

# ULTRA-HYPOFRACTIONATION: LESS THAN 5 FRACTIONS

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# RADIATION DOSE AND FRACTIONATION

- Alpha/Beta ratio is a way of describing how tissues responds to radiation based on cell survival curves
- High alpha/beta ratios (8-10 range) represent tissues that are rapidly dividing such as skin, mucosa and rapidly dividing tumors. They are most sensitive to total radiation dose and less to dose per fraction.
- Low alpha/beta ratios (1.5 to 3) represent tissues that are slow growing such as bone, muscle, cartilage and slow growing tumors. They are most sensitive to the dose per fraction
- Radiobiology studies have demonstrated that prostate cancers have a low alpha beta ratio (1.5-3 range)
- Therefore, prostate cancer would be most sensitive to higher doses per fraction
- Higher doses per fraction require fewer fractions and lower total doses compared to lower doses per fraction

# ALPHA/BETA RATIOS

- PROSTATE CANCER: 1.5 – 3
- RECTUM: 2-3
- LATE BLADDER TOXICITY: 3-6
- NEURO VASCULAR BUNDLES: 2-3

# THE FOUR RS OF RADIOBIOLOGY

- **Repair:** cells have the ability to fix radiation-induced DNA damage, a process that happens between radiation doses
- **Reassortment:** cells progress through the cell cycle. As cells move between fractions, more cells enter the more sensitive phases
- **Reoxygenation:** tumors can have poorly oxygenated area which makes them radiation resistant. Between doses hypoxic cells can be reoxygenated making them more sensitive to subsequent radiation
- **Repopulation:** surviving tumor cells can rapidly divide and grow between treatment fractions



# Virtual HDR CyberKnife SBRT for localized prostatic carcinoma: 5-year disease-free survival and toxicity observations

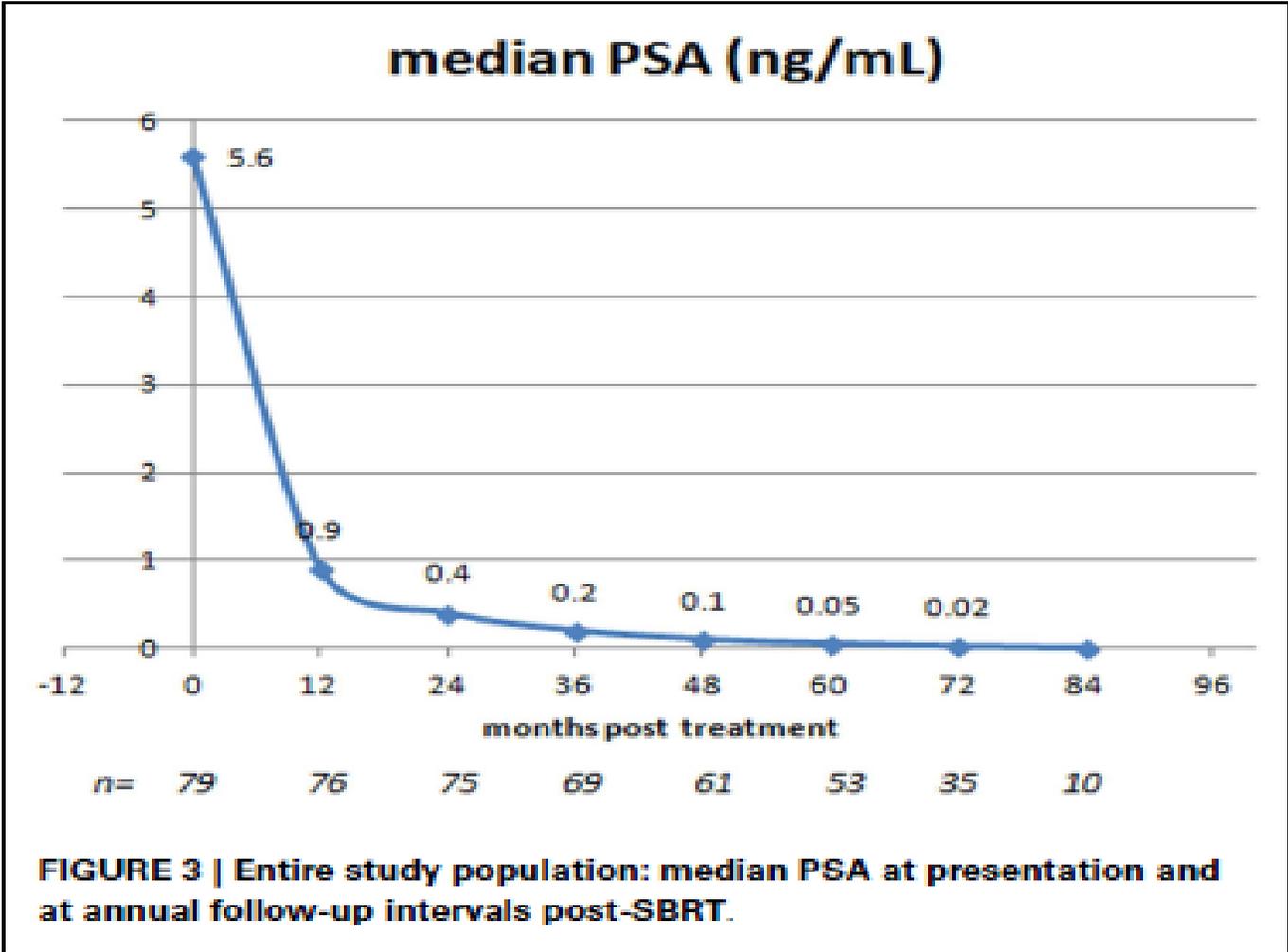
**Donald Blake Fuller<sup>1\*</sup>, John Naitoh<sup>2</sup> and George Mardirossian<sup>1</sup>**

