Radiation Treatment Options for Prostate Cancer

Savita V. Dandapani, MD, PhD
DISCLOSURE

- Grant/Research Support from Bayer
Epidemiology

- In men:
  - Most common cancer.
    - 1 in 8 of all men will be diagnosed with prostate cancer.
  - 2nd most common cause of cancer death.
    - 1 in 41 of all men will die of prostate cancer.
Incidence and death rate over time

- Incidence rates: 1975-2005
- PSA test FDA approved in 1986
- Death rates: 1930-2005
- ?less PSA testing
Staging: T N M

T1a = TURP 5% or less

T1b = TURP > 5%

T1c = PSA

Not all Mets same
Staging: AJCC 8th edition

<table>
<thead>
<tr>
<th>Group</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>PSA (ng/mL)</th>
<th>Grade Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>cT1a-c</td>
<td>NO</td>
<td>M0</td>
<td>PSA&lt;10</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>cT2a</td>
<td>NO</td>
<td>M0</td>
<td>PSA&lt;10</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>pT2</td>
<td>NO</td>
<td>M0</td>
<td>PSA&lt;10</td>
<td>1</td>
</tr>
<tr>
<td>IIA</td>
<td>cT1a-c</td>
<td>NO</td>
<td>M0</td>
<td>PSA≥10&lt;20</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>cT2a</td>
<td>NO</td>
<td>M0</td>
<td>PSA≥10&lt;20</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>pT2</td>
<td>NO</td>
<td>M0</td>
<td>PSA≥10&lt;20</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>cT2b</td>
<td>NO</td>
<td>M0</td>
<td>PSA&lt;20</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>cT2c</td>
<td>NO</td>
<td>M0</td>
<td>PSA&lt;20</td>
<td>1</td>
</tr>
<tr>
<td>IIB</td>
<td>T1-2</td>
<td>NO</td>
<td>M0</td>
<td>PSA&lt;20</td>
<td>2</td>
</tr>
<tr>
<td>IIC</td>
<td>T1-2</td>
<td>NO</td>
<td>M0</td>
<td>PSA&lt;20</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>T1-2</td>
<td>NO</td>
<td>M0</td>
<td>PSA&lt;20</td>
<td>4</td>
</tr>
<tr>
<td>IIIA</td>
<td>T1-2</td>
<td>NO</td>
<td>M0</td>
<td>PSA≥20</td>
<td>1-4</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3-4</td>
<td>NO</td>
<td>M0</td>
<td>Any PSA</td>
<td>1-4</td>
</tr>
<tr>
<td>IIIC</td>
<td>Any T</td>
<td>NO</td>
<td>M0</td>
<td>Any PSA</td>
<td>5</td>
</tr>
<tr>
<td>IVA</td>
<td>Any T</td>
<td>NO</td>
<td>M1</td>
<td>Any PSA</td>
<td>Any</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>Any PSA</td>
<td>Any</td>
</tr>
</tbody>
</table>

*Note: When either PSA or Grade Group is not available, grouping should be determined by T category and/or either PSA or Grade Group as available.

<table>
<thead>
<tr>
<th>Grade Group</th>
<th>Gleason Score</th>
<th>Gleason Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≤0</td>
<td>≤3+3</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>3+4</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>4+3</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>4+4, 3+5, 5+3</td>
</tr>
<tr>
<td>5</td>
<td>9 or 10</td>
<td>4+5, 5+4, 5+5</td>
</tr>
</tbody>
</table>
## NCCN Prostate Groups

### Risk Stratification and Staging Workup

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Clinical/pathologic features</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low²</td>
<td>• T1c AND</td>
<td>Not indicated</td>
</tr>
<tr>
<td></td>
<td>• Gleason score ≤5/grade 1 AND</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PSA &lt;10 ng/mL AND</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Fewer than 3 prostate biopsy fragments/coring positive, ≤50% cancer in each fragment/core² AND</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PSA density &lt;0.15 ng/mL/g</td>
<td></td>
</tr>
<tr>
<td>Low²</td>
<td>• T1-T2a AND</td>
<td>Not indicated</td>
</tr>
<tr>
<td></td>
<td>• Gleason score ≤5/grade 1 AND</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PSA ≤10 ng/mL</td>
<td></td>
</tr>
<tr>
<td>Favorable intermediate⁰</td>
<td>• T2b-T2c OR</td>
<td>Not routinely recommended</td>
</tr>
<tr>
<td></td>
<td>• Gleason score 3-4/grade 2 OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PSA 10-20 ng/mL AND</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Percentage of positive biopsy cores &lt;50%</td>
<td></td>
</tr>
<tr>
<td>Unfavorable intermediate⁰</td>
<td>• T2b-T2c OR</td>
<td>Consider if life expectancy &gt;10 years</td>
</tr>
<tr>
<td></td>
<td>• Gleason score 3-4/grade 2 OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PSA 10-20 ng/mL AND</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bone imaging¹: not recommended for staging</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pelvic + abdominal imaging: recommended if nomogram predicts &gt;10% probability of pelvic lymph node involvement</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>• T3a OR</td>
<td>Consider⁰</td>
</tr>
<tr>
<td></td>
<td>• Gleason score 8/grade 4 OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PSA ≥20 ng/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bone imaging¹: recommended</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pelvic + abdominal imaging: recommended if nomogram predicts &gt;10% probability of pelvic lymph node involvement</td>
<td></td>
</tr>
<tr>
<td>Very high</td>
<td>• T3b-T4 OR</td>
<td>Not routinely recommended</td>
</tr>
<tr>
<td></td>
<td>• Primary Gleason pattern 5 OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• &gt;4 cores with Gleason score 8-10/ grade 4 or 5</td>
<td></td>
</tr>
<tr>
<td>Regional</td>
<td>Any T, N1, M0</td>
<td>Already performed</td>
</tr>
<tr>
<td>Metastatic</td>
<td>Any T, Any N, M1</td>
<td>Already performed</td>
</tr>
</tbody>
</table>

