Adjuvant and Salvage Radiation for Prostate Cancer

Savita Dandapani, MD, PhD
DISCLOSURES

I am a consultant for Reflexion, receive funding from Bayer, and on the Speaker’s Bureau with AstraZeneca.
Post-prostatectomy

• Localized prostate ca patients: 30% of patients progress (PSA) after prostate cancer within 10 years
• ~50% of high risk patients
• When does the PSA rise matter?
Post-prostatectomy radiation

- Adjuvant
- Salvage
- Stereotactic Body Radiation Therapy (SBRT)
- SBRT to prostate fossa
- SBRT to oligometastatic disease post-prostatectomy
## Post-prostatectomy Radiation Issues

<table>
<thead>
<tr>
<th>No tumor / PSA rise alone</th>
<th>Prostate bed vs. prostate bed+pelvic lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing after surgery (adjuvant vs. salvage)</td>
<td>Incorporating novel imaging/ fluciclovine and PSMA PET scans</td>
</tr>
<tr>
<td>Adding ADT</td>
<td>Genomic biomarker to predict recurrence risk</td>
</tr>
<tr>
<td>XRT dose: conventional/hypofractionation/SBRT</td>
<td></td>
</tr>
</tbody>
</table>

- No tumor / PSA rise alone
- Timing after surgery (adjuvant vs. salvage)
- Adding ADT
- XRT dose: conventional/hypofractionation/SBRT
- Prostate bed vs. prostate bed+pelvic lymph nodes
- Incorporating novel imaging/ fluciclovine and PSMA PET scans
- Genomic biomarker to predict recurrence risk
Adjuvant versus Salvage

• Adjuvant: high risk features after surgery, PSA undetectable
• Salvage: PSA >0.2 x 2. Newer studies use cutoff of 0.1
• New ?: ultrasensitive PSA testing at .008
Adjuvant Radiation

- 3 Randomized Trials
- High Risk Features:
  - Positive margins
  - Extracapsular invasion
  - Seminal vesicle invasion
3 Adjuvant Radiation Trials

- EORTC
- SWOG
- ARO
- XRT adjuvant vs. observation
- 60-64Gy
- +margins
- +ECE pT3a
- +SVI pT3b
• 1987
• 1st trial
• 425 men
• 10 yr Metastasis-free survival: 71% (XRT) vs. 61% (obs)
• 10 yr OS: 74% (XRT) vs. 66% (obs)
• Median bPFS 10yrs (XRT) vs. 3 yrs (obs)
EORTC 22911

- 307 men
- 10 yr PFS: 61% (XRT) vs. 41% (obs)
- Median bPFS 13 yrs (XRT) vs. 6 yrs (obs)
ARO 96-02

• Only true adjuvant study
• Modern treatment planning (vs. SWOG & EORTC)
• SWOG And EORTC had 30% of patients with PSA >0.2 so mix of adjuvant/salvage
• 10yr PFS 56% (XRT) vs. 35% (obs)
Adjuvant Radiation

- Adjuvant radiation ~20% benefit
- Overall survival seen in SWOG study but caveat is that 30% already had PSA >0.2
- So still question of when to treat adjuvantly?
- Our approach: we are referred patient early but we work in conjunction with urologist to determine when patient stable from urinary continent standpoint.
Post-prostatectomy XRT fields

• Prostate bed
• Hard to define
• RTOG consensus guidelines
• Margins/issue for how much normal bladder/rectum gets XRT
• Our approach: with daily IGRT can reduce margin on bladder and rectum
Post-prostatectomy XRT issues

- **GU:**
  - Incontinence
  - Our approach: wait until healed 3 months to 6 months *(monitor PSA)*

- **GI:**
  - Radiation proctitis
  - Less with IMRT and IGRT
Adjuvant vs. Early Salvage

- **RAVES (TROG)**
- Radiotherapy adjuvant (PSA <0.1) vs. early salvage (PSA 0.2)
- **RADICALS (UK Study)**
- Like other UK studies 5 arms: radiation early vs. salvage and +/- ADT (no ADT vs. 6 mos vs. 24 mos)
- Goal: assess equivalency of BcF and QOL
Adjuvant vs. Early Salvage

- JAMA 2018
- Retrospective – multi-institutional
- 1500+ pts → 1100 salvage xrt, 400 adjuvant xrt
- Adjuvant better for 12yr biochem control 40% vs. 70%, less mets 5% vs. 15%

Hwang et al JAMA Oncology 2018
Salvage Radiation

- RTOG 9601
- GETUG 16
- RTOG 0534 – ASTRO Fall 2018 Results!

