Contemporary Radiation Therapy Options for Prostate Cancer
A 67-year-old man was diagnosed with Gleason 3+3 prostate cancer in 2006; PSA = 5, managed initially with active surveillance. PSA rose gradually to 11, and repeat biopsy in 2010 showed elements of Gleason 7 cancer.

1. In the Klotz study, criteria for recommending active therapy after initial surveillance for Gleason 6 cancer include the following:
   A. PSA doubling time < 3 years
   B. Worsening urinary obstructive symptoms
   C. Repeat biopsy showing persistent Gleason 6 cancer
   D. New onset erectile dysfunction

2. According to the Agency for Heath Research and Quality (AHRQ) Comparative Effectiveness Report #13, among the different available therapies for clinically localized prostate cancer,
   A. adverse effects on sexual function are equivalent
   B. costs and inconvenience are comparable
   C. patient satisfaction is generally low
   D. no one therapy is a clearly preferred option

3. According to the AHRQ Technology Assessment “Comparative evaluation of radiation treatments for clinically localized prostate cancer: an update”, which statement is true?
   A. Proton therapy is established as superior to all other radiation modalities.
   B. Seed implants tend to cause more urinary toxicity and less gastro-intestinal toxicity than external beam RT
   C. Shortening the course of external beam RT causes more side effects.
Learning Objectives

• Recognize the different radiation therapy modalities utilized in the treatment of prostate cancer
• Understand recent technological developments in this area
• Describe the risks and benefits of radiation oncology treatment modalities in prostate cancer treatment
Disclosure

• Dept of Defense funding for prostate SBRT trial and Hypothesis Development Project
Contemporary RT options for prostate cancer

• Common risk group classifications
• Brief discussion of active surveillance
• Overview of management options for prostate cancer
  – Early v. late stage
• Technology and ongoing studies in radiation therapy for prostate cancer
## Common risk group classifications for non-metastatic prostate cancer*

<table>
<thead>
<tr>
<th>PSA</th>
<th>Primary tumor</th>
<th>Pathologic grade (Gleason sum)</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Low risk</td>
<td>≤10</td>
<td>T1c (non-palpable)</td>
<td>5-6</td>
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<tr>
<td>Intermediate risk</td>
<td>10-20</td>
<td>T2 (palpable but within gland)</td>
<td>7</td>
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<tr>
<td>High risk</td>
<td>&gt;20</td>
<td>T3-T4 (outside gland)</td>
<td>8-10</td>
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*Caveats:
1. These are rough guidelines based on clinical features.
2. Some patients straddle these broad categories.
3. Maybe someday there will be molecular signatures as there are for breast and lung cancer...
Risk vs. consensus opinion

- High risk
- Intermediate risk
- Low risk

Severity of cancer

Debate/controversy about management

- 450 pts, U of Toronto
  - Median age, 70 yrs
  - 7 yrs median follow-up
- Entry criteria*: 
  - Gleason ≤ 6, PSA ≤ 10 ng/mL
- Criteria for offering radical therapy (RT, S, etc)
  - PSA doubling time<3 yrs
  - Higher grade on repeat biopsy
  - New nodule biopsy-proven cancer
- Outcome:
  - 10 yr prostate cancer-specific survival 97%

*initially some Gleason 7
1. What are the comparative risks, benefits, short and long-term outcomes of therapies for clinically localized prostate cancer?

2. How do specific patient characteristics, e.g., age, race/ethnicity, ...affect the outcomes...

3. How do provider/hospital characteristics affect outcomes ...

4. How do tumor characteristics, e.g., Gleason score, tumor volume, screen vs. clinically detected tumors, affect the outcomes ...?
AHRQ Key Question 1. What are the comparative risks, benefits, and outcomes of therapies?

• “No one therapy can be considered the preferred treatment for localized prostate cancer due to limitations in the evidence…”

• “All treatment options result in adverse effects (primarily urinary, bowel, and sexual), although the severity and frequency may vary…”

• “Even if differences in therapeutic effectiveness exist, differences in adverse effects, convenience, and costs are likely to be important factors in individual patient decisionmaking.”