### Molecular testing of tumor

- Not indicated

### Germline testing

- Consider if strong family history

### Initial therapy

- See PROS-4
- See PROS-5
- See PROS-6
- See PROS-7
- See PROS-8
- See PROS-9
- See PROS-13
### NCCN guidelines on radiation therapy

#### PSA < 10
- GS 6

#### PSA 10-20
- GS 3+4
- GS 4+3

<table>
<thead>
<tr>
<th>Regimen for Definitive Therapy</th>
<th>Very-Low¹</th>
<th>Low¹</th>
<th>Favorable or good prognosis²</th>
<th>Unfavorable, or poor prognosis²</th>
<th>High and Very-High³</th>
<th>Node Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beam Therapies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72 Gy to 80 Gy at 2 Gy per fraction</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>75.6 Gy to 81.0 Gy at 1.8 Gy per fraction</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>70.2 Gy at 2.7 Gy per fraction</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>70 Gy at 2.5 Gy per fraction</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>60 Gy at 3 Gy per fraction</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>51.6 Gy at 4.3 Gy per fraction</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>37 Gy at 7.4 Gy per fraction</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>40 Gy at 8 Gy per fraction</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>36.25 Gy at 7.25 Gy per fraction</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td><strong>Brachytherapy Monotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iodine 125 implant at 145 Gy</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>Palladium 103 implant at 125 Gy</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>Cesium implant at 115 Gy</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>HDR 27 Gy at 13.5 Gy in 2 implants</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>HDR 38 Gy at 9.5 Gy BID in 2 implants</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td><strong>Combined EBRT and Brachytherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iodine 125 implant at 110-115 Gy</td>
<td>✔️ ± 4 mo ADT</td>
<td>✔️ ± 4 mo ADT</td>
<td>✔️ with 1-3 y ADT</td>
<td>✔️ with 1-3 y ADT</td>
<td>✔️ with 1-3 y ADT</td>
<td></td>
</tr>
<tr>
<td>Palladium 103 implant at 90-100 Gy</td>
<td>✔️ ± 4 mo ADT</td>
<td>✔️ ± 4 mo ADT</td>
<td>✔️ with 1-3 y ADT</td>
<td>✔️ with 1-3 y ADT</td>
<td>✔️ with 1-3 y ADT</td>
<td></td>
</tr>
<tr>
<td>Cesium implant at 85 Gy</td>
<td>✔️ ± 4 mo ADT</td>
<td>✔️ ± 4 mo ADT</td>
<td>✔️ with 1-3 y ADT</td>
<td>✔️ with 1-3 y ADT</td>
<td>✔️ with 1-3 y ADT</td>
<td></td>
</tr>
<tr>
<td>HDR 21.5 Gy at 10.75 Gy x 2</td>
<td>✔️ ± 4 mo ADT</td>
<td>✔️ ± 4 mo ADT</td>
<td>✔️ with 1-3 y ADT</td>
<td>✔️ with 1-3 y ADT</td>
<td>✔️ with 1-3 y ADT</td>
<td></td>
</tr>
<tr>
<td>EBRT 37.5 Gy at 2.5 Gy ± 12-15 Gy single HDR</td>
<td>✔️ ± 4 mo ADT</td>
<td>✔️ ± 4 mo ADT</td>
<td>✔️ with 1-3 y ADT</td>
<td>✔️ with 1-3 y ADT</td>
<td>✔️ with 1-3 y ADT</td>
<td></td>
</tr>
</tbody>
</table>

