SBRT for Prostate Cancer

Casey Williamson, MD, MAS
Assistant Professor, Radiation Medicine @ OHSU

March 03, 2023
Disclosures

• Employment: OHSU
Learning Objectives

• Definition of, rationale for SBRT in prostate cancer
• Indications for definitive SBRT
• Efficacy and toxicity data
• SBRT for re-irradiation
• Upcoming directions and studies
What is SBRT?

- Stereotactic Body Radiation Therapy
- Precise delivery of high dose to a localized target
- ≤5 treatment fractions
- Used routinely in other settings (lung, brain, GI, mets)
- Reliant on good imaging
- Close attention to dose to nearby organs (rectum, bladder, others)
Conformal Dose Distribution
Fractionation in Prostate Cancer

- **Conventional** fractionation: ~78 Gy in 39 fractions
- **Hypofractionation** = fewer fractions
  - **Moderate** hypofractionation: 70 Gy in 28 fractions, 60 Gy in 20 fractions
  - **Ultra**hypofractionation (AKA SBRT): 36.25 Gy in 5 fractions
Rationale for Prostate SBRT

- Tissues have differential sensitivities to total dose and fractionation: $\alpha/\beta$ ratio
- Prostate cancer felt to have a low $\alpha/\beta$; may imply benefit to hypofractionation
- Patient convenience, cost
- Highly conformal dose
Hesitancy with SBRT

• Long-term follow-up not as robust
• Higher dose, fewer fractions → less room for error
• ? Relative toxicity
• Use by risk group
# NCCN & Prostate SBRT

## NCCN Guidelines Version 1.2023

### Prostate Cancer

#### PRINCIPLES OF RADIATION THERAPY

*Table 1: Below are examples of regimens that have shown acceptable efficacy and toxicity. The optimal regimen for an individual patient warrants evaluation of comorbid conditions, voiding symptoms and toxicity of therapy. Additional fractionation schemes may be used as long as sound oncologic principles and appropriate estimate of BED are considered.*

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### General Principles

- **EBRT**
  - Moderate Hypofractionation
    - **Regimen:** 3 Gy x 20 fx
    - **Preferred Dose/Fractionation:** 2.7 Gy x 28 fx
    - **Conventional Fractionation:** 1.8-2 Gy x 37-45 fx
      - **EBRT Ultra-Hypofractionation:**
        - 9 Gy x 4 fx
        - 7.25-8 Gy x 6 fx
        - 6.1 Gy x 7 fx
        - 6 Gy x 8 fx
  - **NCCN Risk Group:**
    - Very Low and Low
    - Favorable Intermediate
    - Unfavorable Intermediate
    - High and Very High
    - Regional N1
    - Low Volume M1<br>

- **Brachytherapy Monotherapy**
  - **LDR**
    - Iodine 125
      - 145 Gy
    - Palladium 103
      - 125 Gy
    - Cesium 131
      - 115 Gy
  - **HDR**
    - Iodulum-152
      - 13.5 Gy x 2 implants
      - 9.5 Gy BED x 2 implants
  - **EBRT and Brachytherapy (combined with 45-50.4 Gy x 25-28 fx or 37.5 Gy x 15 fx)**
    - **LDR**
      - Iodine 125
        - 110-115 Gy
      - Palladium 103
        - 90-100 Gy
      - Cesium 131
        - 85 Gy
    - **HDR**
      - Iodulum-152
        - 16 Gy x 1 fx
        - 10.75 Gy x 2 fx

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*High-volume disease is differentiated from low-volume disease by visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis vertebral column. Patients with low-volume disease have less certain benefit from early treatment with docetaxel combined with ADT.*
Utilization of Prostate SBRT

- National trends approach 20% utilization for low and intermediate risk
Review of Recent Data
SBRT vs. Longer Course RT
HypoRT