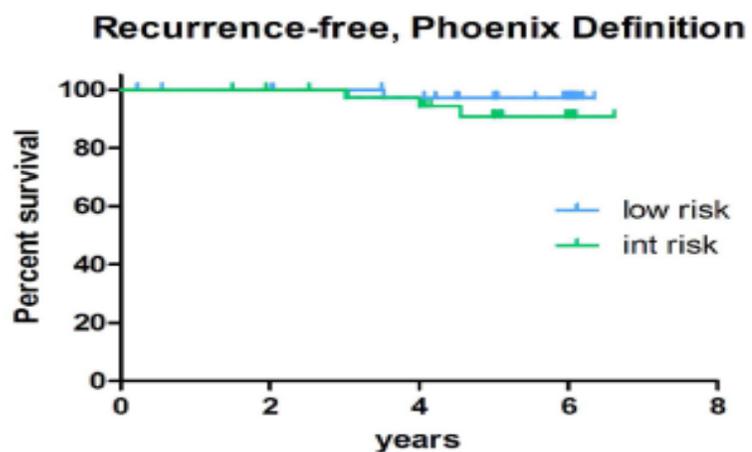
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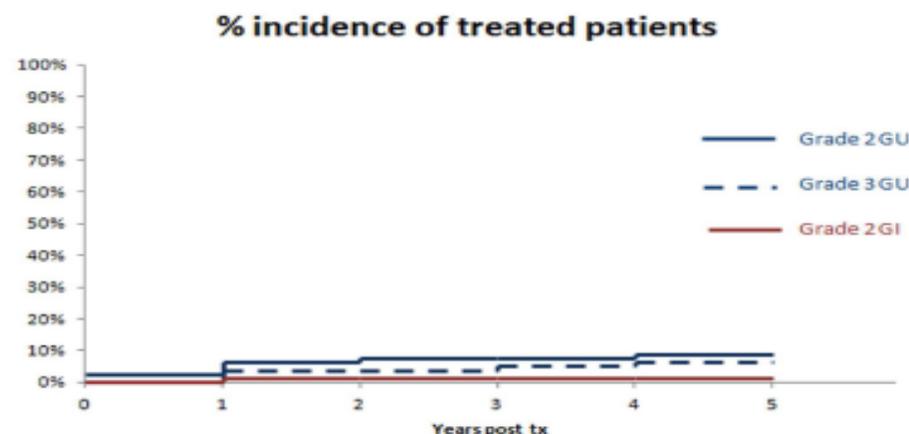
**Methods:** Seventy-nine patients were treated from 2006 to 2009, 40 low-risk, and 39 intermediate-risk, under IRB-approved clinical trial, to 38 Gy in four fractions. The planning target volume (PTV) included prostate plus a 2-mm volume expansion in all directions, with selective use of a 5-mm prostate-to-PTV expansion and proximal seminal vesicle coverage in intermediate-risk patients, to better cover potential extraprostatic disease; rectal PTV margin reduced to zero in all cases. The prescription dose covered >95% of the PTV ( $V_{100} \geq 95\%$ ), with a minimum 150% PTV dose escalation to create “HDR-like” PTV dose distribution.

## 38 Gy in 4 fractions

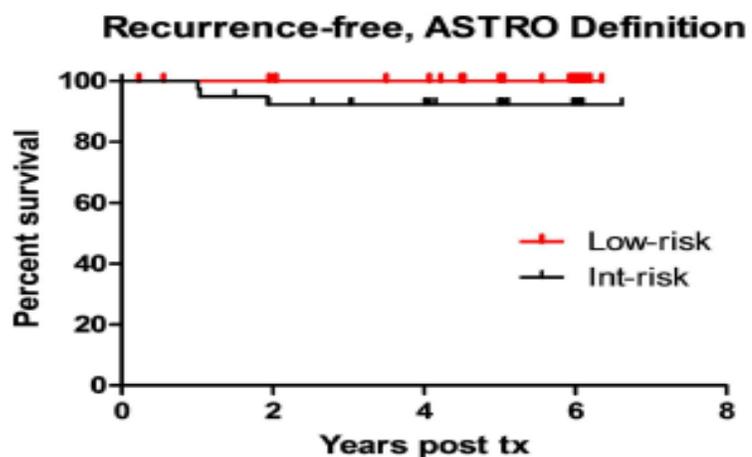




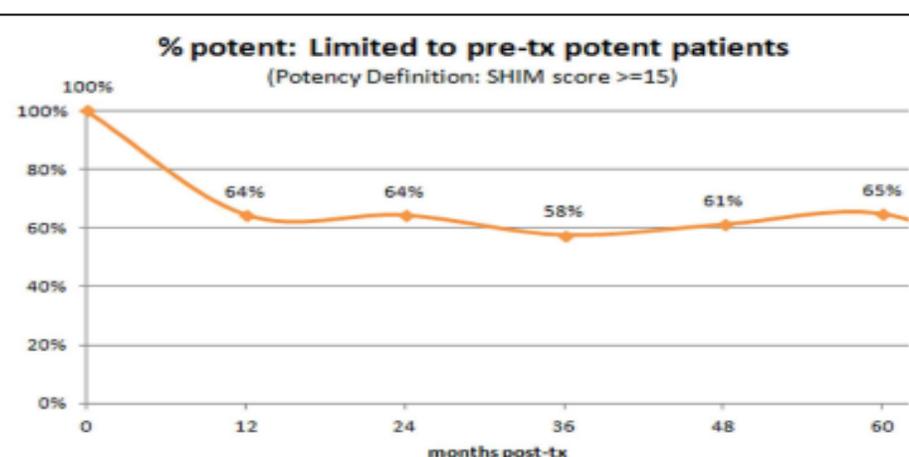
**FIGURE 4 |** Biochemical-relapse-free survival post-SBRT stratified by risk-group: Phoenix definition.