¹ Active surveillance should be strongly considered

---

**Standard external beam radiation therapy**

**SBRT**

**Brachytherapy**

**combo**

[City of Hope logo]
Radiation and different stages of prostate cancer

- **Early stage/definitive:**
  - Standard External beam radiation alone
  - brachytherapy (permanent seeds or temporary needles)
  - Stereotactic body radiation therapy (SBRT)
  - Clinical Trial: MRI guided focused ultrasound

- **Clinical advanced disease (definitive or postoperative):**
  - Standard External beam radiation + androgen deprivation therapy (ADT)
  - Standard External beam + brachytherapy boost + ADT (ASCENDE Trial)

  - Post radical prostatectomy:
  - Adjuvant Radiation for high risk prostate cancer features (pT3 (extracapsular extension, seminal vesicle involvement, positive margins)
  - Salvage Radiation for PSA recurrence
  - Standard External beam radiation + ADT
  - Prostate bed SBRT + ADT
  - Oligometastatic disease: early stage IV: SBRT to metastatic sites
Radiation and different stages of prostate cancer

- Stereotactic body radiation therapy (SBRT)
- A current direction in radiation oncology field:
  - Smaller fields, less normal tissue treated
  - Higher doses, so close proximity of normal tissue is the greatest risk

Options for all stages of prostate cancer:
- Clinical trials for:
  - Early stage (many multi-institutional trials)
  - Salvage post prostatectomy (my colleague Dr. Sampath)
  - Metastatic disease (my oligomet trial)
Early Stage/Early Intermediate Risk Prostate Cancer

- NCCN:
- GS 3+3 = 6
- GS 3+4 = 7
- cT1c-T2a
- PSA < 10
“Beams” carry xrays (same as CT cat scans, PETCT scans) that are able to disrupt the target tissue and cause damage to the cells, causing cell death.

- Particularly affects cells that rapidly divide which are cancer cells. (other cells in body that rapidly divide are in Gastrointestinal system and skin, hair, nails)

- Prostate Target sits in middle between normal tissue of bladder and rectum/bowels.
Standard External Beam Radiation

- 30 minute sessions, 5 days a week, 6-8 weeks
Brachytherapy

- Brachytherapy (anatomy important!)
- Internal radiation
Prostate SBRT

- SBRT versus standard external beam radiation
- High Dose/Small Area
- Space between prostate and rectum: small mm
- Normal Tissue protect from High Dose
  - Rectal space OAR
  - Hydrogel (PEG based gel) injected between rectum and prostate
  - Hydrodissection to give space for hydrogel (to separate denovilliers’ fascia from anterior rectal wall)
  - OR under anesthesia
  - Transperineal injection by Urology with TRUS (Bertram Yuh)
  - Hydrogel stable for 3 months, liquefies in 6 months
Rectal Balloon vs. SpaceOAR
Rectal Balloon vs. SpaceOAR

![Graph comparing Rectal Balloon and Spacer Gel](image)
Prostate SBRT
-- Looks similar but tighter margins
-- More rigid immobilization of patient
-- Spaceoar helps posterior/rectal dose
-- Treatment over 5 sessions versus 45 sessions
Prostate SBRT

- King et al 2013
- SBRT pooled analysis from prospective phase II trials
- 1100 patients
- 36.25Gy in 4-5 fractions (7.25Gy x 5 fx NCCN)
- 14% had some ADT
- 36 month f/u (only 3 years!):
- Biochemical psa control:
  - GS 6: 95%
  - GS 7: 83%
  - GS 8: 78% (NCCN not recommended for GS 8)
- **maybe 3% increase in GU toxicity with SBRT
Prostate SBRT Trial – Higher dose?

- Hannan, Timmerman et al (2016)
- GS 6, PSA <20, GS 7, PSA<15, <T2b
- Dose escalation, phase I/II
- **45Gy/5fx, 47.5Gy/5fx, 50Gy/5fx**
- Biochemical psa control: 100% at 3 years, 98.6% at 5 years
- Toxicity
  - no acute GU but late grade 3 GU in 5.5% of patients
  - 2% grade III acute GI toxicity and 7% late grade GI toxicity
  - Most toxicity if dose >47.5Gy/5fx
- NCCCN guidelines: (40Gy/5fx) 8Gy x 5 or (36.25/5fx)7.25Gy x 5
Prostate SBRT vs. old standards

- Prostate SBRT vs. standard conventional external beam radiation treatment
- Phase III Trials underway
- Prostate SBRT vs. brachytherapy
- Comparison analysis (UCLA)
- No difference in 3 year followup

- Main issue is the followup – prostate cancer has to be followed for years to see a difference! (***original prostate cancer papers years of followup 15 years, 20 years)
- Other main issue is necessity of very good patient setup to reduce toxicity: team effort with physics/dosimetry/technicians
COH – non radiation options for early stage prostate cancer