- Randomized, phase 3, non-inferiority trial
- 12 centers in Sweden and Denmark
- 1,200 men with mostly intermediate risk prostate cancer (small number of high risk)
- Treated with either:
  - SBRT 42.7 Gy in seven fractions every other day
  - Conventional RT: 78 Gy in 39 fractions
- No ADT allowed
HypoRT

• Only 20% used IMRT/VMAT
• MRI recommended but not mandatory
• 4 mm posterior margin
• No hydrogel spacers
Outcomes

• Median follow-up 5 years
• 5 yr FFS:
  – SBRT: 84%
  – RT: 84% (NS)
• 5 yr OS:
  – SBRT: 94%
  – RT: 96% (NS)

Widmark et al. Lancet 2019
HypoRT – urinary toxicity

• Patient-reported higher GI and GU problems at end of treatment with SBRT
  – Grade 2+ acute GU toxicity (p=0.057):
    – SBRT: 28%
    – RT: 23%
• Grade 2+ GU toxicity at 1 year (p=<0.01)
  – SBRT: 6%
  – RT: 2%
• No difference in grade 2+ GU toxicity at 5 yrs (5%)
HypoRT – GI toxicity

- Grade 2+ acute GI toxicity:
  - SBRT: 28%
  - RT: 23%

- Grade 2+ GI toxicity at 1 year
  - SBRT: 1%
  - RT: 4%
HypoRT – erectile function

![Graph showing patient-reported problems over time with two treatments: conventional fractionation and ultra-hypofractionation. The graph includes data points and error bars for symptom severity at different time intervals (baseline, treatment end, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years). The number of patients assessed for each time point and the p-values for the comparison between treatments are also provided.]
HypoRT – conclusions & questions

• Noninferior failure-free survival
• Acute side effects more pronounced, late side effects similar
• Relatively short follow-up
• 11% high risk
• Applicability to 5 fraction US-style SBRT?
• Benefit to MRI, rectal spacer, smaller margins?
• Phase 3 trial at 35 hospitals in UK, Ireland, Canada
• Low/IM risk disease (but excluded GS 4+3)
• 874 men randomized between SBRT (36.25 Gy/5 fractions) vs. conventional fractionation (78 Gy in 39 fractions)
• Primary endpoint: freedom from biochemical or clinical failure @ 5 years
  – 2-year toxicity data published while primary outcome maturing
24 month results

- RTOG grade 2+ GU toxicity
  - CRT: 8 (2%) of 381
  - SBRT: 13 (3%) of 384
  - Absolute difference 1.3% [95% CI –1.3 to 4.0]; p=0.39)

- RTOG grade 2+ GI toxicity
  - CRT: 11 (3%)
  - SBRT: 6 (2%)
  - Absolute difference –1/3% [95% CI –3.9 to 1.1]; p=0.32)

- No serious adverse events (RTOG 4+) or treatment-related deaths

- Overall: 2-year toxicity similar
Higher Dose?

- 91 patients with low/IM risk, phase I/II dose escalation trial
- Doses: 45Gy, 47.5Gy, 50Gy (all in 5)
- 3mm margin, fiducials, rectal balloon daily
- 4mg dexamethasone prior to treatment, a-blocker (i.e. tamsulosin) for 6 weeks
- Primary endpoint phase II: late GU/GI toxicity
- Secondary endpoints: biochemical control, DSS, OS
- MTD not reached in Phase I → Phase II started at 50Gy/5fx

Hannan et al, EJC 2016
Outcomes

- FFBF 100% for all patients at 3 years
- One biochemical failure in the 45 Gy arm after 3 years
- No deaths from prostate cancer or treatment
• **Toxicity**
  – Acute grade 2 GU tox: 22% (no grade 3 tox)
  – 14/20 reports were in 50Gy arm
  – Late grade 3+ GU tox: 4.4%, all within 50Gy arm
  – 50Gy arm had 1 acute grade 4 GI tox and 2 late grade 4 GI tox (ulceration of rectum requiring diverting colostomy)

• **Conclusions:**
  – Doses of 45 and 47.5 Gy in 5 fractions have high control rates and acceptable toxicity
  – 50 Gy: high rates of late toxicity
SBRT vs Surgery?