**FIGURE 6 |** Cumulative incidence of long-term grade 2 or higher GU or GI morbidity, annualized to 5 years. There were no further events beyond 5 years in this study.



**FIGURE 5 |** Biochemical-relapse-free survival post-SBRT stratified by risk-group: ASTRO definition.



**FIGURE 7 |** Percent of patients with preserved potency – analysis limited to those who were potent pre-SBRT. Note that virtually the entire loss incidence occurs within year one post-SBRT, with relatively stable rates thereafter.

RESEARCH

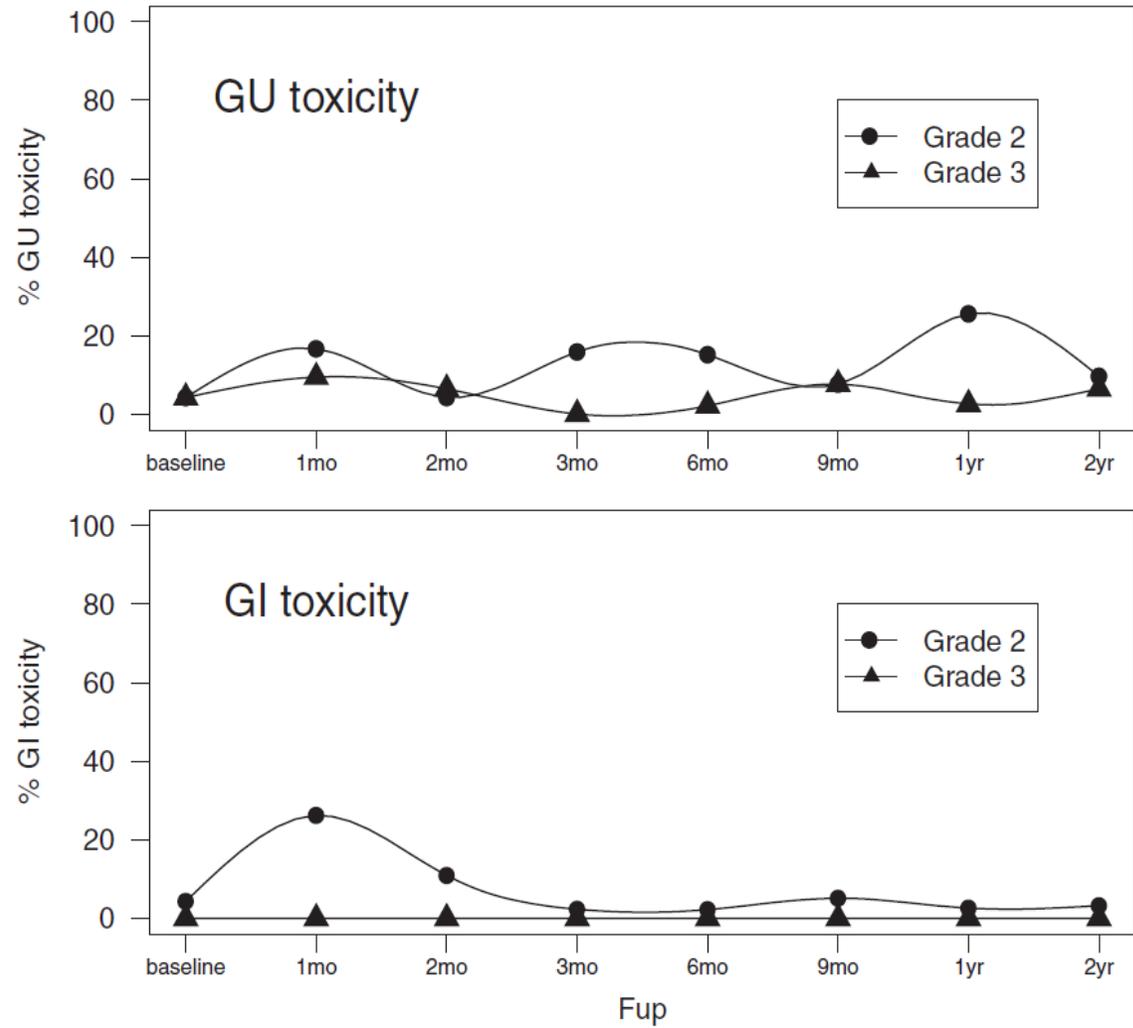
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# Stereotactic body radiotherapy with a focal boost to the MRI-visible tumor as monotherapy for low- and intermediate-risk prostate cancer: early results