• IRB Clinical Trial of MRI Guided focused ultrasound (PI: chair of radiation oncology Dr. Jeffrey Wong)
• Early stage/Early Intermediate risk prostate cancer
• Research alternative to external beam radiation or brachytherapy
• Treat only the biopsy proven site of disease not the whole prostate (partial prostate treatment)
• Treatment with ultrasound not radiation
PCa003
(Protocol Version Date January 11, 2018)

Focal MR-Guided Focused Ultrasound Treatment of Localized Intermediate Risk Prostate Lesions
Patient eligibility (Inclusion Criteria)

- Male subjects age 50 and older
- Biopsy proven adenocarcinoma of the prostate (using a IMAGE-guided 14+ core mapping biopsy)
- Subjects with intermediate risk, early-stage organ-confined prostate cancer (T1a up to T2b, N0, M0)
- Single hemilateral, MRI visible, index Gleason 7 (4 + 3 or 3 + 4) lesion, may have secondary Gleason 6 lesion on ipsilateral or contralateral side

*Key criteria only – complete listings identified in study protocol*
MR Guided focused ultrasound results

• Seven patients treated
  • Started 11/2013 (5 years)
    – 60-68 years old; all cT1c, initial PSA 1.96 - 6.68
    – GS 3+3 (5 patients), GS 3+4 (2 patients)
    – Prostate volume 40 – 67 cc
    – 3 with MRI visible lesion (2 with GS 3+4)

• Treatment
  – Procedure time excluding first patient average 84.5 minutes (51-119)
  – Number of treatment sonications from 6 to 13
  – No. sectors treated: 1 sector (1), 2 sectors (3), 3 sectors (2), 4 sectors (1)
  – NPV from 6.4 cc to 17 cc
MRI guided focused ultrasound results

- PSA 24months: some spike but baseline or lower in 6/7
- Post-treatment biopsies
  - 6 months (5 patients); 24 months (3 patients)
  - 2 patients biopsy positive in treated sectors
    - Patient 3 (4 sectors treated): 1 sector (GS 3+3) at 6 months and 1 (different sector, GS 3+4) at 24 months
    - Patient 4: 1 sector (GS 3+3) at 6 months
- IIEF scores - no major change in all 7 patients
- IPSS scores – no major change from baseline
  - All patients on tamsulosin post therapy
  - One patient required indwelling Foley catheter for one week post-therapy for urinary retention (baseline IPSS 25)
What to choose for early stage prostate cancer?

- External beam radiation
- Brachytherapy
- SBRT
- MR guided focused ultrasound

- Many many choices in prostate – data showing clear winner takes many years to generate
- Issues:
  - prostate volume
  - BPH
  - risk factors for developing GU/GI toxicity
  - proximity of rectum/ability to place spaceOAR
Radiation and different stages of prostate cancer

- Early stage/definitive:
  - Standard External beam radiation alone
  - brachytherapy (permanent seeds or temporary needles)
  - Stereotactic body radiation therapy (SBRT)
  - Clinical Trial: MRI guided focused ultrasound

- Clinical advanced disease (definitive or postoperative):
  - Standard External beam radiation + androgen deprivation therapy (ADT)
  - Standard External beam + brachytherapy boost + ADT (ASCENDE Trial)

- Post radical prostatectomy:
- Adjuvant Radiation for high risk prostate cancer features (pT3: extracapsular extension, seminal vesicle involvement, positive margins)
- Salvage Radiation for PSA recurrence
- Standard External beam radiation + ADT
- Prostate bed SBRT + ADT
- Oligometastatic disease: early stage IV: SBRT to metastatic sites
Advanced Stage
Advanced stage

- Months of ADT needed
- Dose escalation Brachytherapy boost
- Adjuvant and salvage radiation with hormones
Advanced stage

- External Beam Radiation + ADT
- Randomized Trials
- RTOG 9202
- 4 mos ADT vs. **24mos ADT + radiation** (only 70Gy xrt)
- EORTC similar (6 mos ADT vs. 36 mos ADT). **36 mos better**.
- Median f/u: **19.6 years**
- Prostate cancer specific survival at 15 yrs:
  - 84% with 24mos ADT vs. 78% with 4mos ADT (6% difference)
- Distant mets free at 15 yrs:
  - 83% (24mos) vs. 74% (9% difference)
Advanced Stage

- Increase dose of radiation?
ASCENDE Trial (Combo EBRT+brachy + ADT)

- Intermediate/High Risk Patients
- Prostate Dose escalation
- Androgren suppression combined with elective nodal and dose escalated radiation therapy
- 6 centers in Canada
- 2002-2011
- 398 pts
- 70% high risk (30% intermediate)
- ADT for 12 mos
- EBRT radiation dose: 78Gy (pelvis + prostate)
- EBRT + brachy dose escalation

City of Hope
ASCENDE Trial
78Gy RT vs. 46Gy pelvis radiation + brachytherapy boost

