Management of Prostate Cancer

ORCA
March 7th, 2015
Dr. Kelly Casperson
Dr. William Hall
Dr. Marcy Hipskind - case presentations
Case #1

- 57yo male
- PSA 7/2008 = 3.6, 10/2008 PSA = 4.4, 9/2009 = 4.6, no palpable abnormality
- Nocturia x1, weaker than normal stream, normal erectile function
- TRUS – 30mL gland, no echogenic abnormalities (PSA density 0.15)
- Biopsy (Nov 2009)
  - Right: no malignancy
  - Left: 3+3=6, 1/8 cores, 1mm, <1% of biopsy volume, no perineural invasion
- Past Medical History – depression, hyperparathyroidism
Case #2

- 62 y.o. male
- PSA 2/2012 = 2.8, 2/2014 = 3.7, 3/2014 = 4.2
- TRUS – 40mL
- Biopsy #1 (April 2014) – PIN suspicious for malignancy
- Biopsy #2 (July 2014)
  - Right: 4+3 = 7, 4/9 cores, 7/128mm (5%)
  - Left: 3+3= 6, 1/8 cores, 1/132mm (1%)
- Medical History: factor V Lieden mutation, pilonidal cyst, hemorrhoids
Case #3

- 65 y.o.

- PSA 1/2007 = 3.84, 7/2007 = 3.53

- PSA 2012 7.7, free PSA 12%, nodule palpated on exam, repeat PSA 9.3

- Mild ED symptoms

- Biopsy
  - Right: 3+4=7, 4/8 cores, 19/110mm (17%), no PNI
  - Left: 3+3=6, 2/9 cores, 3/118mm (2.5%), no PNI
Case #4

- 50 y.o. male
- FH – father prostate CA age 70
- 1997 PSA 2.0, 1999 PSA 4.7, “abnormal exam” per urology
- Biopsy
  - Right: 3+4=7, 3/5 cores+ Gleason
  - Left: 3+4=7, 1/5 cores +
Case #4

- Initial Treatment Radical Prostatectomy 1999
  - Trans-capsular invasion- Rt base
  - Bilateral Seminal vesicle invasion
  - Positive margin

- Initial PSA <0.1 2000-2003

- PSA 2004: 0.4

- Salvage Treatment = Prostate Bed Radiation

- PSA late 2004 = 0.1

- PSA early 2005 = 0.28, late 2005 = 0.58
Case #4

- Pt starts lycopene, selenium, avoids red meat
- SCCA
- PSA rises steadily to 5.8 by 2013
- 2014 Pt develops multiple spine metastases while on hormone therapy
- 2015 PSA 15.6
Very low risk prostate cancer is defined by:

1. T1c
2. PSA = 10
3. Gleason Sum = 6
4. PSA density < 0.15ng/mL/g
5. Fewer than 3 cores positive, <50% involvement any one core
6. All of the above
Very low risk prostate cancer is defined by:

A. T1c
B. PSA ≤ 10
C. Gleason Sum ≤ 6
D. PSA density < 0.15ng/mL/g
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F. All of the above
Which of the following should be performed in a patient with a T1c, PSA 9, Gleason 7 prostate cancer patient prior to undergoing definitive treatment?

1. Bone scan
2. CT abdomen/pelvis
3. MRI pelvis
4. All of the above
5. None of the above
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Which of the following patients has high risk prostate cancer?

1. 65 yo, T1c, gleason sum 8, PSA 6
2. 72yo, T2b, gleason 3+4 = 7, PSA 11
3. 69 yo, T1c, gleason sum 6, PSA 14
4. 77 yo, T2a, gleason sum 4+3=7, PSA 10
Which of the following patients has high risk prostate cancer?