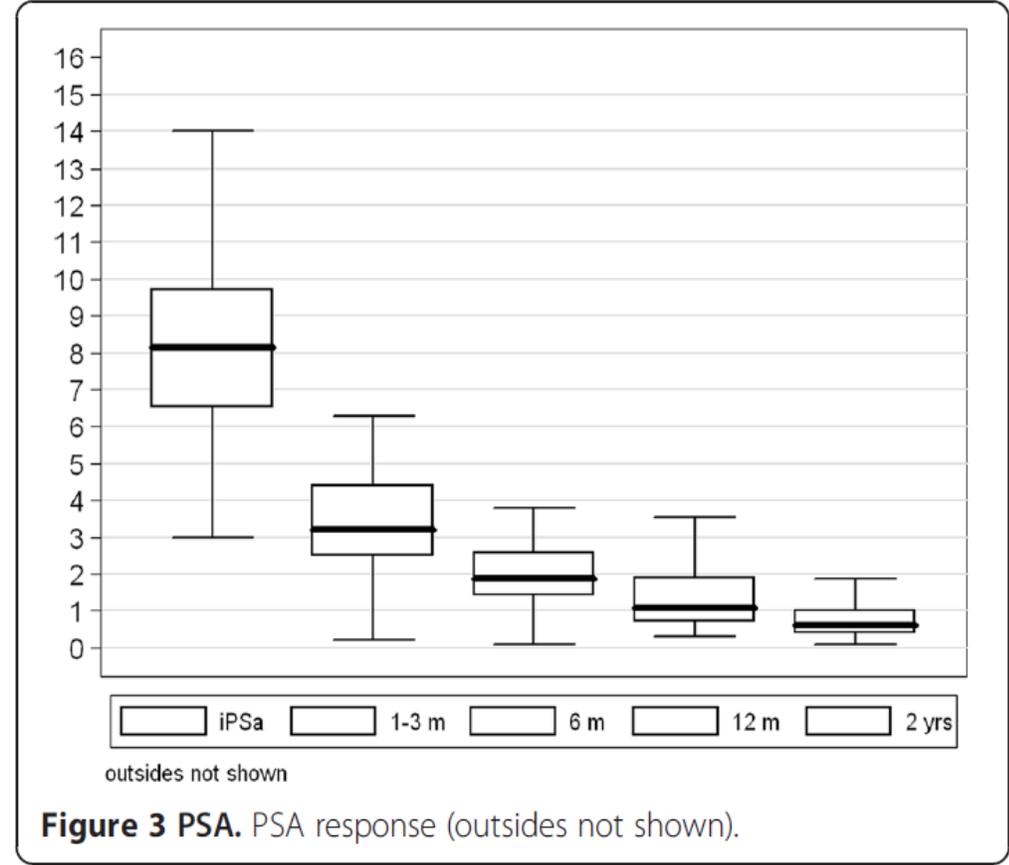
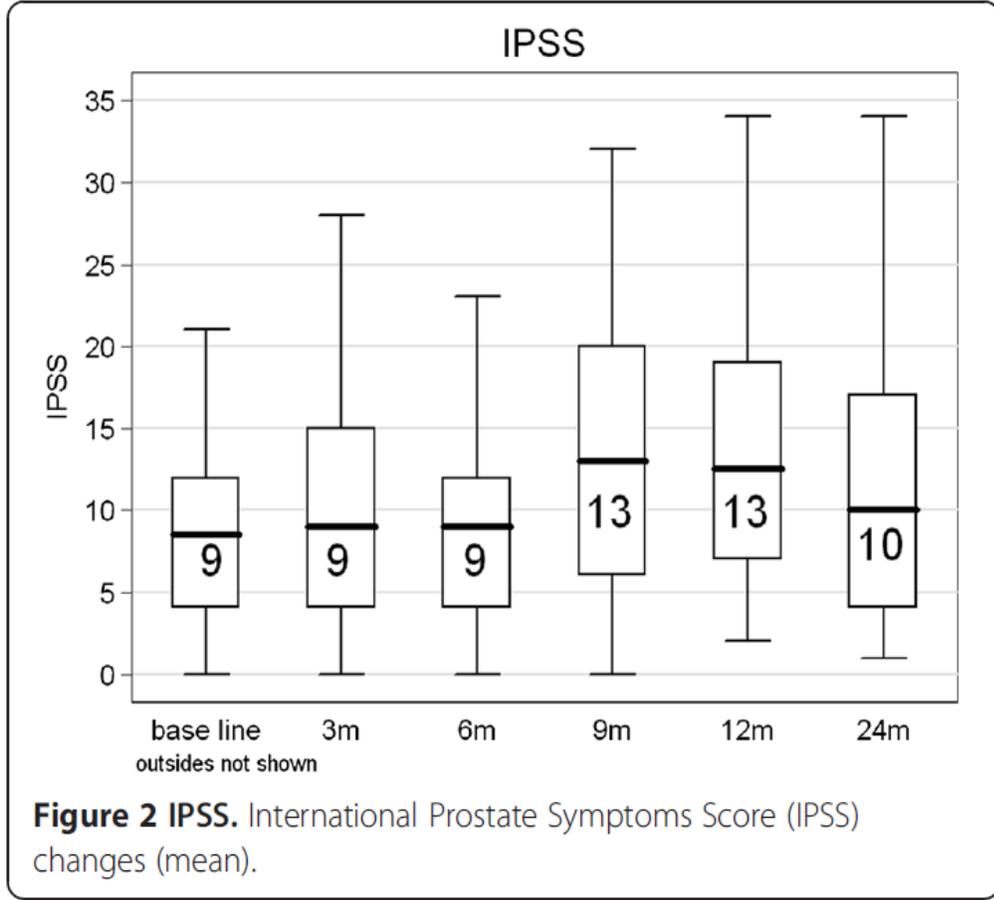
Shafak Aluwini<sup>1\*</sup>, Peter van Rooij<sup>1</sup>, Mischa Hoogeman<sup>1</sup>, Wim Kirkels<sup>2</sup>, Inger-Karine Kolkman-Deurloo<sup>1</sup> and Chris Bangma<sup>2</sup>

**Methods:** Over the last 4 years, 50 hormone-naïve patients with low- and intermediate-risk PC were treated with SBRT to a total dose of 38 Gy delivered in four daily fractions of 9.5 Gy. An integrated boost to 11 Gy per fraction was applied to the dominant lesion if visible on MRI. Toxicity and QoL was assessed prospectively using validated questionnaires.

