ARRO-Case
Postoperative Radiotherapy in Prostate Cancer

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Case: HPI

64 year old man with ↑PSA (1.1 in 2007 → 9.0 in 2013). Asymptomatic aside from nocturia once per night. Normal GI/GU ROS, no erectile dysfunction

- ROS, PMHx, PSHx, Meds: unremarkable.
- FHx: No family history of cancers

- SHx: Married, artist, no tobacco/ETOH/drugs, 2 kids

- Physical exam: external genitalia normal, DRE reveals good tone, no blood, small prostate without nodule
Case: TRUS Biopsy

• 12 core biopsy
• Right lower: adenocarcinoma, GS 7= 4+3 in 2/2 cores
• Right upper: no pathologic abnormality
• Left lower: no pathologic abnormality
• Left upper: no pathologic abnormality

• cT1cNxMx, initial PSA 9, GS 7= 4+3
• AJCC Group IIA
• NCCN Intermediate Risk

GS = Gleason Score
AJCC Staging

Primary Tumor

T1 – clinically unapparent by palpation or imaging
  T1a: incidental histologic finding in ≤ 5% tissue resected
  T1b: incidental histologic finding in > 5% tissue resected
  T1c: identified by needle biopsy

T2 – Tumor confined to within prostate
  T2a: unilateral, involves ≤ one-half of one lobe
  T2b: unilateral, involves > one-half of one lobe
  T2c: bilateral, involves both lobes

T3 – Tumor extends through prostate capsule
  T3a: extracapsular extension (EPE)
  T3b: seminal vesicle invasion (SVI)

T4 – Tumor fixed or invades other structures (e.g. Bladder, rectum, pelvic wall)

Regional Lymph Nodes

Nx – lymph nodes not assessed
N0 – no regional lymph node metastasis
N1 – metastasis in regional lymph nodes*

Distant Metastases

Mx – metastatic disease not assessed
M0 – no distant metastasis
M1 – distant metastasis
  M1a: non-regional lymph nodes**
  M1b: bone
  M1c: other sites with or without bone disease

*Regional lymph nodes: pelvic, hypogastric, obturator, iliac (internal, external), sacral

**Non-regional lymph nodes: aortic, common iliac, inguinal (deep), inguinal (superficial, femoral), supraclavicular, cervical, scalene, retroperitoneal

Per AJCC, clinical stage may be diagnosed by DRE (digital rectal exam) or imaging (such as MRI). For research purposes, specify the T stage by DRE only or by DRE and imaging.
AJCC Grouping

• **Group I**:  
  T1a-c, PSA < 10, G ≤ 6  
  T2a, PSA < 10, G ≤ 6  
  T1-2a, PSA X, G X

• **Group IIA**:  
  T1a-c, PSA < 20, G = 7  
  T1a-c, PSA 10-19, G ≤ 6  
  T2a, PSA < 20, G ≤ 7  
  T2b, PSA X, G X

• **Group IIB**:  
  T2c, any PSA, any G  
  T1-2, PSA ≥ 20, any G  
  T1-2, any PSA, G ≥ 8

• **Group III**:  
  T3a-b, any PSA, any G

• **Group IV**:  
  any T4  
  any N1  
  any M1

*When either PSA or Gleason is unavailable, grouping should be determined by T stage and or PSA/Gleason as available.*
NCCN Risk Groups

- **Very low:**
  - T1c, G ≤ 6, PSA < 10, < 3 core biopsies positive
  - ≤50% cancer in each core, PSA density ≤0.15ng/mL/g

- **Low:**
  - T1-T2a, G ≤ 6, PSA < 10

- **Intermediate:**
  - T2b-T2c, G = 7, PSA 10-20

- **High:**
  - T3a, G 8-10, PSA > 20

- **Locally Advanced:**
  - T3b – T4

- **Metastatic:**
  - Any N1 or any M1
Treatment options for intermediate risk

• For expected survival >10 years
  – Radical prostatectomy (RP) + nodal dissection
  – EBRT +/- short term ADT +/- brachytherapy
  – Brachytherapy alone

• The patient went on to receive a radical prostatectomy and nodal dissection
Case: Radical Prostatectomy

- **Prostate**: Gleason 7=4+3 prostatic adenocarcinoma involving 15% of prostate, 1cm dominant, focal **EPE at apical margin (positive margin)**, no seminal vesicle invasion, no lymph vascular space invasion
- **Bilateral iliac lymph nodes**: 3 benign nodes
- **pT3aN0 Mx with + apical margin**
- AJCC Group III
- NCCN High risk
Adverse Pathologic Features