A. 65 yo, T1c, gleason sum 8, PSA 6

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NCCN Guidelines Version 1.2015
Prostate Cancer

INITIAL PROSTATE CANCER DIAGNOSIS

- DRE
- PSA
- Gleason primary and secondary grade

INITIAL CLINICAL ASSESSMENT

Life expectancy
- ≤6 years and asymptomatic
- >6 years or symptomatic

STAGING WORKUP

No further workup or treatment until symptomatic, except in high- or very-high-risk groups

Bone scan if any of these:
- T1c and PSA >20
- T2 and PSA >10
- Gleason score ≥8
- T3, T4
- Symptomatic

Pelvic CT or MRI if any of these:
- T3, T4
- T1c-T2 and nomogram indicated probability of lymph node involvement >10%

Suspicious nodes → Consider biopsy

Preferred treatment for any therapy is approved clinical trial.

All others: no additional imaging

RISK GROUPS:

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

- Intermediate:
  - T1c-T2a
  - Gleason score ≤6
  - PSA <10 ng/mL

- Intermediate:
  - T2b-T2c or
  - Gleason score 7 or
  - PSA 10–20 ng/mL

- High:
  - T3a or
  - Gleason score 8–10 or
  - PSA >20 ng/mL

- Locally Advanced:
  - Very high:
    - T3b-T4
    - Primary Gleason pattern 5 or
    - ≥4 cores with Gleason score 8–10

- Metastatic:
  - Any T, N1
  - Any T, Any N, M1

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.

PROS-1

See Initial Therapy (PROS-2)
See Initial Therapy (PROS-3)
See Initial Therapy (PROS-4)
See Initial Therapy (PROS-5)

See Principles of Life Expectancy Estimation (PROSA)
Men with clinically localized disease could consider use of a tumor-based molecular assay to stratify better risk of adverse pathology at radical prostatectomy or chance of biochemical recurrence or disease-specific mortality after radical prostatectomy.

See Principles of Imaging (PROS-B)
In selected patients where complications such as hydronephrosis or metastasis can be expected within 5 y, androgen deprivation therapy (ADT) or radiation therapy (RT) may be considered. High-risk factors include bulky T3-T4 disease or Gleason score 8–10.

Patients with multiple adverse factors may be shifted into the next highest risk group.
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Prostate Cancer

**RISK GROUP**

**EXPECTED PATIENT SURVIVAL**

- 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

**INITIAL THERAPY**

- Active surveillance
  - PSA no more often than every 6 mo unless clinically indicated
  - DRE no more often than every 12 mo unless clinically indicated
  - Repeat prostate biopsy no more often than every 12 mo unless clinically indicated

- EBRT or brachytherapy

- Radical prostatectomy (RP)
  - ± pelvic lymph node dissection (PLND)
  - If predicted probability of lymph node metastasis ≥2%

**ADJUVANT THERAPY**

- Adverse features
  - EBRT or Observation

- Lymph node metastasis:
  - ADT (category 1) ± EBRT (category 2B)
  - Observation

**See Monitoring (PROS-6)**

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

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**See Principles of Life Expectancy Estimation (PROS-A).**

**See Principles of Radiation Therapy (PROS-D).**

**See Principles of Surgery (PROS-F).**

**Notes:**

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**PROS-2**
Case #1

- Pt chooses active surveillance

- Followed every 6 months in radiation oncology

- Repeat PSA q6months
  - 2010 – 4.0, 4.3
  - 2011 – 5.1, 4.9
  - 2012 – 5.5, 6.2
  - 2013 – 6.7, 8.5
  - 2014 – 7.8, 7.7

- Repeat biopsy
  - 12/2010 – no malignancy
  - 6/2013 – PIN right gland, Gleason 3+6 = 6 involving 2/160mm left gland (1%)
  - Planned repeat biopsy 2015
Active Surveillance
(Not to be confused with watchful waiting or observation)

• PSA no more often than every 6 mo unless clinically indicated

• DRE no more often than every 12 mo unless clinically indicated

• Needle biopsy of the prostate should be repeated within 6 mo of diagnosis if initial biopsy was <10 cores or assessment discordant (eg, palpable tumor contralateral to side of positive biopsy)

• A repeat prostate biopsy should be considered if
  o prostate exam changes or
  o PSA increases

• A repeat prostate biopsy should be considered as often as annually to assess for disease progression, because PSA kinetics may not be as reliable as monitoring parameters to determine progression of disease.