## 38 Gy in 4 fractions



**Figure 1 GI and GU.** Gastrointestinal and Genitourinary toxicity (%).



# Toxicity at 1 Year After Stereotactic Body Radiation Therapy in 3 Fractions for Localized Prostate Cancer

International Journal of  
Radiation Oncology  
biology • physics

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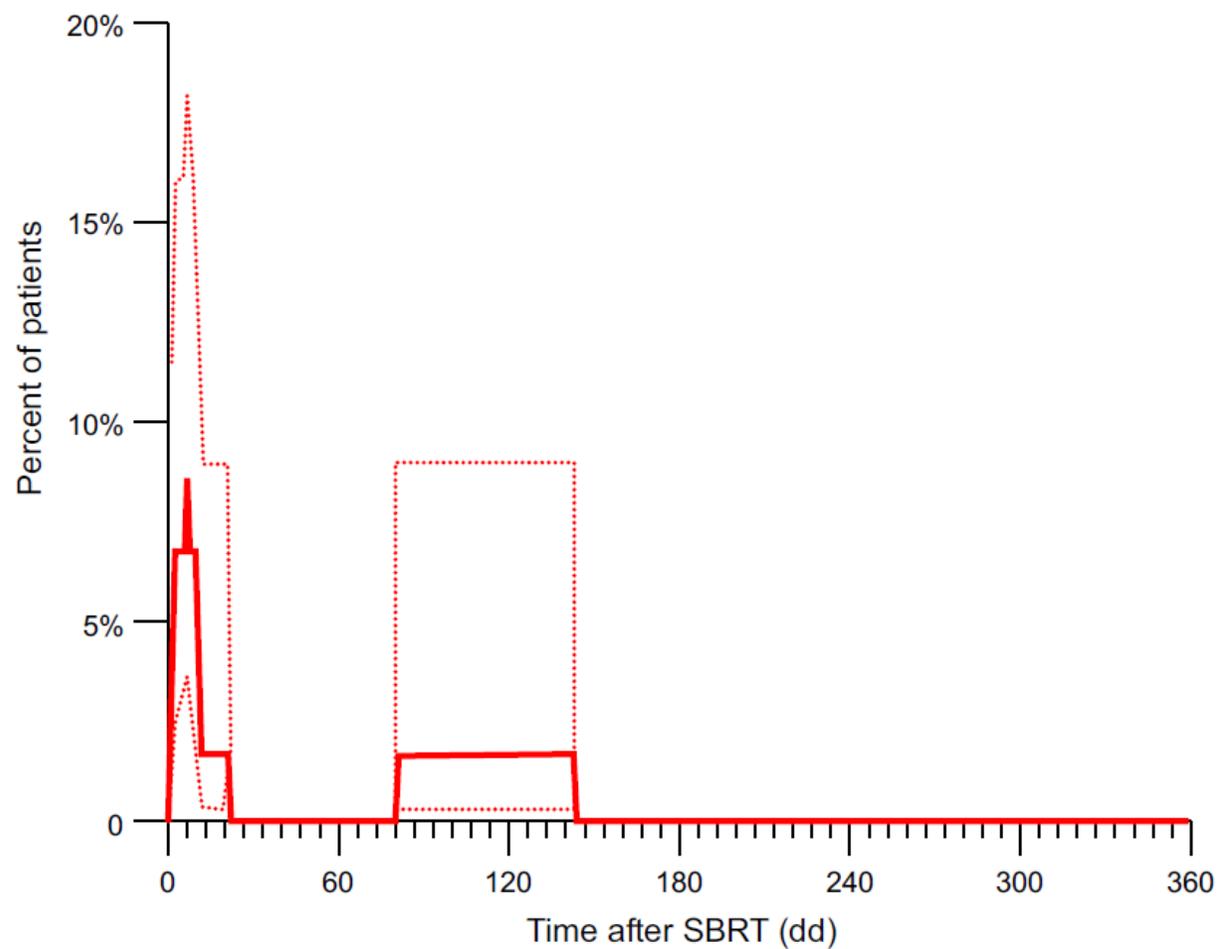
*\*Radiation Oncology, Azienda Sanitaria-Universitaria Friuli Centrale, Udine, Italy; †Radiation Oncology, IRCCS Regina Elena National Cancer Institute, Rome, Italy; ‡Urology, IRCCS Regina Elena National Cancer Institute, Rome, Italy; §Physics, IRCCS Regina Elena National Cancer Institute, Rome, Italy; ||Biostatistics, IRCCS Regina Elena National Cancer Institute, Rome, Italy; ¶Physics, Azienda Sanitaria-Universitaria Friuli Centrale, Udine, Italy; and #Radiation Oncology, San Giovanni-*

**Purpose:** To assess the toxicity profile of prostate cancer stereotactic body radiation therapy (SBRT) in 3 fractions.

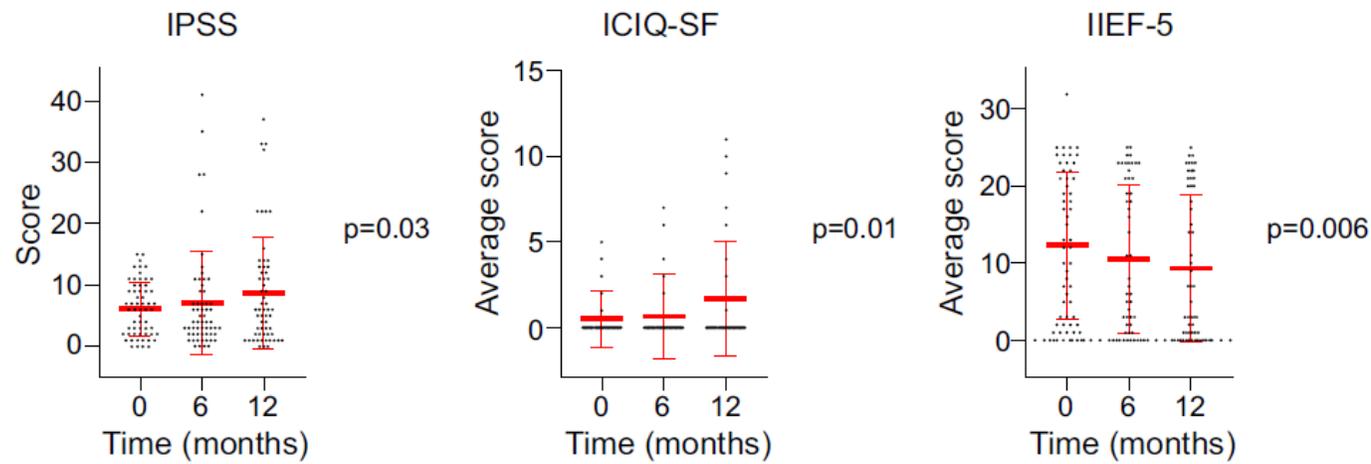
**Methods and Materials:** This was a prospective, multicenter phase 2 toxicity study enrolling patients with low to favorable intermediate-risk prostate cancer. Before simulation, 3 to 4 fiducial markers along with a rectal spacer were placed. The target (prostate only) was prescribed 40 Gy, whereas the maximum dose to the urethra was limited to 33 Gy with the highest priority at planning; less stringent objectives were placed on the bladder, the filling of which was controlled via a Foley catheter. Treatment was delivered every other day. Toxicity was prospectively scored with Common Terminology Criteria for Adverse Events, and several patient-reported outcomes were collected. The maximum allowed prevalence rate of grade 2+ genitourinary (GU) toxicity at 1 year was set at 15%, and the study was sized accordingly.

