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.

- J.F. Fowler. Development of radiobiology for oncology - a personal view. Physics in medicine and biology,51(13):263, 2006.

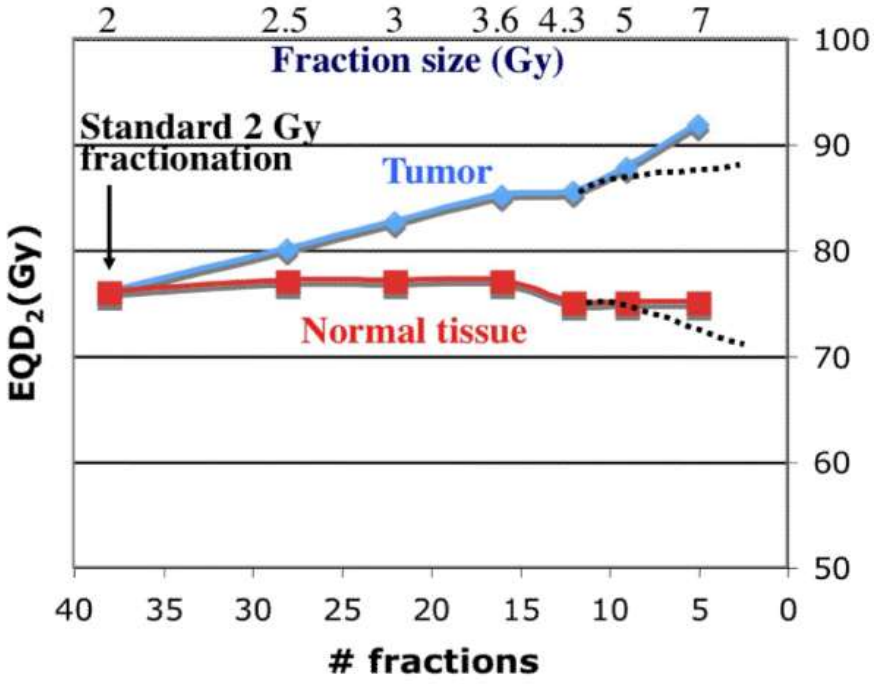
Why SBRT

- 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

Parameters	Conventional fractionation	Moderate fractionation	Extreme fractionation
Equi effective dose	74Gy/37#	60Gy/20#	36.25Gy/5#
Dose/#	2Gy	3 Gy	7.5Gy

Prostate BED (α/β :10)	89 Gy	78 Gy	60 Gy
Rectum BED (α/β :3)	123 Gy	120 Gy	106 Gy
Prostate BED (α/β : 2)	148 Gy	150 Gy	154 Gy

Overview

Prostate Radiotherapy in India: Evolution, Practice and Challenges in the 21st Century

V. Murthy *, I. Mallick †, M. Arunsingh †, P. Gupta *

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

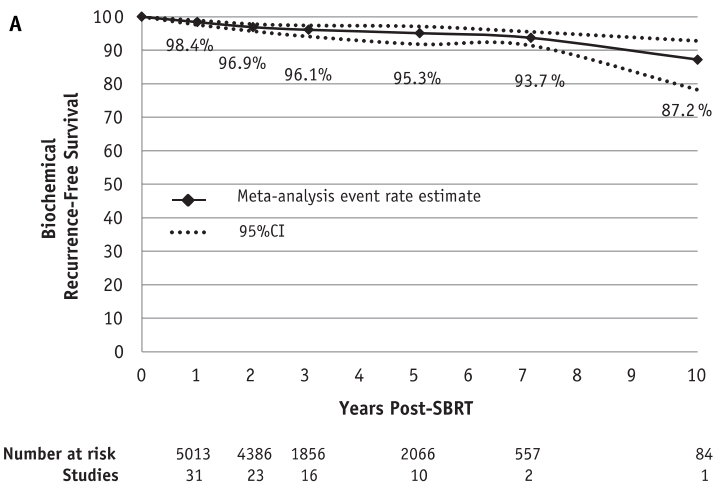
- Is it safe?