• Repeat prostate biopsies are not indicated when life expectancy is less than 10 y or appropriate when men are on observation
Risks of Prostate Biopsy

• Remember not a screening test

• PLCO trial lists risk at 0.7%
  o Bruising and discomfort at the biopsy site
  o Prolonged bleeding from the biopsy site
  o Infection near the biopsy site
    • 1% hospitalization risk
    • Increasing not because of biopsy, but because of antibiotic use and resistance
  o Difficulty urinating

• Our protocol
  o Enema
  o Cipro 4 tabs, night before, am of, night of, AM after
Risk Grouping

- **Very Low Risk**
  - T1c
  - PSA ≤ 10
  - Gleason Sum ≤ 6
  - PSA density < 0.15ng/mL/g
  - Fewer than 3 cores positive, <50% involvement in any one core

- **Low Risk**
  - T1-T2a
  - Gleason <6
  - PSA <10 ng/mL

- **Intermediate Risk**
  - T2b-T2c or
  - Gleason score 7 or
  - PSA 10–20 ng/mL

- **High Risk**
  - T3a or
  - Gleason score 8–10 or
  - PSA >20 ng/mL
Case #2

• 62 y.o. male

• PSA 2/2012 = 2.8, 2/2014 = 3.7, 3/2014 = 4.2

• TRUS – 40mL

• Biopsy #1 (April 2014) – PIN suspicious for malignancy

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• Medical History: factor V Lieden mutation, pilonidal cyst, hemorrhoids
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B. CT abdomen/pelvis
C. MRI pelvis
D. All of the above
E. None of the above
What Treatment is Best?

• Institute of Medicine recently included treatment for localized prostate cancer among the 25 most important topics for comparative-effectiveness research
What Treatment is Best?

- Low Risk – Brachy, EBRT, RRP no real differences, but no head to head comparisons
  - ≥ 80% -85% bRFS @ 10 yrs.
  - ≥ 90-95% without LR or DM @ 10 yrs.

- Choosing Toxicity
- EBRT
  - Acute – fatigue, tenesmus, rectal frequency/urgency, hemorrhoid irritation, obstructive urinary symptoms – frequency, urgency, nocturia
  - Late – Rectal bleeding (~5-10%), urethral stricture (rare), ED

- Brachy
  - Acute – virtually no GI, but worse obstructive urinary symptoms than EBRT (~6mo)
  - Late – urethral stricture rate higher than EBRT

- RRP
  - Acute – Surgery/Postop Recovery, Incontinence
  - Late – Incontinence? ED

- Hormone Therapy – Hot flashes, weight gain, loss of muscle mass, cardiac
What Treatment is Best?

• Intermediate Risk
  o Probably equal. No randomized trials comparing Rad to surgery.
    • Typically not brachy alone
    • ERBT+hormone therapy or EBRT + Brachy
  o RP is better than AS or no treatment – Randomized!
    • From 10 to 18 years of follow-up, the number needed to treat to prevent one death decreased from 20 to 8 in the whole cohort, and from 8 to 4 among men younger than 65 years of age.

• High Risk
  o Radiation/Hormone Therapy for 2-3 years
    • EORTC (T3/4, mean PSA >20) – 10 year OS 58%, CSS 89%
    • RTOG (T2c-4, median PSA 20) – 10 year OS 54%, CSS 89%
  o Surgery
    • 30,379 men (mean age 62.5 years) who underwent RP for Gleason 8-10 non-metastatic PCa, at University of Missouri-Columbia School of Medicine in Columbia found that the overall survival rates at 5, 10, 15, 20, and 25 years were 92.8%, 78.6%, 59.5%, 38.6%, and 20.0%, respectively. Cancer-specific survival rates were 96.4%, 89.5%, 82.0%, 72.9%, and 68.8%, respectively.
### PARTIN TABLES