**Results:** Between November 2015 and May 2019, 59 patients were enrolled by 3 participating institutions. Acute gastrointesti-

## 40Gy in 3 fractions



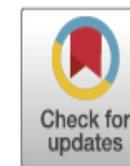
**Fig. 3.** Prevalence of grade 2+ genitourinary toxicity (solid line) up to 1 year after treatment completion. Dotted lines represent 95% confidence intervals.



**Fig. 4.** Mean (SD) scores for the International Prostate Symptom Score, International Consultation on Incontinence Questionnaire-Short Form, and International Index of Erectile Function by time after stereotactic body radiation therapy. 0 indicates baseline/pretreatment values. The number of patients in each group is reported in [Table E2](#).

**Conclusions:** The results suggest that at 12 months after treatment, the toxicity profile of SBRT in 3 fractions is acceptable.

# Two StereoTactic ablative radiotherapy treatments for localized prostate cancer (2STAR): Results from a prospective clinical trial



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**Purpose:** Ultrahypofractionation is appealing for prostate cancer (PCa) due to low  $\alpha/\beta$ , and increasing the dose per fraction could improve the therapeutic index. Here we report the outcomes of a phase II prostate SABR trial using two fractions.

**Methods:** Patients had low or intermediate risk prostate cancer. Three gold fiducials were implanted for image guidance. The clinical target volume (CTV) included the prostate only, and the planning target volume (PTV) was a 3 mm expansion enabled through the use of a rectal immobilization device. The dose prescribed was 26 Gy in 2 weekly fractions (EQD2 110 Gy<sub>1.4</sub>). The primary endpoint was quality of life using EPIC, and minimal clinically important change (MCIC) was defined as an EPIC QOL decrease >0.5 SD.