- Adding brachytherapy boost
- Improved biochemical control at 6.5 years (doubled control of PSA at ~6.5yrs)
- 9 year PFS 83% vs. 62%
- No overall survival difference
- Toxicity increased
- Increased urinary toxicity (temporary catherization and/or incontinence pads)
- Increased urinary toxicity (18% vs. 5%)
- Worse GU health related quality of life
- Future conclusions: maybe better dosimetry of brachytherapy would lead to decreased toxicity
ASCENDE Trial/Advanced Stage

• Same question in advanced stage: how to escalate radiation dose to prostate safely while minimizing toxicity
Lymph node positive prostate

- STAMPEDE
- Large conglomerate trial in UK
- Subset analysis published in JAMA 2016 (James et al)
  **Benefit of adding radiation to lymph node positive prostate cancer
- Initially not planned for treatment of lymph node positive prostate cancer (just ADT alone)
- Added arm to trial, 177 pts accrued thus far
- 2 year prostate failure free survival (81% with addition of XRT versus 53% with no XRT)
- Early data need to see long term results
Figure 2. Failure-Free Survival for Reported Radical Radiotherapy Status, in N0MO and N+MO Subcohorts

(A) N0MO subcohort

(B) N+MO subcohort

<table>
<thead>
<tr>
<th>No. at risk (events)</th>
<th>Time, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No RT</td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. at risk (events)</th>
<th>Time, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No RT</td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td></td>
</tr>
</tbody>
</table>
Lymph node prostate cancer

- With IMRT we can now boost the prostate lymph node radiation dose

- **patient plan showing hotspot in lymph node (EH)**
Salvage Radiation

- Radiation dose/standard: 64.8Gy – 70.2 Gy over 6-7 weeks (2months)
- 2 recent trials showed benefit of adding ADT

<table>
<thead>
<tr>
<th>Trial/Hormones</th>
<th>Biochemical control</th>
<th>Distant metastases</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>GETUG 16/goserelin x 6 months (Carrie et al Lancet 2016)</td>
<td>5yr (80% vs. 60% xrt alone)</td>
<td>(overall only 5 year data so any progression was only 4-7%)</td>
<td>8% hot flashes with goserelin</td>
</tr>
<tr>
<td>RTOG 9601/bicalutamide x 2 years (Shipley et al NEJM 2017)</td>
<td>12yr (60% vs. 30% with xrt alone)</td>
<td>12 year: 15% in casodex group (vs. 23% in xrt alone)</td>
<td>70% gynecomastia with bicalutamide vs. 11% with xrt alone</td>
</tr>
</tbody>
</table>
Salvage radiation and prostate bed SBRT (PB-SBRT)

- Phase I dose escalation trial (Sampath et al)
- October 2013
- PSA recurrence after prostatectomy (median PSA 0.44)
- Lymph node negative, prostate confined
- Some patients had short course ADT
- Prelim results: 14 patients. max toxicity grade 2 GI.
- Arm 1: 7Gy x 5 (1/3 with biochem PSA control <0.2)
- Arm 2: 8Gy x 5 (6/7 with biochem PSA control)
- Arm 3: 9Gy x 5 (4/4 patients with biochem control)
Radiation and different stages of prostate cancer

• Early stage/definitive:
  – Standard External beam radiation alone
  – brachytherapy (permanent seeds or temporary needles)
  – Stereotactic body radiation therapy (SBRT)
  – Clinical Trial: MRI guided focused ultrasound

• Clinical advanced disease (definitive or postoperative):
  – Standard External beam radiation + androgen deprivation therapy (ADT)
  – Standard External beam + brachytherapy boost + ADT (ASCENDE Trial)

• Post radical prostatectomy:
  • Adjuvant Radiation for high risk prostate cancer features (pT3 (extracapsular extension, seminal vesicle involvement, positive margins)
  • Salvage Radiation for PSA recurrence
  • Standard External beam radiation + ADT
  • Prostate bed SBRT + ADT
  • Oligometastatic disease: early stage IV: SBRT to metastatic sites
## Staging: AJCC 8th edition / Metastatic Disease