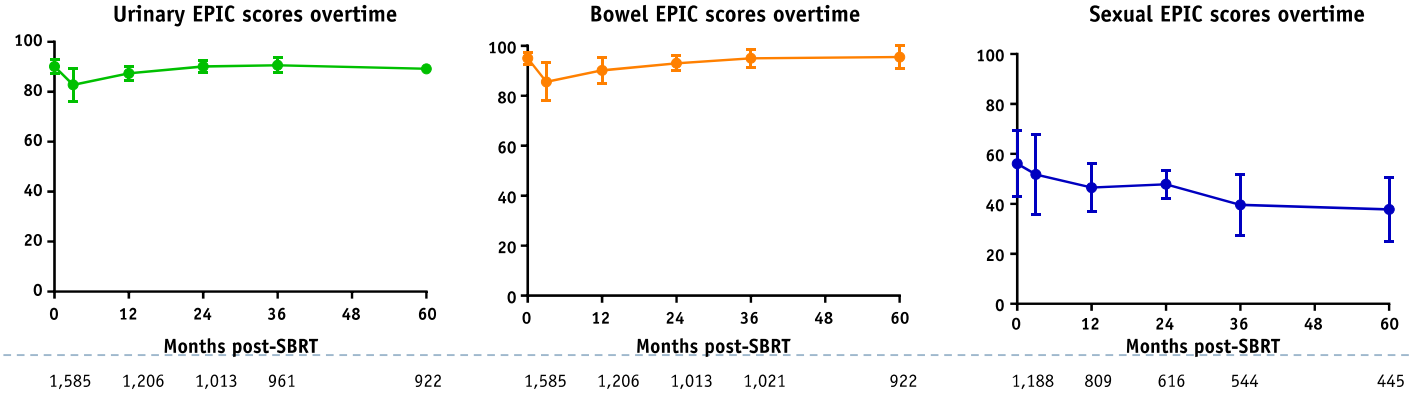
- Is it effective?

Int J Radiation Oncol Biol Phys, Vol. 104, 2019

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,†





Extreme Hypofractionation trials

Trial Name	PACE B	Hypo RT-PC	NRG-GU 005	PRIME
Study/Group	Royal Marsden NHS Foundation Trust	Scandinavian	NRG Oncology	**Tata Memorial Centre, India**
Stage/ Eligibility	Low risk: Intermediate risk:	cT1c - cT3a: Int risk	Low Risk	**High risk, Very high risk and node positive**
Target Accrual	1716	1200	606	434
Interventions	36.25Gy in 5 fractions vs 78Gy in 39 fractions	42.7Gy in 7 fractions vs 78Gy in 39 fractions	36.25Gy in 5 fractions vs 70Gy in 28 fractions	36.25Gy in 5 fractions vs 68Gy in 25 fractions

Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial

Lancet 2019; 394: 385–95

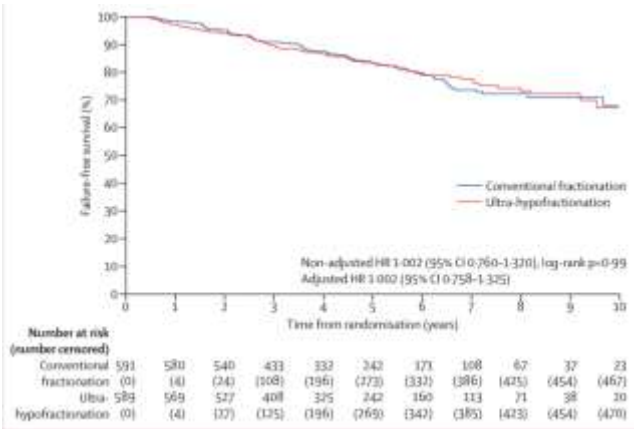
Anders Widmark, Adalsteinn Gunnlaugsson, Lars Beckman, Camilla Thellenberg-Karlsson, Morten Hoyer, Magnus Lagerlund, Jan Kindblom,