Abstract
Salvage Radiation (after prostatectomy, PSA rising)

- 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>Biochem/PSA control</th>
<th>Distant metastases</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>GETUG 16/goserelin x 6 months</td>
<td>5yr biochem control (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>(Carrie et al Lancet 2016)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG 9601/bicalutamide x 2 years</td>
<td>12yr 2nd biochem recurrence (44% vs. 68% 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>
<tr>
<td>(Shipley et al NEJM 2017)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
RTOG 9601

OS
Takes long time to report on OS in prostate
1996 trial reported in 2017
12 yr OS
71% vs. 76% (+casodex)
12 yr death from prostate cancer
13% vs. 6% (+casodex)
Salvage Radiation Fields

- Prostate bed only
- Prostate bed + Pelvic Lymph nodes
- Other?
- Next eschelon lymph nodes: Paraaortic, oligomet bones
How I treat Salvage Radiation

PSA

Gleason Score

Adverse Risk Factors

Pelvic Lymph node dissection

PET scan identify any source of PSA?

: prostate fossa vs. prostate fossa+pelvic lymph nodes
RTOG 0534

- 3 arms
- Prostate bed
- Prostate bed +ADT
- Prostate bed +pelvic lymph nodes +ADT
- Late breaking abstract at ASTRO 2018
RTOG 0534

- 3 arms:
  - Prostate bed
  - Prostate bed + ADT 4-6 mos
  - Prostate bed + pelvic lymph nodes + ADT 4-6 mos
RTOG 0534

- Modern radiation
- Consensus definition on prostate bed fields
- 87% used IMRT fields
- 45Gy pelvis
- 64.8-70.2Gy pelvis + prostate bed (68Gy)
- ADT: antiandrogen + LHRH agonist
RTOG 0534

- More is better!
- 1800 pts
- 50% T2! 25% T3a (80% not very high risk!)
- 70% GS 7 (more 3+4)
- LND: mean 7

- Mean PSA: 0.34
- 26% actually adjuvant PSA 0.1-0.2
- Prostate bed + pelvic lymph nodes + ADT did best!
RTOG 0534

- 16% benefit of biochem control for adding pelvic lymph node radiation and ADT to PBRT
  - 5yr biochem control
  - PBRT: 71%
  - PBRT+ADT: 81%
  - PBRT+pelvic lymph nodes+ADT: 87%

- 3% less mets
- Less benefit of adding pelvic lymph nodes if PSA is <0.34 (early salvage)
Cost of adding Pelvic Lymph Nodes

- Slightly more toxic:
- Acute:
- Grade 2 GI 7% (2%)
- Grade 2&3 Bone Marrow 8% (3%)
- Late:
- Only grade 2 bone marrow 4% (3%)
RTOG 0534

• Going back to treating more pelvic lymph nodes (NNT 6 to prevent 1 BcF!)
• New imaging may change this! i.e. finding oligometastatic disease in lymph nodes on imaging
• Axumin/Fluciclovine PET
• PSMA PET
Salvage Prostate Radiation: Quicker?

- Hypofractionated radiation
- Stereotactic body radiation treatment (SBRT)
Hypofractionated salvage radiation post-prostatectomy

- Clinical Trial
- Treatment days: 38 days standard vs. 20-28d even 5 days!
- Caveat: no gross tumor so giving higher dose per fraction to a larger area of normal bladder and rectum
- Short term followup – need longer term followup to validate use
- If safe then it would decrease cost
Hypofractionated salvage XRT

• Radiation Doses: 50/20d, 72.8/29d
• Main concern GU side effects with hypofx:
  • 7% vs. 18% (1000pts studied one study)
  • Urethral stenosis
  • Bladder neck strictures
• Issue: larger margins with postop vs. definitive xrt
• Pelvic LN: few do hypofx, if added still at standard XRT doses 1.8-2Gy/day

Cozzarini et al Eur Urol 2014
Hypofractionated Prostate XRT

• Need for longer followup
• Concern for toxicity because we use larger margins in postop setting
• Biochem control not better
• Risk/benefit ratio not there yet…
• Maybe new PET can help us localized xrt and we can use hypofx
3 Hypofx Trials to watch for!