<table>
<thead>
<tr>
<th>Group</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>PSA (ng/mL)</th>
<th>Grade Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>cT1a-c</td>
<td>NO</td>
<td>MO</td>
<td>PSA &lt;10</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>cT2a</td>
<td>NO</td>
<td>MO</td>
<td>PSA &lt;10</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>pT2</td>
<td>NO</td>
<td>MO</td>
<td>PSA &lt;10</td>
<td>1</td>
</tr>
<tr>
<td>IIA</td>
<td>cT1a-c</td>
<td>NO</td>
<td>MO</td>
<td>PSA ≥10 &lt;20</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>cT2a</td>
<td>NO</td>
<td>MO</td>
<td>PSA ≥10 &lt;20</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>pT2</td>
<td>NO</td>
<td>MO</td>
<td>PSA ≥10 &lt;20</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>cT2b</td>
<td>NO</td>
<td>MO</td>
<td>PSA &lt;20</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>cT2c</td>
<td>NO</td>
<td>MO</td>
<td>PSA &lt;20</td>
<td>1</td>
</tr>
<tr>
<td>IIB</td>
<td>T1-2</td>
<td>NO</td>
<td>MO</td>
<td>PSA &lt;20</td>
<td>2</td>
</tr>
<tr>
<td>IIC</td>
<td>T1-2</td>
<td>NO</td>
<td>MO</td>
<td>PSA &lt;20</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>T1-2</td>
<td>NO</td>
<td>MO</td>
<td>PSA &lt;20</td>
<td>4</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3-4</td>
<td>NO</td>
<td>MO</td>
<td>Any PSA</td>
<td>1-4</td>
</tr>
<tr>
<td>IIIC</td>
<td>Any T</td>
<td>NO</td>
<td>MO</td>
<td>Any PSA</td>
<td>5</td>
</tr>
<tr>
<td>IVA</td>
<td>Any T</td>
<td>N1</td>
<td>MO</td>
<td>Any PSA</td>
<td>Any</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>Any PSA</td>
<td>Any</td>
</tr>
</tbody>
</table>

*Note: When either PSA or Grade Group is not available, grouping should be determined by T category and/or either PSA or Grade Group as available.*

**Grade Group**

<table>
<thead>
<tr>
<th>Grade Group</th>
<th>Gleason Score</th>
<th>Gleason Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≤0</td>
<td>≤3+3</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>3+4</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>4+3</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>4+4, 3+5, 5+3</td>
</tr>
<tr>
<td>5</td>
<td>9 or 10</td>
<td>4+5, 5+4, 5+5</td>
</tr>
</tbody>
</table>
Conventional Management of Metastases: Systemic therapy

- Castrate Naive
  - Orchiectomy or LHRH agonist ± antiandrogen(s) ≥ 27 days to prevent testosterone flare or LHRH agonist + antiandrogen(s) or M1 → LHRH antagonist(s) or ADT and docetaxel 75 mg/m² for 6 cycles (category 1) or ADT and abiraterone with prednisone (category 1)
  - No XRT use in early stage IV NCCN

- Castrate resistant
  - Consider tumor testing for MSI-H or dMMR
  - Consider genetic counseling and germline testing for homologous recombination gene mutations
  - Continue ADT to maintain castrate levels of serum testosterone (<50 ng/dL)
  - Additional treatment options:
    - Bone antiresorptive therapy with denosumab or zoledronic acid (both category 1) if bone metastases present
    - Immunotherapy with sipuleucel-T (category 1)
    - Abiraterone with prednisone (category 1)
    - Docetaxel (category 1)
    - Epoetin alfa (category 1)
    - Radium-223 for symptomatic bone metastases (category 1)
    - Clinical trial
    - Other secondary hormone therapy
  - Palliative RT for painful bone metastases
  - Best supportive care
Stage IV Prostate Cancer

- Not all stage IV prostate cancer the same
- HORRAD Trial (2018 ASCO GU abstract, Boeve et al 2018)
  - Primary bone metastatic
  - Randomized trial: stage IV. ADT vs. ADT+EBRT to prostate
  - 67yo
  - 432 patients
  - f/u: 47mos
  - 63% had >5 osseous mets
  - Median OS: 45mos xrt prostate vs. 43 mos with ADT alone
  - Multivariate: maybe trend for patients with lower psa, oligomets (<5 bone lesions), and GS <9.
Oligometastases

- Hellman & Weischelbaum 1995
- University of Chicago
- Observation of patients with metastatic disease having limited metastases
- Intermediate state of cancer spread
Oligometastases: Not all stage IV are the same

- Many definitions used in literature.
Management of metastases: radiation for prostate bone metastases

- Standard conventional radiation
- Low dose radiation
- Goal: palliation, pain and symptom management
- Risk: minimal has been used for decades

- Stereotactic body radiation therapy (SBRT)
- High dose radiation
- Goal: ablative to tumor
- Risk: more risk to critical organs nearby so cannot apply SBRT to all
- Has been used for oligometastatic prostate cancer
SBRT (stereotactic body radiation therapy)

- Conventional low dose: 2Gy, 3Gy per fraction per day
- SBRT: 9Gy, 10Gy per fraction per day
- Similar to IMRT planning in that goal is to avoid critical organs but SBRT the dose is higher and given over 1-5 days (versus IMRT is given over 5-8 weeks)
Radiation: conventional versus SBRT

90% radiation dose
3Gy x 10days
versus
10Gy x 3days
Radiation: conventional versus SBRT
Radiation: conventional versus SBRT
SBRT protocols for metastatic prostate cancer

