SBRT in Prostate Cancer
Evidence and Methodologies and tips

Vedang Murthy, Professor, TMH
Overview

- Why SBRT (Extreme Hypofractionation)
  - Rationale
  - Evidence

- How is it done?
  - Methodology

- India Specific issues
  - Evidence
  - Tips for Practice
It is rare that nature hands us a cancer situation where an improved treatment goes hand in hand with a shorter and convenient one.

Why SBRT

- Offers opportunity to **optimize therapeutic ratio**
- Probable similar efficacy and toxicity profile
- Short course treatment
- Cost effective
- Resource effective
Why Hypofractionate?

- Clinical Rationale
  - More convenient for patients
    - Travel
    - Stay
  - More patients can be treated with the same number of linear accelerators
    - Throughput
  - Lower the costs of treatment

- Biological rationale
  - Low a/b ratio
## Fractionation in prostate cancer

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Conventional fractionation</th>
<th>Moderate fractionation</th>
<th>Extreme fractionation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Equi effective dose</strong></td>
<td>74Gy/37#</td>
<td>60Gy/20#</td>
<td>36.25Gy/5#</td>
</tr>
<tr>
<td><strong>Dose/#</strong></td>
<td>2Gy</td>
<td>3 Gy</td>
<td>7.5Gy</td>
</tr>
</tbody>
</table>

Prostate BED ($\alpha/\beta : 10$)  
- Conventional: 89 Gy  
- Moderate: 78 Gy  
- Extreme: 60 Gy

Rectum BED ($\alpha/\beta : 3$)  
- Conventional: 123 Gy  
- Moderate: 120 Gy  
- Extreme: 106 Gy

Prostate BED ($\alpha/\beta : 2$)  
- Conventional: 148 Gy  
- Moderate: 150 Gy  
- Extreme: 154 Gy
Extreme Hypo-fractionation : Practice

- 15% of respondents reported that SBRT was one of their clinically used schedules for radical treatment
- Five centers reported using SBRT for more than 50% of their patients
Evidence for SBRT

- Is it safe?

- Is it effective?
Stereotactic Body Radiation Therapy for Localized Prostate Cancer: A Systematic Review and Meta-Analysis of Over 6,000 Patients Treated On Prospective Studies

William C. Jackson, MD, * Jessica Silva, BS, * Holly E. Hartman, MS, †

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**Graph A:**
- **Y-axis:** Biochemical Recurrence-Free Survival
- **X-axis:** Years Post-SBRT
- **Data Points:** 98.4%, 96.9%, 96.1%, 95.3%, 93.7%, 87.2%
- **Studied Numbers:** 5013, 4386, 1856, 2066, 557, 84
- **Studies:** 31, 23, 16, 10, 2, 1

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**Graphs B & C:**
- **Graph B:** Urinary EPIC scores overtime
- **Graph C:** Bowel EPIC scores overtime
- **Graph D:** Sexual EPIC scores overtime

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**Time Periods:**
- **Urinary EPIC:** 1,585, 1,206, 1,013, 961, 922
- **Bowel EPIC:** 1,585, 1,206, 1,013, 1,021, 922
- **Sexual EPIC:** 1,188, 809, 616, 544, 445
## Extreme Hypofractionation trials

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>PACE B</th>
<th>Hypo RT-PC</th>
<th>NRG-GU 005</th>
<th>PRIME</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study/Group</strong></td>
<td>Royal Marsden NHS Foundation Trust</td>
<td>Scandinavian</td>
<td>NRG Oncology</td>
<td>Tata Memorial Centre, India</td>
</tr>
<tr>
<td><strong>Stage/Eligibility</strong></td>
<td>Low risk: Intermediate risk: cT1c - cT3a: Int risk</td>
<td>Low Risk</td>
<td>High risk, Very high risk and node positive</td>
<td></td>
</tr>
<tr>
<td><strong>Target Accrual</strong></td>
<td>1716</td>
<td>1200</td>
<td>606</td>
<td>434</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>36.25Gy in 5 fractions vs 78Gy in 39 fractions</td>
<td>42.7Gy in 7 fractions vs 78Gy in 39 fractions</td>
<td>36.25Gy in 5 fractions vs 70Gy in 28 fractions</td>
<td>36.25Gy in 5 fractions vs 68Gy in 25 fractions</td>
</tr>
</tbody>
</table>
N= 1200
Intermediate risk (89%)
ADT : not allowed
Technique : 3DCRT (80%) or IMRT (20%)

