multiple SREs compared to Z (HR = 0.82)
  - Rate for osteonecrosis of the jaw similar: 22 men treated with D and in 12 men treated with Z
  - OS and TTP were similar

Fizazi, JCO, 2010
Which is not true?

1. Cabazitaxel prolongs survival in men with castration-recurrent CaP who have progressed on docetaxel
2. Denosumab prolongs survival over placebo or zoledronic acid
3. Cabazitaxel's dose-limiting toxicity is neutropenia
4. Denosumab may cause osteonecrosis of the jaw
Which is not true?

1. Cabazitaxel prolongs survival in men with castration-recurrent CaP who have progressed on docetaxel
2. Denosumab prolongs survival over placebo or zoledronic acid
3. Cabazitaxel's dose-limiting toxicity is neutropenia
4. Denosumab may cause osteonecrosis of the jaw
Conclusions

• PSA is best when compared to prior values
• Estimate Life Expectancy
• Risk stratify using Stage, Gleason Sum and PSA
• Observation should be the first option discussed against which the benefits (potential and need for cure) and risks (mortality, urinary incontinence and impotence) of treatment should be compared.
Conclusions

- Observation may be the best choice for many men with low-risk CaP
- Radical prostatectomy can be performed open, laparoscopic or robotic; almost all men should regain urinary continence and most men should regain erectile function
- Radiation should use dose-escalation when appropriate and daily localization; side effects short-term are less but long-term may be more than operation
Disaster Prevention

• Use what we’ve learned about
  – The basics of prostate cancer
  – Life expectancy estimation and patient counselling
  – Expectant management, operation and radiation
  – Emergency and difficult situations

• To improve quality of care by referring appropriately while still stewarding resources

• Since the best outcomes result from receiving the best care first
Fundamentals and Quality of Care

- Patient-appropriate: age, comorbidities, family history
- Cancer-appropriate: PSA, Gleason grade, stage, PSADT
- MD-appropriate: training, experience, outcomes
- Technology-appropriate: state-of-the-art, optimal operation, outcomes
Fundamentals and Quality of Care
Active Surveillance

- Patient-appropriate – age, comorbidities, family history of longevity, embraces uncertainty
- Cancer-appropriate – low PSA, low Gleason score, low stage, slow PSA doubling time
- MD appropriate – monitoring system in place
Indications for Referral
Active Surveillance

• Disincentives for expectant management
  – External beam $40k, brachytherapy $30k, combination $70k, proton $100k
  – Radical prostatectomy $20k
  – Time consuming
  – Medico-legal liability
“Stop and Think” Situations

• Happened: Overtreatment disaster - 81 yo with clinically insignificant cancer treated with combination brachytherapy/external beam/6 mo ADT → 60 lb wt loss and 5 hospitalizations over 3 yrs

• Should have happened: Active surveillance with every 6-12 mo PSA and prostate exam because chance of prostate cancer death < 1%
Fundamentals and Quality of Care
Radical Prostatectomy

- Volume
- “Center of Excellence”
- Outcome Data
  - Urinary Continence
  - Potency
  - Oncologic
- Cost of Failure
  - $
  - QOL
- Technology
  - Open
  - Robotic
  - Laparoscopic
  - Other
- Cryotherapy
- HIFU
Indications for Referral
Radical Prostatectomy

• RP by surgeon with:
  – <30 per yr and <100 in career
  – Outcome data unavailable
  – Not board certified or member of Society of Urologic Oncology

• High risk operation
  – Neurogenic bladder, coagulopathy, hx of deep vein thrombosis or pulmonary embolism
  – Prior cryotherapy, brachytherapy, external beam radiotherapy, TURP/urethral or bladder neck surgery, rectal surgery/abdominal perineal resection

• High risk CaP
  – Super-radical dissection or CALGB 90203
CALGB 90203
Neo-Adjuvant Chemo-Hormonal Therapy Prior to Radical Prostatectomy

RANDOMIZE

6 cycles of chemohormonal therapy
Docetaxel 75 mg/m² IV every 21 days
LHRH agonist therapy (18-24 weeks)

Surgical Intervention
Staging pelvic lymphadectomy
Radical prostatectomy

Surgical Intervention
Staging pelvic lymphadectomy
Radical prostatectomy

PUNCH
Pre-surgical Study Using Neoadjuvant Chemotherapy
“Stop and Think” Situations

• Happened: Robot disaster - incomplete prostate removal → castration-recurrent cancer in 50 yo

• Should have happened: Referral to robotic center with >100 cases/yr and robotic surgeon with >30 cases/yr and >100 cases/career
Hypothesis

• Surgical Performance = Judgement x Skill

• If one improves skill and/or judgment, performance and outcome will follow
Medical Errors

• Institute of Medicine
  • 98,000 Deaths/Year
  • Cost $29 Billion
• Nat Acad Press, 1999
  • 54% of surgical errors preventable
• Performance Level of 99.9%
  • Airlines- 2 dangerous landings/day
  • Banking- 32,000 checks incorrectly deducted/hour
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<thead>
<tr>
<th>Procedure</th>
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<th>6-10</th>
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Begg, JAMA, 1998
Radical Prostatectomy and Hospital Volume 1992-1996 (n=11,522) =

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<th>Outcome (% of patients)</th>
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<td>BNC/stx</td>
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<td>Incontinence</td>
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Begg, JAMA, 2002
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<th>Outcome (% of patients)</th>
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<td>BNC/stx</td>
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<tr>
<td>Incontinence</td>
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</tbody>
</table>