- SBRT
  - NRG-RTOG – BR 001 (IRB #14297)
  - STOMP
  - ORIOLE

- SBRT combined with Radium-223
  - My Investigator Initiated Trial funded by Bayer
NRG-BR001: NCT02206334 (IRB #14297)
A Phase 1 study of SBRT for the treatment of multiple (oligo) metastases

Primary: breast, lung, prostate ≤ 4 metastases

- Accruing toward goal of 84 patients

Treat all metastases with SBRT
Treat primary site per standard of care
Phase I: SBRT Multiple Site Design

3-4 metastases:
Each ≤ 5cm diameter

2 metastases:
Within ≤ 5cm of each other
Each ≤ 5cm diameter

Surgical resection of 1 metastasis

No surgical resection

SBRT to all remaining known metastases (1-4)

Phase I: 36-72 patients
Target dose and credentialing

1) Multiple Treatment Sites
2) Varying dose/fraction

<table>
<thead>
<tr>
<th>Metastatic Locations</th>
<th>Initial Starting Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung—Peripheral</td>
<td>45 Gy (3 fractions)</td>
</tr>
<tr>
<td>Lung—Central</td>
<td>50 Gy (5 fractions)</td>
</tr>
<tr>
<td>Mediastinal/Cervical Lymph Node</td>
<td>50 Gy (5 fractions)</td>
</tr>
<tr>
<td>Liver</td>
<td>45 Gy (3 fractions)</td>
</tr>
<tr>
<td>Spinal/Paraspinal</td>
<td>30 Gy (3 fractions)</td>
</tr>
<tr>
<td>Osseous</td>
<td>30 Gy (3 fractions)</td>
</tr>
<tr>
<td>Abdominal-pelvic metastases (lymph node/uterine gland)</td>
<td>45 Gy (3 fractions)</td>
</tr>
</tbody>
</table>
STOMP

Eligible:
1. Symptoms
2. <=3 bone metastases
3. No visceral metastases

Randomize

Metastasis directed therapy (MDT) to all metastatic sites (SBRT and/or surgery)

Observation

Primary endpoint: ADT free survival
STOMP Results

- 62 patients enrolled in 3 years (2012-2015)
- Median followup: 3 years
- ADT-free survival
  - Observation arm: 13 months
  - MDT (SBRT and or surgery): 21 months
- Quality of life similar in both groups
- 6 grade 1 toxicities in the MDT group (no grade 2-5 toxicities!)
- Consider MDT therapy in future phase III trials
  - (surgery and or radiation alone for stage IV M1)
ORIOLE

Eligible:
1. Symptoms
2. <= 3 bone metastases
3. No visceral metastases

• Primary endpoint: progression at 6 months

SBRT to all metastatic sites

Observation
Summary of SBRT Trials

- Goal: eradicate all tumor in metastatic prostate cancer patients in oligometastatic state (i.e. <=3 metastases)
- Hope that SBRT radiation alone is enough to delay patients needing chronic systemic treatment
- Newer trials in medical oncology incorporate chemotherapy for newly diagnosed metastatic prostate cancer patients
- How to balance systemic treatment versus metastasis directed therapy (SBRT/Surgery)?
- Micrometastases not visualized not treated by SBRT
Oligometastatic prostate cancer

- SBRT can treat gross tumor that we can visualize on imaging (CT, bone scan, prostate specific PET scans)
- Bone metastases ~90% of all prostate cancer metastases

- What about **micrometastases** that SBRT does not eradicate?
- Radium-223
- “Radiation Injection”
- Similar to samarium, strontium but shorter range of penetration so less damage to bone marrow theoretically (and shown clinically with less drop in blood counts)
Radium-223

- Analog of calcium
Ra-223 deposited into bone metastases.

- Deposited into bone metastases by osteoblasts that are activated by tumors.
- Emits alpha particles, with short range.
ALSYMPCA trial: phase III trial of Ra-223 in symptomatic prostate cancer

Eligible:
1. Symptoms
2. $\geq 2$ bone metastases
3. No visceral metastases
4. Previously received docetaxel (or unfit)

Randomize

Ra-223 (50 kBq/kg) + standard of care

Placebo (saline) + standard of care

Median overall survival
14 months

11.2 months
P=0.002
Radium-223

- Administered as radiation injection (now 55kBq/kg standard)
- ~Slow IV push 1min
- 1 injection per month for 6 months total
- Can only be given once in a patient lifetime currently
- **Recent abstract about giving Radium-223 twice (Emory et al)**
Trials with Radium-223

- Immunotherapy combination: i.e. Atezolizumab with radium-223
- Niraparib + radium-223
- Exemestane/everolimus + radium-223 in breast cancer patients
- Multiple myeloma: bortezomib+dexamethasone + radium-223
- Bladder cancer
Combine SBRT and Radium-223 and ADT