**PSA:** 4.1-6.0

**Gleason Score:** 4+3

**Clinical Stage:** T1c

**Find Results**

<table>
<thead>
<tr>
<th>OC: organ confined (1439)</th>
<th>EPE: extraprostatic extension (371)</th>
<th>SV+: seminal vesicle involvement (37)</th>
<th>LN+: lymph node involvement (11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 (55-65)</td>
<td>31 (26-36)</td>
<td>6 (4-9)</td>
<td>3 (2-5)</td>
</tr>
</tbody>
</table>

Numbers represent percentage of patients with the specified PSA, clinical stage, and biopsy Gleason score who would have organ-confined disease (OC), extra-prostatic extension (EPE), cancer invading into the seminal vesicles (SV+), or cancer invading regional lymph nodes (LN+). Numbers in parentheses represent 95% confidence intervals.
**NCCN Guidelines Version 1.2015**

**Prostate Cancer**

**RISK GROUP**

**EXPECTED PATIENT SURVIVAL**

- Intermediate: T2b-T2c or Gleason score 7 or PSA 10–20 ng/mL

**INITIAL THERAPY**

- EBRT with ADT (4–6 mo) ± brachytherapy or brachytherapy alone

**ADJUVANT THERAPY**

- Adverse features:
  - EBRT or Observation
  - Lymph node metastasis: ADT (category 1) ± EBRT (category 2B) or Observation (category 2B)

- Undetectable PSA or nadir

**See Monitoring (PROS-6)**

- See Radical Prostatectomy Biochemical Failure (PROS-7)

- PSA failure

**See Radiation Therapy Recurrence (PROS-8)**

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*aSee Principles of Life Expectancy Estimation (PROS-A).*

*bPatients with multiple adverse factors may be shifted into the next highest risk group.*

*cSee Principles of Radiation Therapy (PROS-D).*

*dSee Principles of Surgery (PROS-E).*

*eAdverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.*

*fObservation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).*

*gSee Principles of Androgen Deprivation Therapy (PROS-F).*

*hActive surveillance of intermediate and high-risk clinically localized cancers is not recommended in patients with a life expectancy >10 years (category 1).*

**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.
Case #2

- Pt sees several surgeons who recommend against surgery b/c of factor V leiden mutation and concerns about post-op DVT/stroke

- Pt chooses EBRT with short course (6 months) androgen deprivation therapy.
Case #3

• 65 y.o.

• PSA 1/2007 = 3.84, 7/2007 = 3.53

• PSA 2012 7.7, free PSA 12%, nodule palpated on exam, repeat PSA 9.3

• Mild ED symptoms

• Biopsy
  o Right: 3+4=7, 4/8 cores, 19/110mm (17%), no PNI
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**EXPECTED PATIENT SURVIVAL**

**INITIAL THERAPY**

**ADJUVANT THERAPY**

- **Intermediate:**
  - T2b-T2c or
  - Gleason score 7 or
  - PSA 10–20 ng/mL

  - **RP + PLND if predicted probability of lymph node metastasis ≥2%**

  - ≥10 y
  - EBRT + ADT (4–6 mo) ± brachytherapy or brachytherapy alone
  - Observation

  - <10 y
  - Observation

- **Adverse features:** EBRT or Observation

- **Lymph node metastasis:** ADT (category 1) ± EBRT (category 2B) or Observation (category 2B)

- **Undetectable PSA or nadir**
  - See Monitoring (PROS-6)

- **PSA failure**
  - See Radical Prostatectomy (PROS-7)

- **See Radiation Therapy Recurrence (PROS-8)**

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**Footnotes:**

1. See Principles of Life Expectancy Estimation (PROS-A).
2. Patients with multiple adverse factors may be shifted into the next highest risk group.
5. Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.
6. Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).
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Case #3

• Pt ops for radical prostatectomy

• Nodes
  o Right: 1 node negative
  o Left: 3 nodes negative

• Prostate
  o 3+4 = 7
  o Bilateral involvement
  o 2.75mL, spanning 3.4cm
  o No extra-prostatic extension, margins negative, no SV involvement

• pT2cN0
Which of the following patients has high risk prostate cancer?