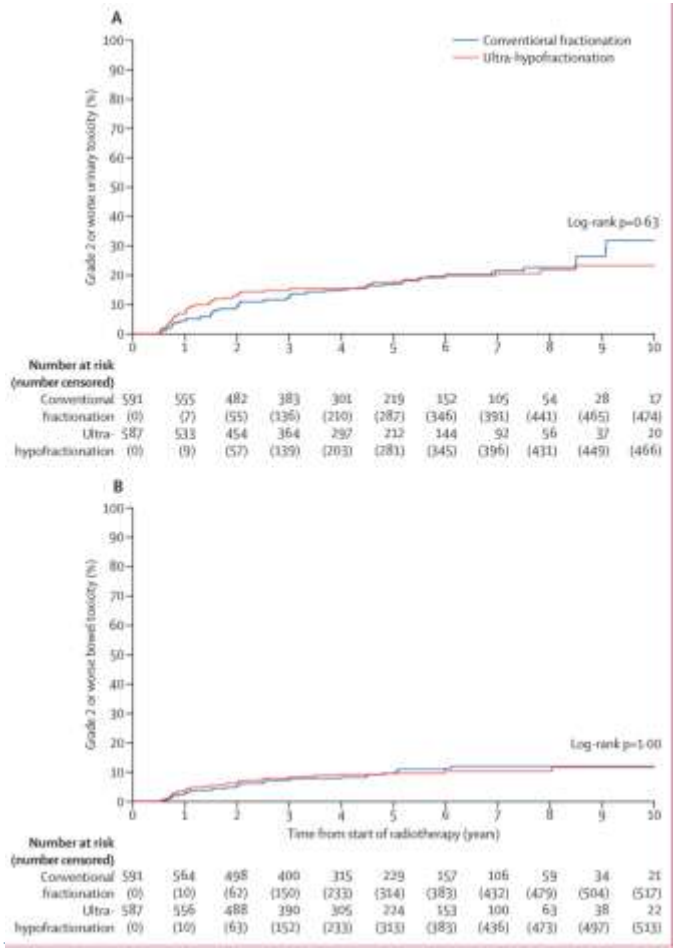
- **N= 1200**
- **Intermediate risk (89%)**
- ADT : not allowed

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**





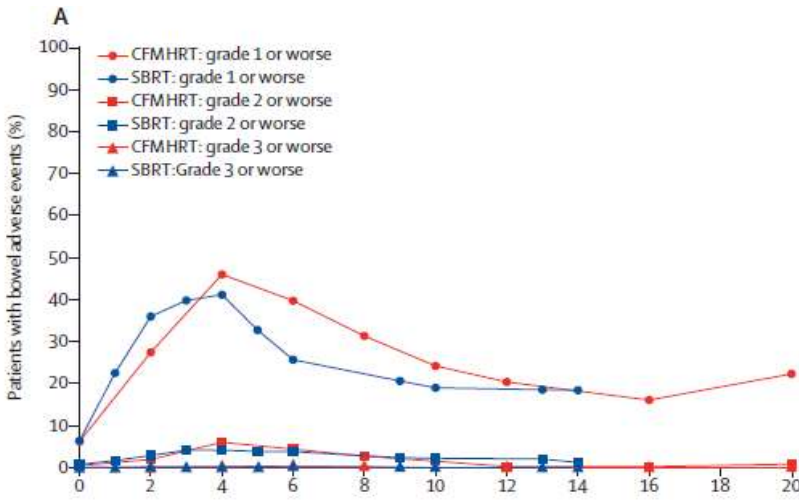
Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial

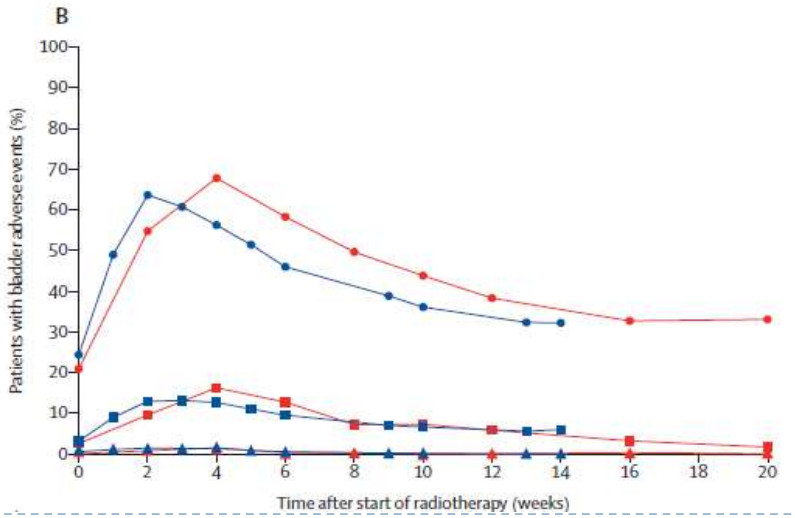
Douglas H Brand*, Alison C Tree*, Peter Ostler, Hans van der Voet, Andrew Loblaw, William Chu, Daniel Ford, Shaun Tolan, Suneil Jain, Alexander Martin, John Staffurth, Philip Camilleri, Kiran Kancherla, John Frew, Andrew Chan, Ian S Dayes, Daniel Henderson, Stephanie Brown,

www.thelancet.com/oncology Vol 20 November 2019

- 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?