- Investigator initiated trial with Bayer as sponsor
- A Phase 2 Trial of Radium Ra 223 Dichloride in Combination With Androgen Deprivation Therapy and Stereotactic Body Radiation Therapy for Patients With Oligometastatic Castration Sensitive Prostate Cancer
- IRB #17085
- Clinical Trials.gov: NCT03361735
- Using Radium-223 off label – Radium 223 given to patients early in their metastatic disease presentation (i.e. before chemotherapy docetaxel, before other ADT drugs)
Combine SBRT and Radium-223 and ADT
IRB#17085

Eligible:
1. Symptoms
2. <=4 bone metastases
3. No visceral metastases

ADT for 9 months
SBRT to all metastatic sites
Radium-223

Radiation dose:
9Gy x 3 to bone

Other mets/single:
10Gy x 5 (one lung)
5Gy x 5 (lymph node)

Primary endpoint: Progression free survival with limited treatment 9 months total
Stage M1 Oligometastatic Castration-Sensitive Prostate Cancer
with 54 metastatic lesions:
- Must have at least 1 bone lesion and each non-visceral lesion should be less than 5 cm.
- Visceral lesions will be limited to one lung lesion (<2cm); no liver lesions allowed.
24 participants

Protocol Therapy (Cycle = 28 days)*

Androgen Deprivation Therapy (ADT) = 36 weeks

Follow-up = 5 years

Stereotactic body radiation therapy (Cycle 1)
Day 1, then dosing administered minimum every 40 hours over 7-21 days
- 9Gy x 3 fractions (bone lesions)
- 5Gy x 5 fractions (lymph node lesions)
- 10Gy x 5 fractions (lung lesions)

Radium Ra 223 dichloride (55 kBq/kg)
Slow IV over 1 minute
Cycles 2-7: Day 1

ADT: Leuprolide OR goserelin
Per physician discretion and package insert

Response Follow-up
Until progression/initiation of new anti-cancer therapy
- every 3 months
- PSA
- Long-term toxicities
- every 6 months
- Tumor evaluation^  
^ Also at time of PSA progression
Study Overview: ADT+SBRT+Radium-223

- **Purpose:** hypothesize that aggressive treatment of oligometastatic disease with combination of ADT+SBRT+Ra223 will improve treatment outcomes, delay disease progression, and delay castration resistant phenotype.

- **Goal SBRT:** ablate gross tumor
- **Goal Radium-223:** control micrometastases
- **Goal ADT (9 months):** ablate gross and micrometastases tumor, additive with radiation
ADT+SBRT+Radium223

- Bayer: Investigator Initiated Trial
- Phase II
- 24 patients
- 1-4 metastases
- Accrual: 16 months
- 60 months follow-up

- ADT can be started in outside clinic 1 month before trial starts (outside referrals)
Study Overview

- Objectives:
  - To assess the time to treatment failure (TTF) in oligometastatic patients who receive ADT+SBRT+ at least one dose of Ra223 (standard Ra223 dose 6 cycles)
  - Goal: TTF of at least 25 months (9 month improvement over historical data)

- 2nd objectives:
  - assess biomarkers before and after administration of SBRT
  - Bone specific progression free survival
  - PSA control
  - 5 year toxicity assessment

- 2 patient accrued thus far
Conclusion

• SBRT gives ablative radiation to tumor in attempt to eradicate the metastatic tumor instead of just palliation
• SBRT is given in 1-5 days of radiation versus 2-5 weeks of conventional palliative radiation for metastatic disease (or 8 weeks for primary prostate cancer)
• SBRT as definitive treatment for early prostate cancer is feasible and with rectal SpaceOAR can limit toxicity risk
• SBRT for oligometastatic prostate cancer is feasible and can delay time to systemic treatment for certain subset of patients
• Radium-223 can be given for patients with metastatic prostate cancer for pain relief
• Radium-223 is easily administered
• Radium-223 is FDA approved to be given after progression on other lines of metastatic prostate cancer treatment and usually to castrate resistant prostate cancer patients
• Radium-223 can provide pain relief from bone metastases and help delay skeletal related events
• This talk did discuss use of Radium-223 on investigator initiated trial (IRB #17085) sponsored by Bayer in castrate sensitive prostate cancer patients
Future studies

• Identifying true oligometastatic patients
  – Biomarker studies, genetic testing
• Identifying best candidates for SBRT studies (prostate, prostate bed, oligomets)
• Identifying patient’s risk of radiation toxicities/sensitivities to individualize prostate treatment
Acknowledgements

- **Medical Oncology**
  - Przemyslaw Twardowski
  - Tanya Dorff
- **Radiation Oncology**
  - Jeffrey Wong
  - Nayana Vora
  - Eric Radany
  - Yi-Jen Chen
  - Sagus Sampath
  - Arya Amini
  - Scott Glaser

- **Physics/Dosimetry**