Hot off the presses from ASCO GU 2023
PACE-A: An international phase 3 randomized controlled trial (RCT) comparing stereotactic body radiotherapy (SBRT) to surgery for localized prostate cancer (LPCa)—Primary endpoint analysis.

Nicholas J. Van As, Alison Tree, Peter J. Ostler, Hans van der Voet, Daniel Ford, Shaun Tolan, Paula Wells, Rana Mahmood, Mathias Winkler, Andrew Chan, Alan Thompson, Christopher Ogden, Stephanie Brown, Julia Pugh, Stephanie M. Burnett, Clare Griffin, Jaymini Patel, Olivia Naismith, Emma Hall

- Presented at ASCO GU 2023 (Feb 16 2023)
PACE-A

- Phase 3: T1-T2, Gleason ≤ 3+4, PSA ≤ 20, suitable for surgery
- SBRT (36.25 Gy/5 fractions) vs laparoscopic or robot-assisted prostatectomy
- ADT not permitted
- Co-primary endpoints: expanded prostate index composite (EPIC-26) number of pads per day and EPIC bowel subdomain score at 2 years
- Analysis by treatment received
- 123 men from 10 centers randomized (goal sample size 234 but stopped recruitment after a 2-year gap during COVID)
PACE-A Results

• Median follow-up 50 months
• At 2 years:
  – 2/43 (4.5%) SBRT patients used pads vs 15/32 (46.9%) in surgery, p<0.001
  – 7/45 (15.6%) SBRT patients vs 0/31 (0%) surgery patients reported moderate/big problem with bowel symptoms (p=0.04)
  – SBRT patients: significantly worse bowel subdomain score (mean 88.4 vs. 97.3)
  – SBRT patients: significantly better sexual subdomain score
  – No evidence of difference in urinary subdomain score
  – GU grade 2+ was seen in 5/54 (9.3%) SBRT vs 4/42 surgery (9.5%), NS
  – No GI G2+ in either group
PACE-A

- SBRT associated with less urinary incontinence but worse bowel bother
- Awaiting further follow-up and publication
Can we predict toxicity?

Patient Factors
Treatment Factors
Predictors of Toxicity

• Patient Specific Factors
  – **Large prostate**: Late grade 2+ GU toxicity 15% for prostate > 60cc vs. 8%
  – **Prior TURP** increases risk of GU toxicity including hematuria, 21% vs 2%
  – **High baseline urinary symptoms** (IPSS > 15)
  – **Anticoagulant use** associated with late rectal bleeding, 47% vs 18%

Katz et al. Front Oncol 2014
Gurka et al. Radiat Oncol 2015
Jackson et al. PRO 2018
Musunuru et al. IJROBP 2016
Predictors of Toxicity

• Treatment-Specific Factors
  – Higher Prescription Dose:
    • Grade 2+ urinary toxicity was 48% in patients receiving 40 Gy vs. 5% in patients receiving 35 Gy
    • In another study, 6 of 61 patients (10%) treated to 50 Gy in 5 fractions experienced high grade rectal toxicity, 5 of whom required temporary or permanent colostomy
  – Higher doses to the rectum, bladder, and probably urethra
  – Daily versus every other day treatment?
    • In one series QD was associated with increased rates of late grade 1-2 urinary (56% vs. 17%) and bowel (44% vs. 5%) toxicity