Early Results of Extreme Hypofractionation Using Stereotactic Body Radiation Therapy for High-risk, Very High-risk and Node-positive Prostate Cancer

Clinical Oncology 30 (2018) 442–447

V. Murthy, M. Gupta, G. Mulye, S. Maulik, M. Munshi, R. Krishnatry, R. Phurailatpam, R. Mhatre, G. Prakash, G. Bakshi

Patient characteristics	N= **68** patients	**N (%)**
Median age	68 years (44-89)	
Risk grouping	High risk	20 (29%)
	Very high risk	11 (17%)
	Node positive	**37 (54%)**

Toxicity	**Grade I**	**Grade II**	**Grade III/IV**
Acute Genitourinary	27 (41%)	8 (12%)	0
Acute Gastrointestinal	7 (11%)	3 (4%)	0
Late Genitourinary	11 (16%)	3 (4.5%)	2 (2.5%) /0
Late Gastrointestinal	7 (10%)	3 (4%)	0

SBRT in Patients with a prior TURP

- Is it safe?
- How does one select the right patient?
- What precautions should be taken?

Safety of Prostate Stereotactic Body Radiation Therapy after Transurethral Resection of Prostate (TURP): A Propensity Score Matched Pair Analysis

pro practical radiation oncology ASTRO

October, 2019

Vedang Murthy, MD[a,*], Shwetabh Sinha, MD[a], Sadhana Kannan, MSc[b], Debanjali Datta, MBBS[a], Rabi Das, MBBS[a], Ganesh Bakshi, MS[c], Gagan Prakash, MS[c], Rahul Krishnatry, MD[a]

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

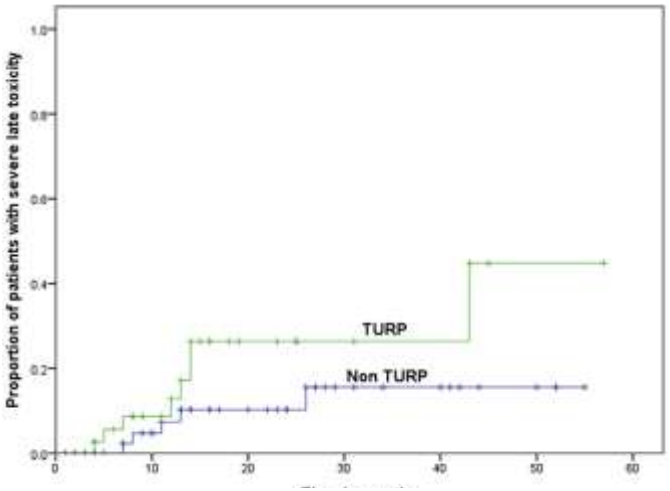
Methods: N=100 (50 TURP , 50 Non TURP)
Matching done for DM and volume of RT

Median follow-up for the entire cohort was 26 months

Parameter	Non TURP	TURP
RTOG ≥ Gr II acute GU toxicity	8%	6% (p=0.34)
RTOG ≥ Gr II late GU toxicity	8%	12% (p=0.10)
Stricture rate	4%	6% (p=0.64)
Incontinence rate	0%	4% (p=0.12)

Time to Severe toxicity

October, 2019



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
AVOIN in stricture/ overflow incontinence

Evidence in making

BMJ Open

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 ,[1] Indranil Mallick,[2] Abhilash Gavarraju ,[1] Shwetabh Sinha,[1] Rahul Krishnatry,[1] Tejshri Telkhade ,[1] Arunsingh Moses,[2] Sadhna Kannan,[3]

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)

Murthy V, *et al. BMJ Open* 2020;**10**:e034623. doi:10.1136/bmjopen-2019-034623

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)

Patient Name: _____ **Date of birth:** _____ **Date completed** _____

In the past month:	Not at All	Less than 1 in 5 Times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	Your score
1. Incomplete Emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5	
	None	1 Time	2 Times	3 Times	4 Times	5 Times	
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5	
Total I-PSS Score							

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

Quality of Life Due to Urinary Symptoms	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
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?	**0**	**1**	**2**	**3**	**4**	**5**	**6**