- SHARP
  - 31Gy/5fx adjuvant
  - 32.5Gy/5fx salvage
- PRIAMOS
  - 54Gy/18fx
  - +/-pelvic LN
- Virginia University
  - 65Gy/26fx
  - 42.6Gy/10fx
Salvage Prostate Radiation: Even Quicker?

- Stereotactic Body Radiation Treatment
- SBRT
- High radiation dose/fraction
- Less number of days
- Not really cheaper!
- More testing idea that prostate slow growing needs more dose/fraction to ablate
Radiation: conventional versus SBRT

SBRT: advantage: treat less normal tissue. Risk: high dose radiation to nearby critical structures.
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)
- Risk: at least 1 patient had ureter injury at ureter insertion to bladder neck
Postop XRT

• Main issue: we can’t see what we are treating!
New Imaging

- Axumin/Fluciclovine PET
- PSMA PET
- Detect oligometastatic disease earlier
- Data emerging to still treat the primary prostate of stage IV prostate cancer (i.e. prostatectomy or radiation)
Post-prostatectomy/2 recent examples on oligomet prostate trial

CT and Bone Scan negative: Axumin identified 3 lesions. MRI confirmed lesions.
CT and Bone Scan negative: PSMA identified 1 lesion. MRI confirmed lesion.
Genomics

- Genome Dx
- Decipherx
- Post-prostatectomy: determine risk of metastasis (independent of PSA and Gleason Score)
- May also lead to more restaging post-prostatectomy to identify oligometastases
- With combo of genomics & novel PET scans: I think we may identify more oligometastases this way!
High Risk: recommend adjuvant or early salvage radiation

22 RNA expression
**Oligometastatic prostate cancer**

- Primary prostate controlled (prostatectomy or radiation)
- Oligomets: Intermediate stage
- I think of this as another treatment post-prostatectomy!
Oligometastatic prostate cancer

- Oligometastatic disease: generally less than 5 visible metastatic lesions
- SBRT can treat gross tumor that we can visualize on imaging (CT, bone scan, prostate specific PET scans – axumin and PSMA)
- *micrometastases* that SBRT does not eradicate? Or that we cannot seen on current imaging?
- Radium-223
- “Radiation Injection”
- Similar to samarium, strontium but shorter range of penetration (alpha) so less damage to bone marrow theoretically (and shown clinically with less risk of drop in blood counts)
Post-prostatectomy
Combine SBRT and Radium-223 and ADT
IRB#17085

Eligible:
1. Symptoms
2. \( \leq 4 \) bone metastases
3. One LN met ok
4. No visceral metastases

Radiation dose:
- ADT for 9 months
  - SBRT to all metastatic sites
  - Radium-223
- Other mets/single:
  - 10Gy x 5 (one lung)
  - 5Gy x 5 (lymph node)

- Primary endpoint: Progression free survival with limited treatment
- (9 months total of treatment vs. indefinite hormones/systemic treatment!)
STOMP Trial

- Oligometastases post definitive treatment of prostate (surgery or radiation)
- SBRT/Surgery to oligometastases versus observation
- No ADT
- Results (Time to ADT initiation):
  - SBRT/surgery: 21 mos
  - Observation: 13 mos
- Local treatment to mets can delay need for ADT
- Better QOL!
Future studies

- Molecular subtyping of prostate cancer to determine who has highest risk of local recurrence versus metastasis
- Better imaging to assess oligometastasis before prostate therapy
- Better imaging to determine where to target radiation post-prostatectomy
- Identifying true oligometastatic patients
- Identifying best candidates for SBRT studies
- 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