78.0 Gy in 39 fractions, daily
42.7 Gy in seven fractions, alt day

Non-inferiority margin : 4% at 5 years
N= 874
Low or intermediate risk
ADT : not allowed

78.0 Gy in 39 fractions, daily
36.25 Gy in 5 fractions, alt day
Our unique problems for SBRT

- Is SBRT Feasible for
  - Advanced stage at diagnosis (T3-4)/High Risk
  - Higher incidence of node positive disease
  - Higher incidence of TURP (22-30%)
SBRT for high risk Prostate cancer

- Is it safe?
- Is it effective?
- Should you treat the pelvic nodes prophylactically?
### Patient characteristics

<table>
<thead>
<tr>
<th>N= 68 patients</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>68 years (44-89)</td>
</tr>
<tr>
<td>Risk grouping</td>
<td>High risk: 20 (29%)</td>
</tr>
<tr>
<td></td>
<td>Very high risk: 11 (17%)</td>
</tr>
<tr>
<td></td>
<td>Node positive: 37 (54%)</td>
</tr>
</tbody>
</table>

### Toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III/IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Genitourinary</td>
<td>27 (41%)</td>
<td>8 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>Acute Gastrointestinal</td>
<td>7 (11%)</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Late Genitourinary</td>
<td>11 (16%)</td>
<td>3 (4.5%)</td>
<td>2 (2.5%) /0</td>
</tr>
<tr>
<td>Late Gastrointestinal</td>
<td>7 (10%)</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
</tbody>
</table>
SBRT in Patients with a prior TURP

- Is it safe?

- How does one select the right patient?

- What precautions should be taken?
Purpose: To determine GU toxicity outcomes in prostate cancer patients treated with SBRT who have undergone a prior TURP and compare it to a similar non-TURP cohort.

Methods: N=100 (50 TURP, 50 Non TURP). Matching done for DM and volume of RT.

Median follow-up for the entire cohort was 26 months.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Non TURP</th>
<th>TURP</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG ≥ Gr II acute GU toxicity</td>
<td>8%</td>
<td>6% (p=0.34)</td>
</tr>
<tr>
<td>RTOG ≥ Gr II late GU toxicity</td>
<td>8%</td>
<td>12% (p=0.10)</td>
</tr>
<tr>
<td>Stricture rate</td>
<td>4%</td>
<td>6% (p=0.64)</td>
</tr>
<tr>
<td>Incontinence rate</td>
<td>0%</td>
<td>4% (p=0.12)</td>
</tr>
</tbody>
</table>

October, 2019
Time to Severe toxicity

The median time to severe late toxicity: 13 months

- Non-TURP 16 months
- TURP cohort 10 months

AVOID in multiple TURPs
AVOID upto 6 months of TURP
AVOID in stricture/ overflow incontinence
Evidence in making
Study protocol of a randomised controlled trial of prostate radiotherapy in high-risk and node-positive disease comparing moderate and extreme hypofractionation (PRIME TRIAL)

Vedang Murthy, Indranil Mallick, Abhilash Gavarraju, Shwetabh Sinha, Rahul Krishnatry, Tejshri Telkhade, Arunsinh Moses, Sadhna Kannan

STANDARD ARM (Target- 217)
- Moderate Hypofractionation
  - 68Gy/25 to primary (2.72Gy/#)
  - 5 weeks
  - Node positive disease – 50Gy/25# to pelvis

EXPERIMENTAL ARM (Target- 217)
- Extreme Hypofractionation/SBRT
  - 36.25Gy/5# to primary (7.25Gy/#)
  - 7-10 Days
  - Node positive disease – 25Gy/5# to pelvis

Primary end point: 4 year biochemical failure free survival
Secondary End Points: Toxicity, QOL, OoP Expenditure

Total target: 434 patients

Clinicaltrials.gov Identifier (NCT03561961)
Methodology
Simulation

**SHOULD BE USED**

- **Strict Bladder Protocol**
  - Void → Drink 500ml water and hold for 45 mins
- **Empty Rectum: No Gas**
  - Low residue/Fibre
- **COMFORTABLE, Supine, with arms folded on the chest**
- **Knee Rest/Ankle stocks**
- **CT MRI fusion**