Helou et al. Radiother Oncol 2017
King et al. IJROBP 2012
What about a rectal spacer?
• Multicenter randomized trial, 260 patients
• 12 centers within the US, Australia, and Spain, with a 6-month follow-up
• T1 to T2 prostate cancer with a Gleason score 7 or less and prostate-specific antigen level of 20 ng/mL or less
• Stratified by intended 4-month androgen deprivation therapy use and erectile quality
• Patients received 60 Gy in 20 fractions – **first trial looking at moderately hypofractionated RT**
• Primary outcome: hypothesized that more than 70% of patients in the spacer group would achieve a 25% or greater reduction in the rectal volume receiving 54 Gy (V54)
• Secondary Outcome: hypothesized that the spacer group would have noninferior acute (within 3 months) grade 2+ GI toxic effects compared with the control group, with a margin of 10%
Results

- 131 of 133 (98.5%) spacer group had a 25%+ reduction in rectum V54, greater than the minimally acceptable 70% ($P < .001$).
  - Mean reduction 85.0%
- Acute grade 2+ GI toxicity:
  - Spacer: 4 of 136 patients (2.9%)
  - Control: 9 of 65 patients (13.8%) in control group
  - Difference: -10.8%, $p = 0.01$
- Patient reported QOL similar

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<th>6-mo Toxic effect</th>
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Conclusions, Questions

• Rectal spacer can improve dosimetry, associated with small reduction in GI toxicity and is generally well-tolerated
• Applicability to SBRT?
• Relevance of primary endpoint?
• Larger margins used
• Consistent with other studies showing statistically significant but relatively small effect
SBRT for locally recurrent disease?
A Systematic Review and Meta-analysis of Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER)
MASTER meta-analysis

- 150 studies included; salvage RP, HIFU, cryotherapy, SBRT, brachytherapy
- Adjusted 5-year RFS ranged from 50% after cryotherapy to 60% after brachytherapy and SBRT
- No significant differences between any modality and radical prostatectomy
- Less severe GU toxicity with cryo/brachy/SBRT vs. RP
- Less severe GI toxicity with brachytherapy vs. RP
Clinical Investigation

Retreatment for Local Recurrence of Prostatic Carcinoma After Prior Therapeutic Irradiation: Efficacy and Toxicity of HDR-Like SBRT

Donald Fuller MD *, James Wurzer MD †, Reza Shirazi MD *, Stephen Bridge MD †, Jonathan Law DABR †, Tami Crabtree PhD †, George Mardirosian PhD *

https://doi.org/10.1016/j.ijrobp.2019.10.014
SBRT reirradiation

• Biopsy-proven locally recurrent disease at least 2 years out from initial RT, no evidence of disease elsewhere, no worse than G1 toxicity from initial course
• 50 patients, 43 treated with SBRT alone (no ADT)
• Median time to salvage 98 months
• 34 Gy in 5 consecutive daily treatments of 6.8 Gy
Future Directions,
Ongoing Studies
Ongoing Trials

- **NRG-GU 005**: SBRT (36.25 Gy/5 fractions vs. 70 Gy in 28 fractions)
- **HYPO-RT-PC**: SBRT (42.7 Gy/7 fractions) vs. 78 Gy in 39 fractions
- **HEAT**: SBRT (36.25 Gy/5 fractions) vs 70.2 Gy in 26 fractions
NRG GU-06

• Patients:
  – Favorable intermediate risk PC
  – Prostate volume < 60 cc
  – IPSS <15
• Dose 36.25 Gy in 5 fractions every other day
• Target: Prostate +/- 1 cm SV defined on MRI
• PTV margin: 5 mm, 3 mm post
• Fiducials recommended but not required
• Hydrogel Spacer optional
Areas of Interest

- Focal boost within prostate
- Spacer with SBRT
- Comparison to brachytherapy
Conclusions

• SBRT is a safe and effective radiation modality for localized prostate cancer
  – Potentially appropriate for any risk group although less data for high risk and not for treating lymph nodes
  – Caution with very large prostates, significant obstructive urinary symptoms, prior TURP
  – Highly recommend MRI for treatment planning
• Awaiting longer follow-up and additional comparative studies
• Rectal spacer may reduce GI toxicity
• An option for locally recurrent disease after initial RT
Thank You!