• “Patient satisfaction with therapy is high…”

• “Data from nonrandomized trials are inadequate…”
AHRQ Technical Assessment: Comparative evaluation of radiation treatments for clinically localized prostate cancer: an update

1. What are the benefits and harms of radiation therapy for clinically localized prostate cancer compared to no treatment or no initial treatment …?

2. What are the benefits and harms of different forms of radiation therapy for clinically localized prostate cancer in terms of clinical outcomes? …stereotactic body radiation therapy (SBRT, including CyberKnife® therapy), classically fractionated external beam radiation therapy, … brachytherapy …?

3. How do specific patient characteristics …affect the outcomes …?
AHRQ Technical Assessment of RT, continued

**Figure 1: Overview of radiation therapy modalities**

- **Radiation Therapy**
  - **Teletherapy**
    - External Beam RT (EBRT)
      - 2D RT
      - 3D CRT
      - IMRT/IGRT
      - Protons
    - Sterotactic Body RT (SBRT)
      - "Linac" based
      - CyberKnife(R)
      - Protons
  - **Brachytherapy**
    - Low-dose Rate Brachytherapy (LDRBT)
      - I-125
      - Pd-103
      - Cs-131
    - High-dose Rate Brachytherapy (HDRBT)
      - Ir-192

2D RT is two-dimensional radiation therapy; 3D CRT is three-dimensional conformal radiation therapy; IMRT is intensity modulated radiation therapy; IGRT is image-guided radiation therapy; I-125, Pd-103, Cs-131, and Ir-192 are radionuclides used in brachytherapy.
Intensity Modulated Radiation Therapy (IMRT)

A refinement in external beam RT based on treatment delivery technology that modulates the intensity of the radiation beam across the profile of the beam. Generally done with IGRT.*

VMAT = volumetric modulated arc therapy

Image guided radiation therapy, ie using CT or other means of verifying pt position
AHRQ Technical Assessment of RT, conclusions

- For comparative effectiveness between different forms of radiation treatments (BT, EBRT, SBRT), available data ... could not determine if one form of radiation therapy is superior to another form in terms of overall or disease-specific survival.

- Available data suggest that higher EBRT dose is associated with increased rates of long-term biochemical control compared with lower EBRT dose.

- Available data also suggest BT is associated with more genitourinary toxicity and less gastrointestinal toxicity compared with EBRT.

- Whether EBRT is administered as a standard fractionation or moderate hypofractionation seems to make little difference in terms of biochemical control and late genitourinary and gastrointestinal toxicities.
Side effects from therapy for prostate cancer:

anatomically predictable
Quality of Life and Satisfaction with Outcome among Prostate-Cancer Survivors

Martin G. Sanda, M.D., Rodney L. Dunn, M.S., Jeff Michalski, M.D., Howard M. Sandler, M.D., Laurel Northouse, R.N., Ph.D., Larry Hembroff, Ph.D., Xihong Lin, Ph.D., Thomas K. Greenfield, Ph.D., Mark S. Litwin, M.D., M.P.H., Christopher S. Saigal, M.D., M.P.H., Arul Mahadevan, M.D., Eric Klein, M.D., Adam Kibel, M.D., Louis L. Pisters, M.D., Deborah Kuban, M.D., Irving Kaplan, M.D., David Wood, M.D., Jay Ciezki, M.D., Nikhil Shah, D.O., and John T. Wei, M.D.

Institutions represented: Beth Israel Deaconess Medical Center, Boston; University of Michigan, Ann Arbor; Washington University, St. Louis; UCLA; Cleveland Clinic; M.D. Anderson Cancer Center, Houston
QOL after prostate cancer

- 1201 patients, 625 partners surveyed
  - RP patients younger, lower Gleason
  - EBRT pts higher comorbidities
  - Brachy pts earlier stage disease

- Main instruments
  - EPIC (Expanded Prostate Cancer Index Composite)
  - SCA (Service Satisfaction Scale for Cancer Care)
QOL: urinary incontinence or obstruction

Prostatectomy  
External Radiotherapy  
Seed implant

QOL: sexual scores

Prostatectomy
- Nerve-sparing
- Non-nerve-sparing

External Radiotherapy
- Radiotherapy alone
- Radiotherapy plus NHT

Seed implant
- Brachytherapy alone
- Brachytherapy plus radiotherapy, NHT, or both

A 67-year-old man was diagnosed with Gleason 3+3 prostate cancer in 2006; PSA = 5, managed initially with active surveillance. PSA rose gradually to 11, and repeat biopsy in 2010 showed elements of Gleason 7 cancer.