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

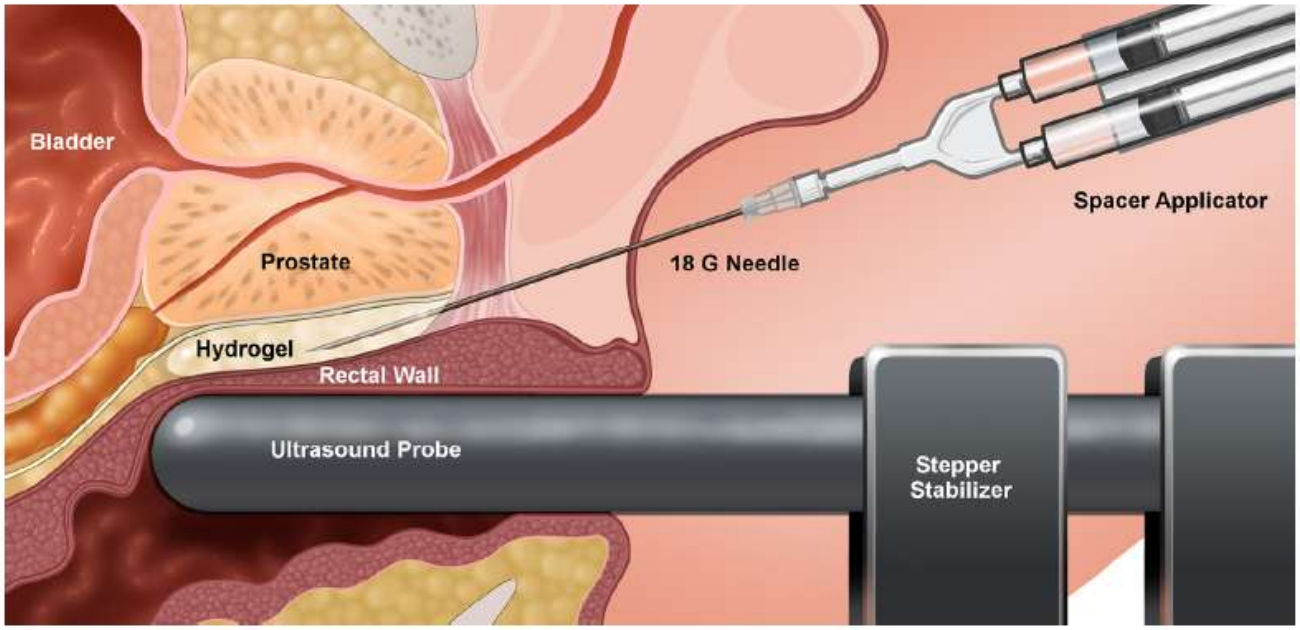


Fig. 1.
after spac

2 months

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,‡

International Journal of Radiation Oncology biology • physics

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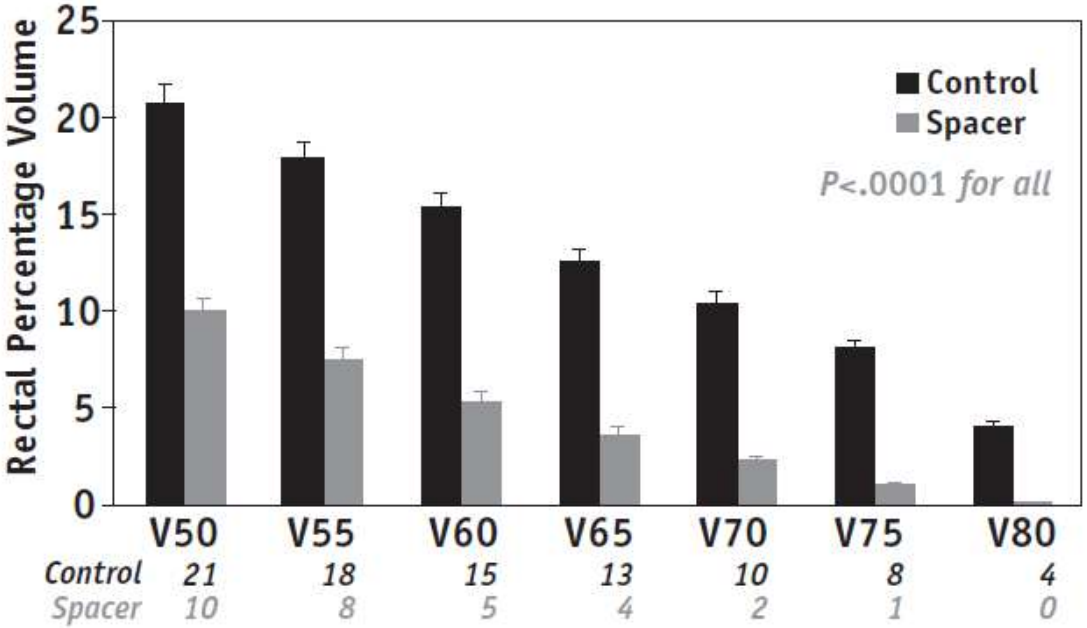
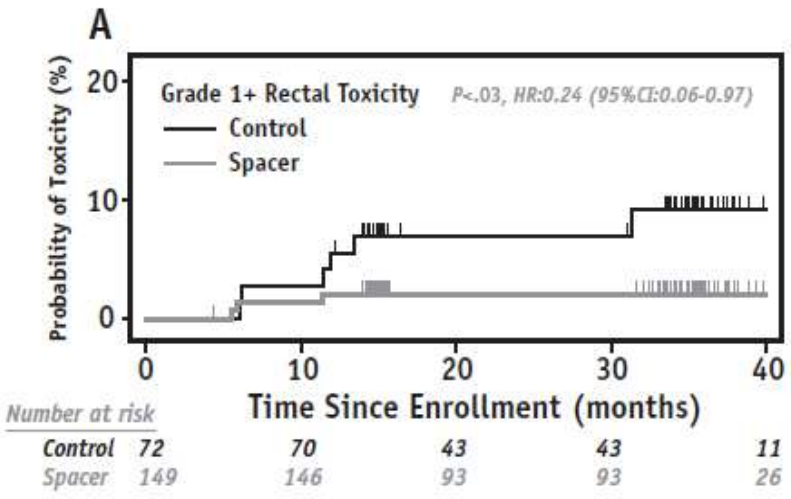
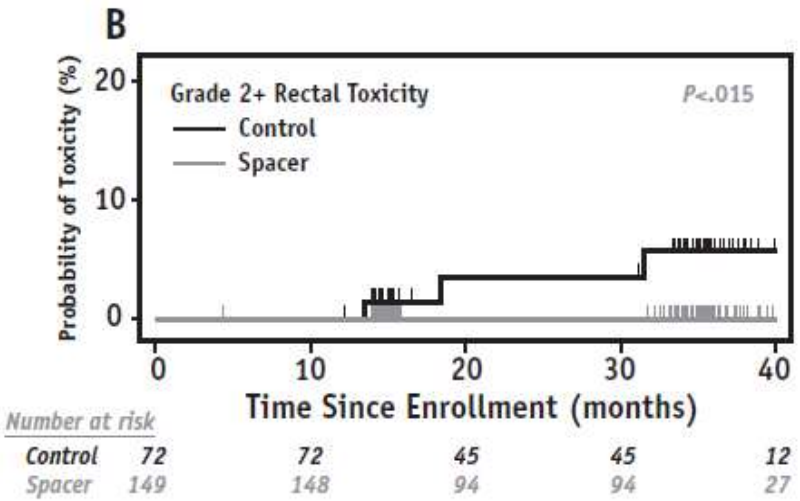


Results


A
Probability of Toxicity (%)
20
10
0
Grade 1+ Rectal Toxicity
P<.03, HR:0.24 (95%CI:0.06-0.97)
Control
Spacer
0
10
20
30
40
Time Since Enrollment (months)
Number at risk
Control 72 70 43 43 11
Spacer 149 146 93 93 26


B
Probability of Toxicity (%)
20
10
0
Grade 2+ Rectal Toxicity
P<.015
Control
Spacer
0
10
20
30
40
Time Since Enrollment (months)
Number at risk
Control 72 72 45 45 12
Spacer 149 148 94 94 27