## 26 Gy in 2 fractions

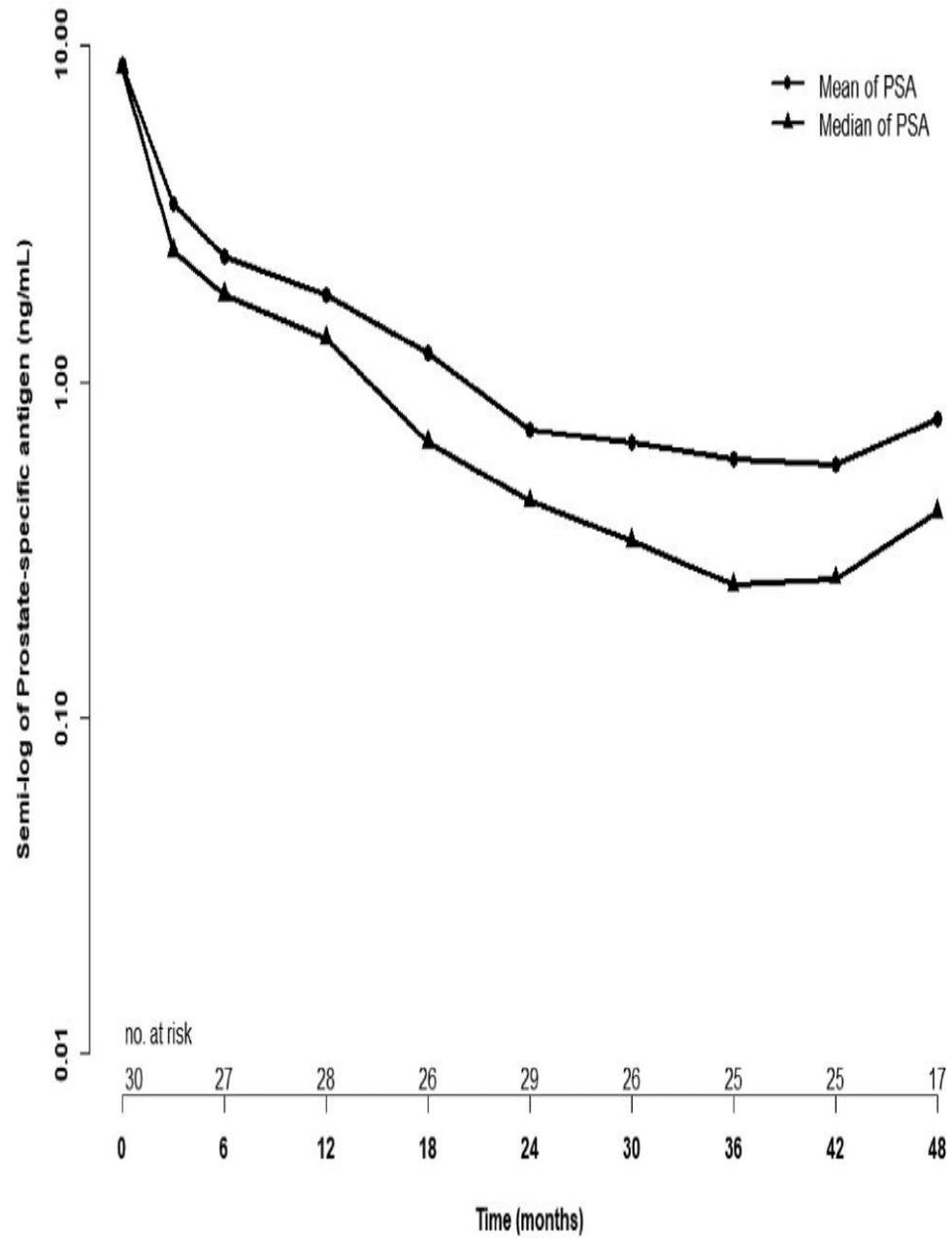
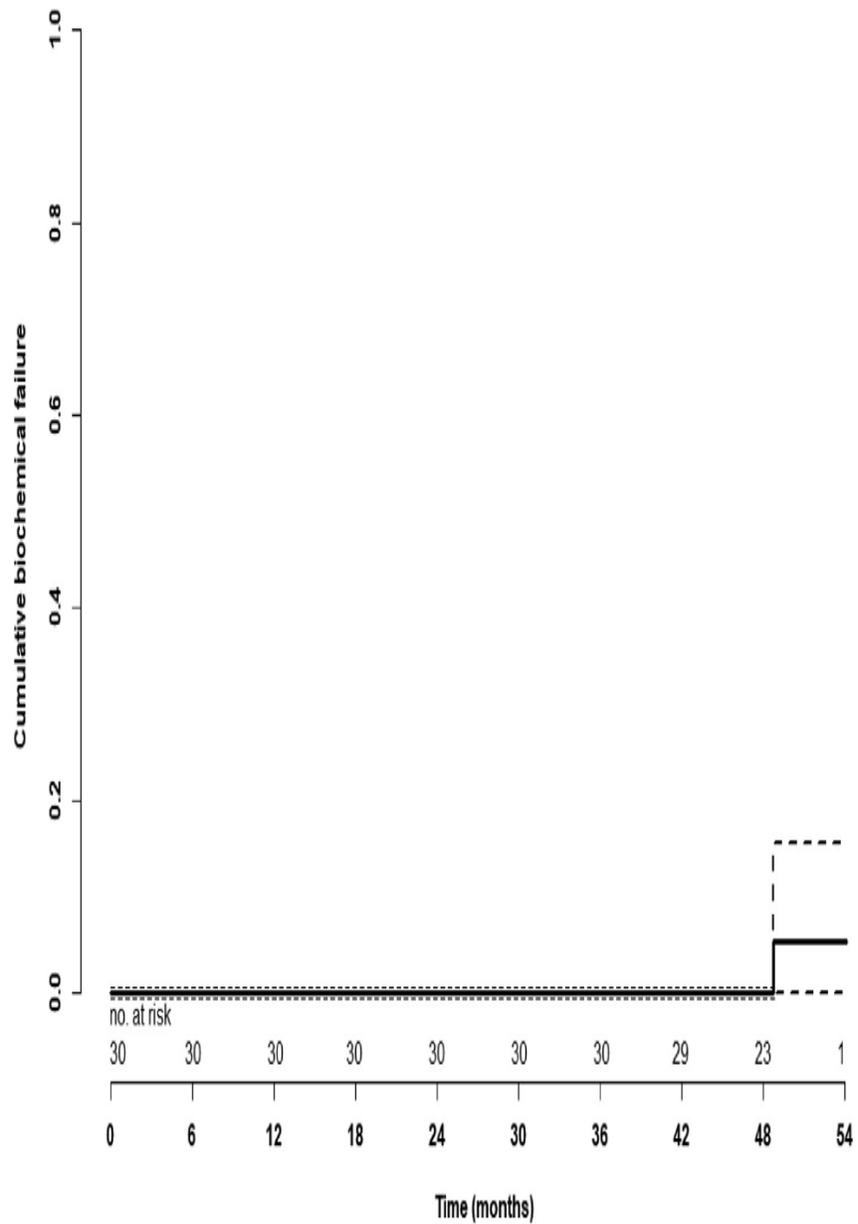


Fig. 2. Mean and median PSA over time.