**MAY BE USED!**

- **ORFIT**
- **VACLOC**
- **Gold Markers**
- **RECTAL BALOON**
- **SPACER**
- **IV Contrast**
# International Prostate Symptom Score (I-PSS)

<table>
<thead>
<tr>
<th>Patient Name:</th>
<th>Date of birth:</th>
<th>Date completed:</th>
</tr>
</thead>
</table>

**In the past month:**

<table>
<thead>
<tr>
<th>Item</th>
<th>Not at All</th>
<th>Less than 1 in 5 Times</th>
<th>Less than Half the Time</th>
<th>About Half the Time</th>
<th>More than Half the Time</th>
<th>Almost Always</th>
<th>Your score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Incomplete Emptying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>2. Frequency</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>3. Intermittency</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>4. Urgency</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>5. Weak Stream</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>6. Straining</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>None</th>
<th>1 Time</th>
<th>2 Times</th>
<th>3 Times</th>
<th>4 Times</th>
<th>5 Times</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Nocturia</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**Total I-PSS Score**

**Score:**

- 1-7: Mild
- 8-19: Moderate
- 20-35: Severe

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**Quality of Life Due to Urinary Symptoms**

<table>
<thead>
<tr>
<th>Delighted</th>
<th>Pleased</th>
<th>Mostly Satisfied</th>
<th>Mixed</th>
<th>Mostly Dissatisfied</th>
<th>Unhappy</th>
<th>Troubled</th>
</tr>
</thead>
<tbody>
<tr>
<td>If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
Newer technique-Insertion of Hydrogel spacers (SpaceOAR system)

Polyethylene glycol hydrogel that expands the perirectal space as an transperineally injected liquid and then polymerizes into a soft, absorbable spacer.

**Fig. 1.** after spacer

**Figure 2.** Illustration of transperineal polyethylene glycol hydrogel spacer injection. The needle is placed at the mid-prostate level between Denonvilliers fascia and rectal wall, hydrodissection is performed to confirm proper positioning, and the hydrogel is injected.
Clinical Investigation

Hydrogel Spacer Prospective Multicenter Randomized Controlled Pivotal Trial: Dosimetric and Clinical Effects of Perirectal Spacer Application in Men Undergoing Prostate Image Guided Intensity Modulated Radiation Therapy

Neil Mariados, MD,* John Sylvester, MD,† Dhiren Shah, MD,*

![Graph showing dosimetric data with control and spacer comparisons.]

P<.0001 for all
Results

A. Grade 1+ Rectal Toxicity

- Control
- Spacer

B. Grade 2+ Rectal Toxicity

- Control
- Spacer

Number at risk:

Control: 72
Spacer: 149

Control: 72
Spacer: 149
Issues with Spacers

- Cost
- Invasive technique
- Limited use in high risk
- Not useful for re-irradiation
- Not useful with rectal involvement
- Not Available in India: Yet.

Alternatives
Contouring Guidelines

ESTRO ACROP guideline

ESTRO ACROP consensus guideline on CT- and MRI-based target volume delineation for primary radiation therapy of localized prostate cancer

Carl Salembier\textsuperscript{a}, Geert Villeirs\textsuperscript{b}, Berardino De Bari\textsuperscript{c}, Peter Hoskin\textsuperscript{d}, Bradley R. Pieters\textsuperscript{e}, Marco Van Vulpen\textsuperscript{f}, Vincent Khoo\textsuperscript{g}, Ann Henry\textsuperscript{h}, Alberto Bossi\textsuperscript{i}, Gert De Meerleer\textsuperscript{j}, Valérie Fonteyne\textsuperscript{k,*}

- **Prostate:**
  - GTV – gross tumor delineated by newer imaging
  - CTV – GTV + Prostate (low risk)
  - GTV + Prostate + SV (intermediate and high risk)
  - PTV – CTV + Margins

- Pelvic nodes (if involved)
- OARs: rectum, bladder, proximal femur, bowel bag
If you can’t find the GU diaphragm, just end your prostate/GTV at least 0.7 cm above penile bulb (ensures PTV does not overlap penile bulb).