Begg, JAMA, 2002
Surgeon Volume

- Representative survey of 2000 urologists in 2005
  - 66% response rate
  - 89% performed radical prostatectomies
  - 7% academic practice
  - 7% urologic oncology fellowship

- Surgeon volume
  - 37% <10/yr
  - 47% 11-30/yr
  - 16% >30/yr

- Nationwide, 46% of radical prostatectomies performed by high volume surgeons (> 30/yr)

Denberg, Brit J Urol, 2007
Robotic Radical Prostatectomy

• Will robotics improve skill and decrease error rate?
• Will this translate into better outcomes?
• At what cost?
  • To patient
  • To hospital
  • To health care system
  • To patient/ society
Open vs Robotic Prostatectomy

- 5% sample of Medicare men 2003-2005
- RoboRp 608 and Open RP 2094
- RoboRP increased 12% 2003 to 31% 2005
- Length of stay- robo 1.4 d; open 4.4 d
- Anastomotic stricture- robo 15%; open 12%
- Salvage therapy- robo 28%; open 9%
- High volume surgeons had lower rates of salvage therapy

Hu, JCO, 2008
Advantages of Robotic vs Open Radical Prostatectomy

- Better cancer control
- Less blood loss
- Improved continence
- Higher potency rate
- Less postoperative pain
- Shorter recovery
- Cost
- Total cost

<table>
<thead>
<tr>
<th>Yes</th>
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Fundamentals and Quality of Care
Radiation

• Volume
• “Center of Excellence”
• Outcome data
  – Oncologic
  – Urinary Continence
  – Fecal Continence
  – Impotence
• Cost of Failure
  – $
  – QOL
• Technology
  – 3D-CRT
  – IMRT
  – IGRT
  – Proton, Neutron, Cyberknife
Indications for Referral Radiation

- Equipment
  - 3D-CRT/IMRT/IGRT
- Personnel
  - Dosimetrist
  - Physicist
  - Radiation Oncologist
- Volume

77%  Conformal dose >70 Gy
88%  CT planning
66%  Patient immobilized
63%  Rectum protected by conformal shaping
82%  High energy linear accelerator (>10 mv)

Spencer, JCO, 2008
“Stop and Think” Situations

• Happened: Brachytherapy disaster - missed prostate → XRT → urethral stx → urinary diversion

• Should have happened: Initial referral to center with >100 cases/yr and implant team with >30 cases/yr and career experience >100 cases; Secondary referral for expert opinion and treatment at initial complication instead of for urinary diversion
Variations in Quality of Care for Clinically Localized CaP

- 2000 – 2001, ACOS Registry, representative 5% sample of 2775 men
- Average age 66, 85% white
- Explicit chart review tool
- 29 RAND quality of care CaP-specific structure and process indicators
- Stratified by race, geographic area, hospital type

Spencer, JCO, 2008
Variations in Quality of Care for Clinically Localized CaP

• MD and Technology
  – Board certified urologist 93%
  – Board certified radiation oncologist 92%
  – Conformal RT 90%

• Preoperative Assessment
  – Staged 76% and Gleason scored 92%
  – Discussed treatment options 83% and treatment risks 88%
  – Assessed urinary continence 78%, sexual function 46% and bowel function 52%

Spencer, JCO, 2008
Variations in Quality of Care for Clinically Localized CaP

• Radiation
  – CT planning 88%
  – >70 cGy 77%
  – Conformal delivery 63%
  – High energy accelerator 82%
  – Patient immobilized 66%

• Operation
  – Pathologically staged 48% and Gleason scored 86%
  – Surgical margins assessed 85%

• Follow-up
  – 55% had ≥2 visits in 12 months after treatment completed

Spencer, JCO, 2008
Variations in Quality of Care for Clinically Localized CaP

- Race
  - No variation

- Geographic region
  - Board certified MDs
  - Conformal radiation

- Type of Hospital
  - Comprehensive cancer center best
  - Teaching hospital average
  - Community hospital worst
  - BUT DIFFERENCES SMALL

Spencer, JCO, 2008
Fundamentals and Quality of Care
Androgen Deprivation Therapy

- Bone loss prevention
- Secondary therapy
- Chemotherapy
- Hospice/end-of-life clinic
- Cost of failure
  - $ 
  - QOL
Indications for Referral
Difficult Situations

• ADT failure
• Chemotherapy failure
• Spinal cord compression
  – Androgen-stimulated prostate cancer → emergency androgen deprivation therapy, steroids, and XRT or surgical fixation
  – Castration-recurrent prostate cancer → steroids, XRT, hospice
Cord Compression: Outcome is a Function of Timely Management

- If you walk in ... you walk out
- “heart attack of the cord”
- Decompression (XRT, operation)
  - improves motor function in 45-60%
  - reverses paraplegia in up to 11%
  - prevention of neurologic progression
- Relief of pain: 70% of patients
- Prevent local recurrence
“Stop and Think” Situations

• Happened: Referral for postRT urinary incontinence prompts review of diagnostic prostate biopsies that reveal focal atrophy or seminal vesicle (2 common causes of CaP misdiagnosis)

• Happened: Referral for salvage prostatectomy after failed brachytherapy for Gleason grade 3+3=6 (number cores not specified), T1c, PSA 3.8 CaP prompts review of diagnostic prostate biopsies that reveals Gleason grade 3+4=7 CaP in 10-80% of 1-2 cores in each sextant

• Should have happened: Bilateral super-radical RP or 3-DCRT/IMRT possibly with 6 mo ADT
CaP Second Opinions at RPCI 2005-2006 (n=201)

• Gleason score consistently undergraded
• 10% of cases reviewed resulted in a “major” change in Gleason score that changed the NCCN risk category
• 6 patients found not to have cancer