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

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

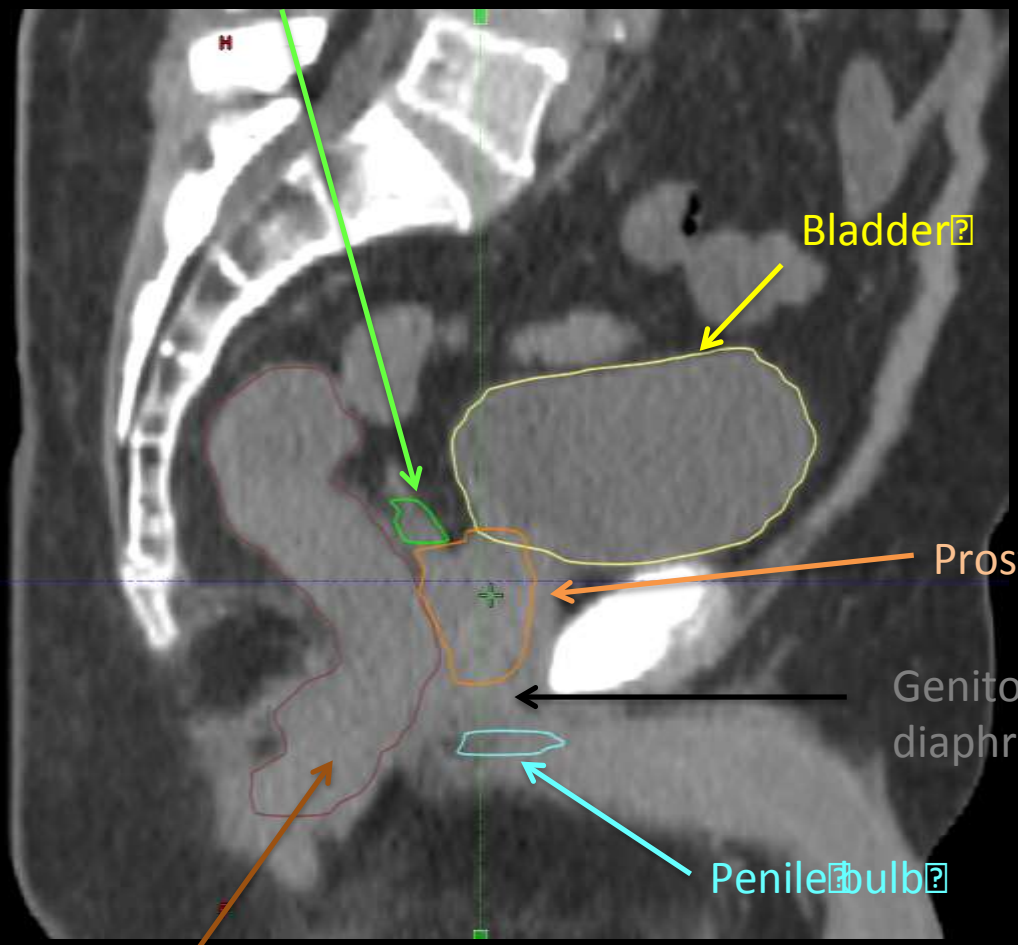
ESTRO ACROP guideline

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

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

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

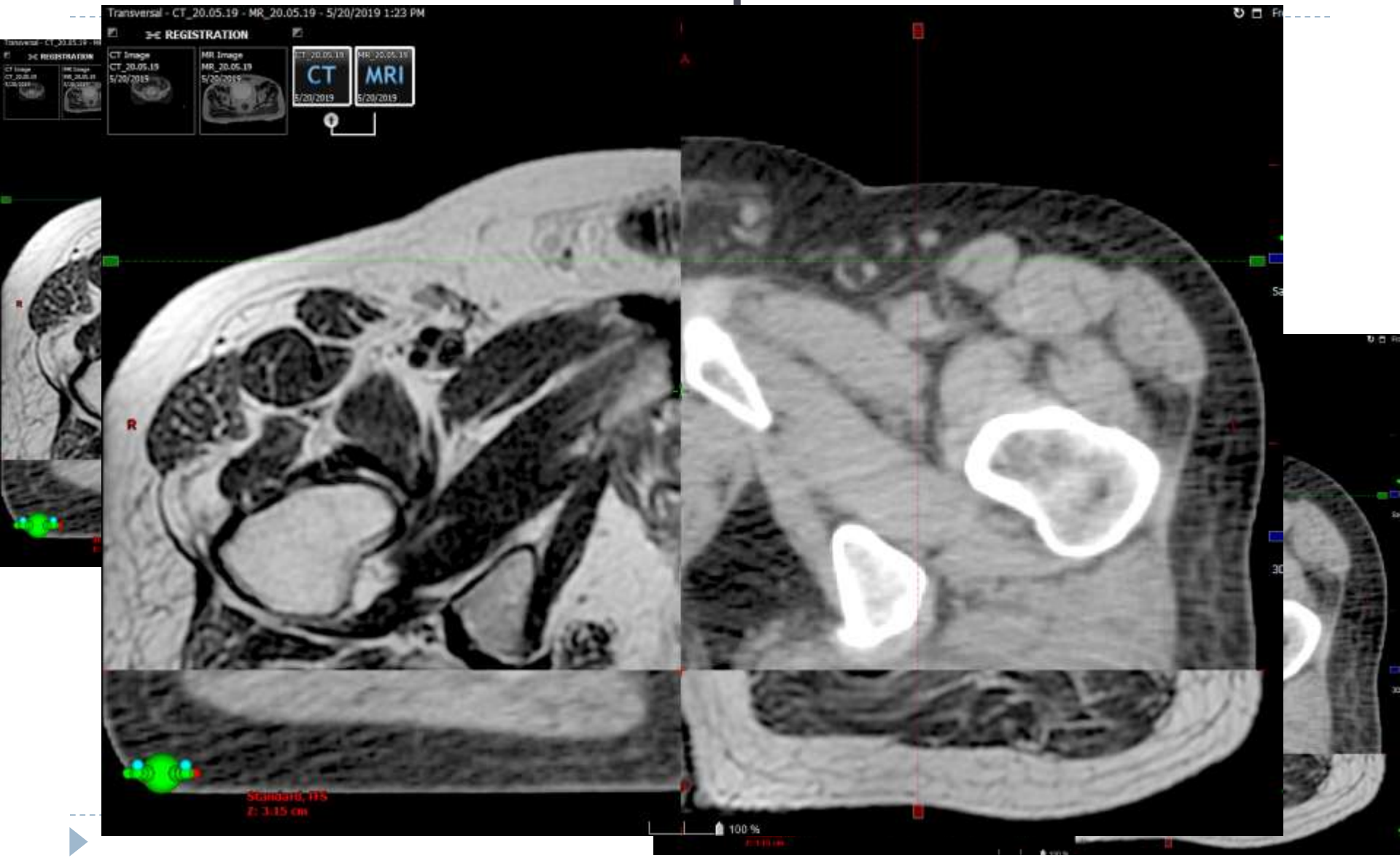
- Pelvic nodes (if involved)
- OARs: rectum, bladder, proximal femur, bowel bag