A. 65 yo, T1c, gleason sum 8, PSA 6

B. 72yo, T2b, gleason 3+4 = 7, PSA 11

C. 69 yo, T1c, gleason sum 6, PSA 14

D. 77 yo, T2a, gleason sum 4+3=7, PSA 10
What about the High Risk Patient?
What treatment is best for High Risk?

- Anything is better than nothing, unless overall health is poor

Oncologist 2012 Sep;17 (Suppl1): 4-8.
Case #4

- 50 y.o. male
- FH – father prostate CA age 70
- 1997 PSA 2.0, 1999 PSA 4.7, “abnormal exam” per urology
- Biopsy
  - Right: 3+4=7, 3/5 cores+ Gleason
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Case #4

- Initial Treatment Radical Prostatectomy 1999
  - Trans-capsular invasion - Rt base
  - Bilateral Seminal vesicle invasion
  - Positive margin

- Initial PSA <0.1 2000-2003

- PSA 2004: 0.4

- Salvage Treatment = Prostate Bed Radiation

- PSA late 2004 = 0.1

- PSA early 2005 = 0.28, late 2005 = 0.58
Salvage Radiation

- Rising PSA after prostatectomy – AUA/ASTRO guideline is any PSA ≥0.2
- We like to limit to pts with PSA <2, but generally the lower the PSA the better
- We consider pelvic MRI to rule out metastatic disease in pts with PSA doubling time <8 months.
- We typically don’t consider bone scans until PSA is >10 in which case we usually recommend androgen deprivation therapy as opposed to salvage RT.

Factors predicting improved bRFS after salvage
  - PSA <0.5
  - + margin at time of RRP
  - Long interval between PSA recurrence and RRP

- Dose 64-70Gy

Efficacy data mainly from single institution series
  - Cancer specific survival ~ 10-20% improvement at 10 years
  - No clear overall survival benefit

- Toxicity
  - Generally incontinence rates are thought to be similar to pts treated with surgery only
  - Erectile function – impact or RT is unclear in surgery patients who retain potency
  - Second malignancy
Adjuvant Radiation

- Risk of recurrence in post RP patients with adverse features is ≥ 60% at 10 years
  - Positive margins
  - Extra-prostatic extension
  - Seminal vesicle invasion

- Clinical trials show that adjuvant radiation improves:
  - 10y Biochemical (PSA) Progression Free Survival - 77% vs. 55%
  - Local recurrence risk – 5-8% vs. 15-22%
  - 5 Clinical progression free survival 85% vs. 77%
  - Hormone therapy free survival 80% vs. 53-66%
  - SWOG trial also shows a 15 year OVERALL SURVIVAL Benefit – 47% vs. 37%

- Consider concurrent androgen deprivation therapy for very high risk patients (Low volume node +, Gleason 9-10, PSA ≥ 20, SV invasion)
Case #4

- Pt starts lycopene, selenium, avoids red meat

- SCCA

- PSA rises steadily to 5.8 by 2013

- 2014 Pt develops multiple spine metastases while on hormone therapy

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ADJUVANT THERAPY

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≥10 y\(^n\)

EBRT\(^h\) ± ADT\(^l\) (4–6 mo) ± brachytherapy or brachytherapy alone\(^h\)

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Adverse features: EBRT\(^h\) or Observation\(^k\)

Undetectable PSA or PSA free"

Intermediate:

- T2b-T2c or
- Gleason score 7 or
- PSA 10–20 ng/mL

<10 y

Observation\(^k\)

See Principles of Life Expectancy Estimation (PROS-A).

Observation involves monitoring the course of disease.
RADIATION THERAPY RECURRENTNESS

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

- Biochemical failure or Positive DRE

- Observation
- RP
- Cryosurgery
- Brachytherapy

TRUS biopsy positive, studies negative for distant metastases
- PSADT
- TRUS biopsy
- Bone scan
- Abdominal/pelvic CT/MRI
- Prostate MRI
- C-11 choline PET

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

STUDIES POSITIVE FOR DISTANT METASTASES
- ADT
- Observation

NOT A CANDIDATE FOR LOCAL THERAPY

See Principles of Imaging (PROS-B).
See Principles of Radiation Therapy (PROS-D).
See Principles of Surgery (PROS-E).
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