Alternative inferior border...
CT-MRI fusion - Apex delineation
PTV considerations: IGRT Dependent

<table>
<thead>
<tr>
<th>AT TMH</th>
<th>PTV all around</th>
<th>Posterior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard fractionation</td>
<td>7 mm</td>
<td>7 mm</td>
</tr>
<tr>
<td>Moderate hypofractionation</td>
<td>7 mm</td>
<td>5 mm</td>
</tr>
<tr>
<td>Extreme hypofractionation</td>
<td>5 mm</td>
<td>5 mm</td>
</tr>
</tbody>
</table>

**IGRT used: Daily CBCT with bone followed by prostate matching**
Scheduling of SBRT

Phase II randomised trial

Once-weekly versus every-other-day stereotactic body radiotherapy in patients with prostate cancer (PATRIOT): A phase 2 randomized trial

Harvey C. Quon \textsuperscript{a,*}, Aldrich Ong \textsuperscript{b}, Patrick Cheung \textsuperscript{c}, William Chu \textsuperscript{c}, Hans T. Chung \textsuperscript{c}, Danny Vesprini \textsuperscript{c}, Amit Chowdhury \textsuperscript{b}, Dilip Panjwani \textsuperscript{d}, Geordi Pang \textsuperscript{c}, Renee Korol \textsuperscript{c}, Melanie Davidson \textsuperscript{c}, Ananth Ravi \textsuperscript{c}, Boyd McCurdy \textsuperscript{b}, Liying Zhang \textsuperscript{c}, Alexandre Mamedov \textsuperscript{c}, Andrea Deabreu \textsuperscript{c}, Andrew Loblaw \textsuperscript{c}

\textsuperscript{a} Tom Baker Cancer Centre, Calgary; \textsuperscript{b} CancerCare Manitoba, Winnipeg; \textsuperscript{c} Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto; and \textsuperscript{d} BC Cancer Agency, Abbotsford, Canada

N = 152 (Low / intermediate risk)
Median follow up: 47 months
Dose: 40 Gy in 5 fractions.

Randomization: once per week (QW) vs. every other day (EOD)

Endpoint: Toxicity and QOL
Results

GI Toxicity

QOL

Severity of changes in EPIC quality of life.

<table>
<thead>
<tr>
<th>Quality of life domain</th>
<th>Once weekly</th>
<th>Every other day</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/very small/small problem</td>
<td>67 (94.4%)</td>
<td>67 (97.1%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Moderate/big problem</td>
<td>4 (5.6%)</td>
<td>2 (2.9%)</td>
<td></td>
</tr>
<tr>
<td>Urinary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/very small/small problem</td>
<td>61 (85.9%)</td>
<td>65 (94.2%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Moderate/big problem</td>
<td>10 (14.1%)</td>
<td>4 (5.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Acute</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/very small/small problem</td>
<td>56 (80%)</td>
<td>30 (43%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate/big problem</td>
<td>14 (20%)</td>
<td>40 (57%)</td>
<td></td>
</tr>
<tr>
<td>Urinary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/very small/small problem</td>
<td>40 (57%)</td>
<td>40 (57%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Moderate/big problem</td>
<td>30 (43%)</td>
<td>30 (43%)</td>
<td></td>
</tr>
<tr>
<td><strong>Late</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/very small/small problem</td>
<td>53 (79.1%)</td>
<td>55 (79.7%)</td>
<td>0.93</td>
</tr>
<tr>
<td>Moderate/big problem</td>
<td>14 (20.9%)</td>
<td>14 (20.3%)</td>
<td></td>
</tr>
<tr>
<td>Urinary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/very small/small problem</td>
<td>46 (68.7%)</td>
<td>47 (68.1%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Moderate/big problem</td>
<td>21 (31.3%)</td>
<td>22 (31.9%)</td>
<td></td>
</tr>
</tbody>
</table>
What else is being **tried** with SBRT?

- Dose escalation: SBRT Boost to DIL
- HDR Like dosimetry/treatment
- Focal Reirradiation after local recurrence
- Combining with Immunotherapy
- SBRT in Post op (Don’t try at home!)
Acknowledgements

- **Uro Oncology Research Fellows**
  - Tejshri Telkhade
  - Abhilash Gavarraju

- **Trial Coordinators**
  - Dipika Chaurasia
  - Gitanjali Panigrahi

- Rahul Krishnatry
- **Department of Radiation Oncology, TMC, Mumbai**