Alternative inferior border…

If you can't find the GU diaphragm, just end your prostate/GTV at least 0.7cm above penile bulb (ensures PTV does not overlap penile bulb).

CT-MRI fusion- Apex delineation



PTV considerations: IGRT Dependent

IGRT used : Daily CBCT with bone followed by prostate matching		
AT TMH	PTV all around	Posterior
Standard fractionation	7 mm	7 mm
Moderate hypofractionation	7 mm	5 mm
Extreme hypofractionation	5 mm	5 mm

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

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

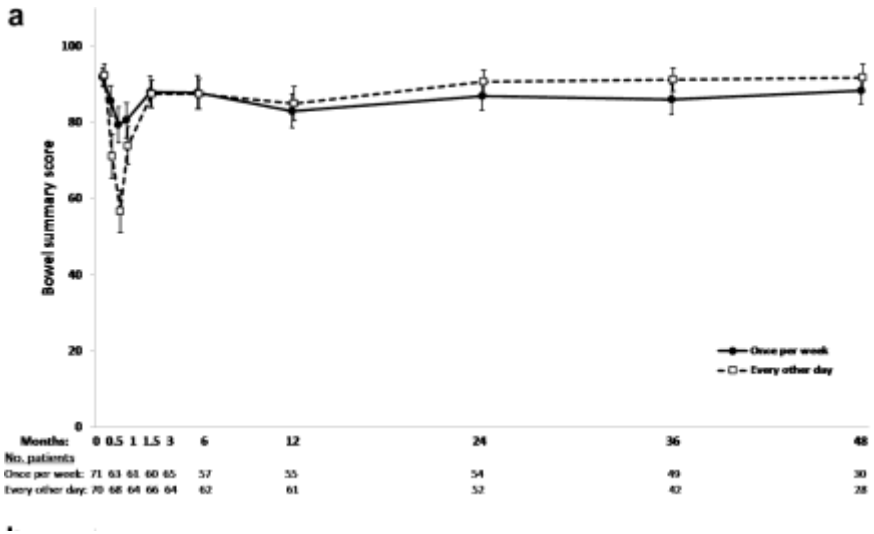
N = 152 (Low / intermediate risk)
Median follow up : 47 months
Dose : 40 Gy in 5 fractions.

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.

Quality of life domain	Once weekly	Every other day	*P*-value
Baseline			
Bowel			0.68
No/very small/small problem	67 (94.4%)	67 (97.1%)	
Moderate/big problem	4 (5.6%)	2 (2.9%)	
Urinary			0.16
No/very small/small problem	61 (85.9%)	65 (94.2%)	
Moderate/big problem	10 (14.1%)	4 (5.8%)	
Acute			
Bowel			<0.001
No/very small/small problem	56 (80%)	30 (43%)	
Moderate/big problem	14 (20%)	40 (57%)	
Urinary			0.99
No/very small/small problem	40 (57%)	40 (57%)	
Moderate/big problem	30 (43%)	30 (43%)	
Late			
Bowel			0.93
No/very small/small problem	53 (79.1%)	55 (79.7%)	
Moderate/big problem	14 (20.9%)	14 (20.3%)	
Urinary			0.95
No/very small/small problem	46 (68.7%)	47 (68.1%)	
Moderate/big problem	21 (31.3%)	22 (31.9%)	

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

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  - Dipika Chaurasia
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