• Factors predicting biochemical recurrence\(^3-7\):
  1. pT3a (EPE)*
  2. pT3b (SVI)*
  3. Positive margin*
  4. Detectable postoperative PSA*
  5. Gleason 8-10*
  6. Nodal involvement
  7. High pre-operative PSA
  8. PSA-DT \(\leq 10\) months and, especially, \(< 3\) months
  9. PSA Velocity \(> 2\)ng/mL/year

* NCCN adverse features
Adverse Pathologic Features

• Highest risk of recurrence:
  1. Seminal vesicle invasion (SVI)\textsuperscript{11}
  2. Extra-prostatic extension (EPE)\textsuperscript{11}
  3. Positive surgical margins\textsuperscript{11}
  4. Detectable postoperative PSA\textsuperscript{9}
  5. Gleason 8-10\textsuperscript{9}
Post-RP Options (NCCN)

1. Adjuvant radiation therapy (ART)

2. Observation with salvage radiation therapy (SRT) if needed
Post-RP Options

1. ART – before recurrence
   - Immediate post-operative
   - Allows for potential overtreatment

2. SRT – after recurrence
   - Serial monitoring of PSA and select SRT for PSA failure
   - Risk of PSA rising rapidly and compromising effectiveness of RT
   - For high grade tumors, may risk metastasis due to delay in therapy
ART or Observation?

• 15-60% of patients develop PSA failure after RP

• Rising PSA after RP:
  • 1/3 will develop DM at median of 8 years
  • 17% will die of prostate cancer within 15 years

• However, ART risks ↑toxicity and ↑cost

• Can upfront post-operative RT reduce distant failure?
Evidence for ART

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>SWOG 8794</th>
<th>EORTC 22911</th>
<th>ARO 96-02</th>
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</thead>
<tbody>
<tr>
<td>Post-RP pT3N0 or +margin</td>
<td>Post-RP pT2-3N0 with extra-capsular disease (+margin, ECE, SVI)</td>
<td>Post-RP pT3N0 or +margin randomized prior to post-op PSA</td>
<td></td>
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<tr>
<td>Randomization Arms</td>
<td>60-64Gy vs observation</td>
<td>60Gy vs observation</td>
<td>60Gy vs observation</td>
</tr>
<tr>
<td>Follow-Up interval</td>
<td>15 years</td>
<td>10 years</td>
<td>10 years</td>
</tr>
<tr>
<td>Results</td>
<td>RT improved DMFS (43% v 54%) *</td>
<td>RT improved bPFS (61% v 41%)*</td>
<td>RT improved bPFS (56% v 35%)*</td>
</tr>
<tr>
<td></td>
<td>RT improved LRF (8% v 22%)</td>
<td>RT improved LRR (7% v 17%)</td>
<td>No significant difference in DMFS or OS (not powered to detect these differences)</td>
</tr>
<tr>
<td></td>
<td>RT improved OS (74% v 66%)</td>
<td>No difference in DM, OS, or CSS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RT improved clinical progression-free survival</td>
<td>RT improved clinical progression-free survival</td>
<td></td>
</tr>
<tr>
<td>Toxicity</td>
<td>GU symptoms and Global QoL initially worse with RT, but no difference at 5 years RT arm higher: urethral stricture, total incontinence, proctitis</td>
<td>Acute: Grade 2 (20%), Grade 3 (≤5%) Late: Grade 2 (10%), Grade 3 (≤2%)</td>
<td>Acute: Grade 2 (12%), Grade 3 (3%) Late: Grade 2 (5%), Grade 3 (1%)</td>
</tr>
</tbody>
</table>

*primary end-point
ART Summary

• If adverse risk factors are present, then adjuvant RT reduces the risk of:
  – biochemical recurrence
  – local recurrence
  – clinical progression of cancer
  – improves OS and distant mets

• If any adverse risk factors are present (see slide 11), ART should be offered as an option$^{13,14}$
# Evidence for SRT

<table>
<thead>
<tr>
<th></th>
<th>Trock et al</th>
<th>Boorjian et al</th>
<th>Stephenson et al</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>Post-RP</td>
<td>Post-RP</td>
<td>Post-RP</td>
</tr>
<tr>
<td></td>
<td>Median PSA ~0.8</td>
<td>Biochemical recurrence</td>
<td>Median PSA 1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median PSA ~ 0.8</td>
<td>51% margin+, 22% GS 8+, 3% N1</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>SRT v observation</td>
<td>SRT v observation</td>
<td>SRT all</td>
</tr>
<tr>
<td></td>
<td>Median RT dose 66.5 Gy</td>
<td></td>
<td>Median RT dose 64.8 Gy</td>
</tr>
<tr>
<td></td>
<td>12% received SRT + ADT</td>
<td>32% received SRT</td>
<td>14% received SRT + ADT</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>RT improved prostate-cancer specific survival (85% v 62%)</td>
<td>RT decreased local recurrence (~90%)</td>
<td>6 year progression-free probability 32%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT decreased risk of systemic progression (~75%)</td>
<td>If PSA &lt;= 0.5 at time of SRT: 6 year FFP 48%</td>
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<tr>
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<td>RT decreased late-ADT (~20%)</td>
<td>If PSA &gt; 0.5 at time of SRT: 6 year FFP 26%</td>
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March 2015
SRT Summary