**Standard options**

- **Prostatectomy**
  - With post-op RT, depending on surgical margin status

- **Radiation therapy**
  - Most conventional would be standard dose daily external beam RT + 6 mos androgen deprivation
  - 6-8 weeks of daily RT

**Investigational options**

- Currently an NCI-sponsored RTOG trial of standard RT + ADT versus higher dose RT

- Also, here we have a multi-institutional trial of SBRT for low-intermediate risk prostate cancer

*(he chose the SBRT trial)*
…brevity is the soul of wit…

Polonius, in Hamlet, Act 2, Scene 2
W. Shakespeare

• Early interest in hypofractionated treatment regimens as long ago as the 1960s

• Sir Laurence Olivier
  • Actor
  • prostate cancer survivor

• Treated in 1967 on an experimental protocol involving 6 fractions of 6 Gy
  • 22 yrs NED after that
SBRT: operational definition

• **Stereotactically** localized, ultra-high-dose radiotherapy
  – Given to discrete tumor nodules in *extracranial* locations
  – Within a *hypofractionated* regimen (1-5 treatments)
    • Unlike typical 6-7 week course of radiotherapy
  – Analogous to cranial stereotactic radiosurgery (SRS)
SBRT-friendly systems now widely available
# Prostate SBRT Prospective Studies

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<th></th>
<th>N</th>
<th>Eligible</th>
<th>SBRT dose to prostate PTV</th>
<th>Median follow-up</th>
<th>Phoenix biochemical control rate, time</th>
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<tbody>
<tr>
<td>Virginia Mason</td>
<td>40</td>
<td>T1-T2a</td>
<td>6.7 Gy x 5F</td>
<td>41 mos</td>
<td>90% @48 mos</td>
<td>23% erectile dysfunction among pts potent pre-SBRT</td>
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<tr>
<td></td>
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<td>Gleason ≤ 6</td>
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<td>No Grade 3+ late toxicity</td>
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<td>PSA ≤10</td>
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<tr>
<td>Stanford</td>
<td>41</td>
<td>T1c-T2a/b</td>
<td>7.25 Gy x 5F</td>
<td>33 mos</td>
<td>100% at time of analysis</td>
<td>Lower severe late rectal toxicity with QOD treatments</td>
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<td>Gleason ≤ 6 (or low volume 3+4)</td>
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<td>Only 5% total RTOG grade 3 late toxicity</td>
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<tr>
<td></td>
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<td>PSA ≤10</td>
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<tr>
<td>Winthrop</td>
<td>304</td>
<td>T1c-T2a</td>
<td>7 Gy x 5F N=50</td>
<td>30 mos</td>
<td>Not reported</td>
<td>57 pts received 3-12 mos hormone therapy</td>
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<td>Gleason ≤ 8</td>
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<tr>
<td></td>
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<td>PSA ≤20</td>
<td>7.25 Gy x 5F N=254</td>
<td>17 mos</td>
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<td>5 conseutive 1500 mg intrarectal amifostine daily</td>
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<td></td>
<td>0.5% (1/254) late grade 3 urinary toxicity</td>
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UTSW Multi-center Prostate SBRT Trial

- DOD funded at UTSW, Prairie Lakes Hospital Watertown, SD, Univ. Minn, Univ. Colo., MD Anderson Orlando
- Phase I/II
  - starting dose 9 Gy X 5 fractions, safely up to 10 Gy x 5
  - Phase II dose: 10 Gy x 5
- Primary endpoint 18 month late toxicity, secondary endpoint PSA DFS
5 fraction VMAT-based SBRT

Note rectal balloon for planning and treatment
Thanks for your attention!