• Consider re-staging evaluation in patient with PSA failure
  – i.e. Bone Scan and MRI Pelvis
  – Identify local recurrence v. metastatic disease

• SRT should be offered for local recurrence with no DMs\textsuperscript{2}

• SRT is most effective when pre-RT PSA is low
  - \(\leq 0.4\text{ng/mL}\) or at least \(\leq 1.0\text{ng/mL}\)\textsuperscript{15,16}

• If limited life expectancy or slow PSA rise, SRT may have limited benefit survival benefit over ADT or observation
Adjuvant RT? or Salvage RT?

• SRT exposes less patients to RT than an ART approach
• SRT may allow for disease progression
• The option of SRT potentially limits:
  – Toxicity (acute and late GU, GI, and sexual)
  – Cost

• Ongoing clinical trials to evaluate ART v SRT:
  – RADICALS
  – RAVES
Case: Postoperative course

- Post-op PSA <0.02, patient chose observation

- Patient’s PSA trend:

<table>
<thead>
<tr>
<th>Time since RP</th>
<th>3mo</th>
<th>6mo</th>
<th>12mo</th>
<th>15mo</th>
<th>18mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA (ng/mL)</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.12</td>
<td>0.16</td>
</tr>
</tbody>
</table>

- Re-staging CT Abdomen & Pelvis and Bone Scan: no evidence of disease
Post-RP PSA failure\textsuperscript{3, 9}

• PSA levels post-RP should be undetectable

• Biochemical Recurrence: PSA ≥ 0.2 ng/mL confirmed by a second determination ≥ 0.2

• ½ of men with PSA doubling time > 10-12 months will die from prostate cancer in 10-13 years
Post-op RT Recommendations

• **Treatment volume:** Prior trials used small-volume RT with no pelvic nodal irradiation. 
  (*RTOG 0534 is an ongoing post-op trial evaluating prostate bed RT alone +/-ADT versus pelvic lymph node RT + prostate bed RT + ADT*)

• **Dose:** > 64-65 Gy per ASTRO/AUA consensus panel (NCCN: 64-72Gy), but higher dose with high PSA or nodule
Case: Radiotherapy Technique

- Prostate fossa target atlas available through RTOG Contouring Atlas
- IMRT
- 68 Gy in 34 fractions
Planning Parameters (per RTOG 0534)

- Rectum
  - V65 < 35%
  - V40 < 55%
- Bladder (bladder minus CTV)
  - V65 < 50%
  - V40 < 70%
- Femoral Heads
  - V50 < 10%
Case: Toxicity & Follow up

- PSA: undetectable
- Grade II diarrhea improved with Carafate enemas and Imodium. 3 day treatment break due to this toxicity.
- 1 month follow up:
  - Grade I urinary leakage and frequency
- 6 month follow up:
  - Erectile Dysfunction – effectively treated with Tadalafil (Cialis)
- 1 year follow up:
  - Nocturia: x 2 per night
  - Urinary leakage/frequency: resolved
  - ED: stable
What about ADT?

• The data to support ADT + ART or SRT post-RP is still unclear

• Clinical Trials to evaluate this question:

  **RTOG 9601** – DFS advantage with 2 years of Bicalutamide$^{16}$

  **RTOG 0534** (SPPORT protocol) – open, to determine the advantage of ADT + post-op RT
What about ADT?

- If very unfavorable risk factors, it is reasonable to recommend ADT

- Logistics to consider:
  - ADT may obscure interpretation of PSA response
  - Significant side effects
    - RTOG 9601 with Bicalutamide: gynecomastia
    - RTOG 0534 with Lupron/Bicalutamide: weight gain, hot flashes, hyperglycemia, fatigue

March 2015
ASTRO/AUA
Key Recommendations

Please see the following recently published paper for Key Recommendations for Adjuvant and Salvage Radiotherapy After Prostatectomy:


RTOG Contouring Atlas

References

16. ASTRO Meeting abstract: Shipley WU, Hunt D, et al. Initial Report of RTOG 9601: A Phase III Trial in Prostate Cancer: Anti-androgen Therapy (AAT) with Bicalutamide during and after Radiation Therapy (RT) Improves Freedom from Progression and Reduces the Incidence of Metastatic Disease in Patients following Radical Prostatectomy (RP) with pT2-3, N0 Disease, and elevated PSA Levels. JROBP 2010; 78 (3).

ASSOCIATION OF RESIDENTS IN RADIATION ONCOLOGY

ARRO

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