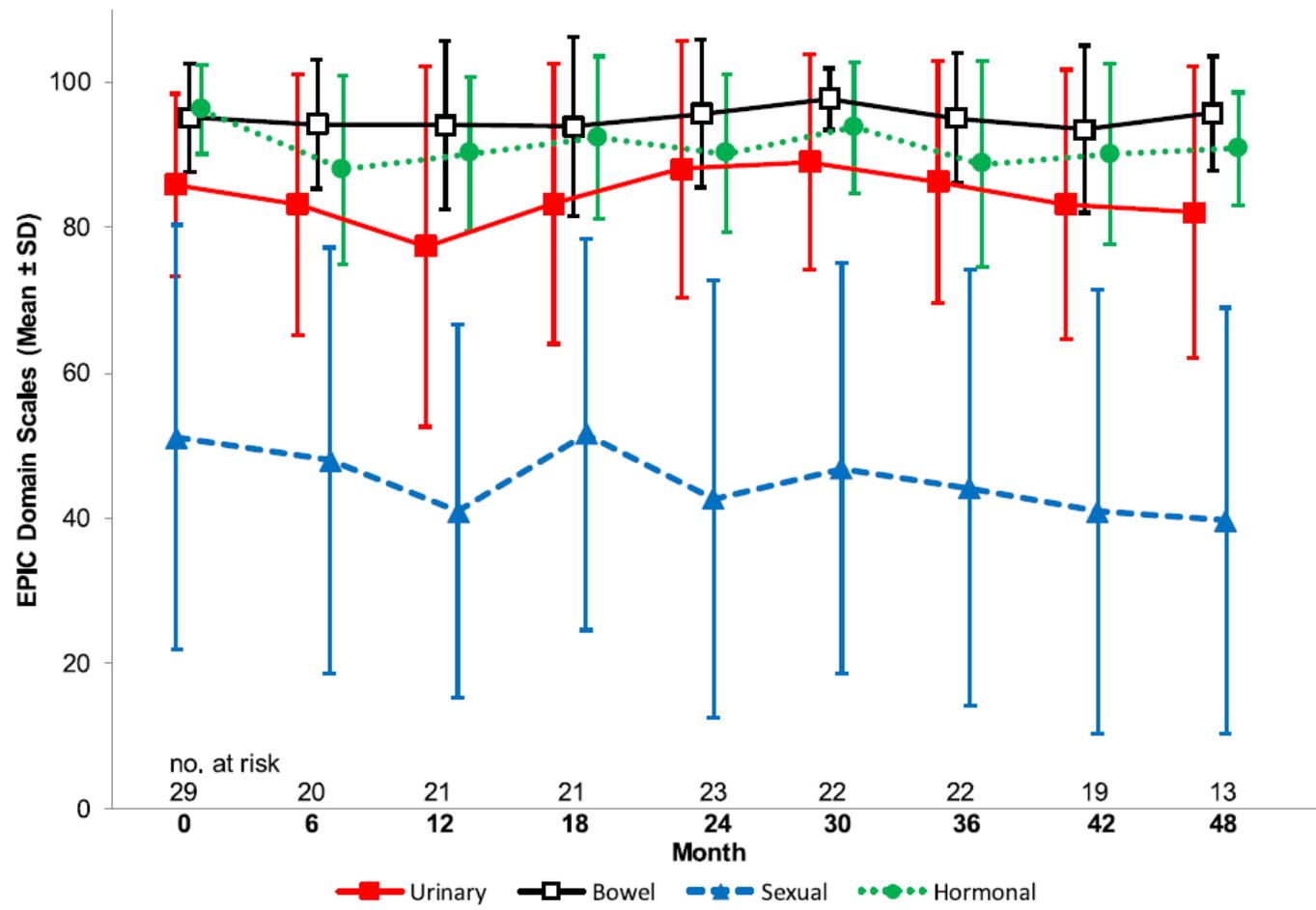


Fig. 3. EPIC QOL change from baseline in the urinary, bowel, sexual and hormonal domains.

# Two versus five stereotactic ablative radiotherapy treatments for localized prostate cancer: A quality of life analysis of two prospective clinical trials



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<sup>a</sup> Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto; <sup>b</sup> Department of Radiation Oncology, University of Toronto, Canada; <sup>c</sup> Division of Radiation Oncology, College of Medicine, King Saud University, Riyadh, Saudi Arabia; <sup>d</sup> Department of Radiation Oncology, Tom Baker Cancer Centre, Calgary; <sup>e</sup> CancerCare Manitoba, Winnipeg, Canada; <sup>f</sup> Compassionate Cancer Centers, India; <sup>g</sup> Department of Radiation Oncology, University of Toronto, Princess Margaret Cancer Centre; and <sup>h</sup> University Health Network, Toronto, Canada

**Methods:** Patients had low or intermediate risk PCa. The doses prescribed were 26 Gy/2 and 40 Gy/5. Expanded prostate cancer index composite was collected. Urinary, bowel and sexual domains were analyzed. Minimal clinically important change (MCIC) was defined as >0.5 standard deviation.

**Results:** 30 and 152 patients were treated with 2-fraction and 5-fraction SABR. Median follow-up was 55 and 62 months. Five-year biochemical failure rate was 3.3% and 4.6%. The 2-fraction cohort had a significantly better mean QOL over time in the bowel domain ( $p = 0.0004$ ), without a significant difference in the urinary or sexual domains. The 2-fraction cohort had a significantly lower rate of bowel MCIC (17.8% vs 42.3%,  $p = 0.01$ ), but there was no difference in urinary (24.1% vs 35.7%) or sexual (15.3% vs 29.2%) MCIC. For MCIC x2 (moderate QOL change), the 2-fraction trial had significantly lower MCIC rates in both the bowel (7.1% vs 24%,  $p = 0.04$ ) and sexual (0 vs 17.6%,  $p = 0.01$ ) domains.

## 26Gy/2 fractions versus 40Gy/5 fractions

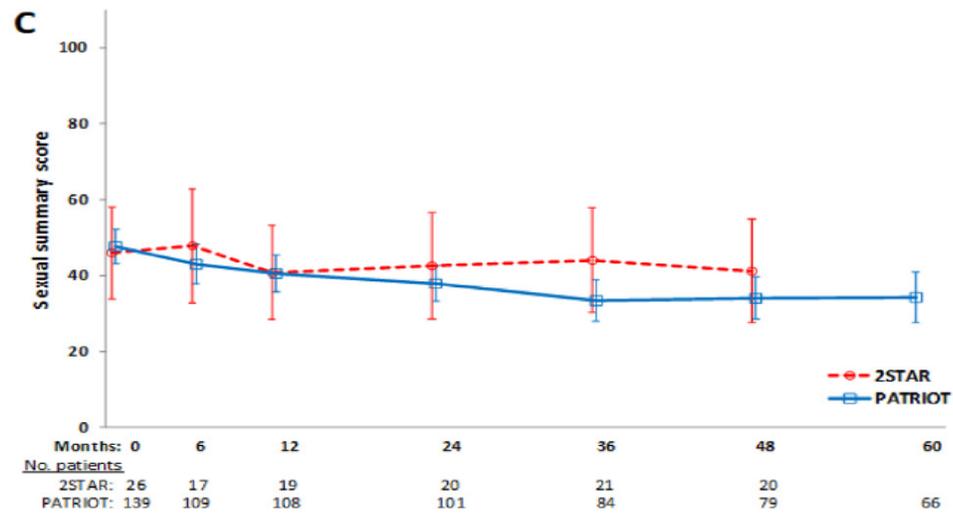
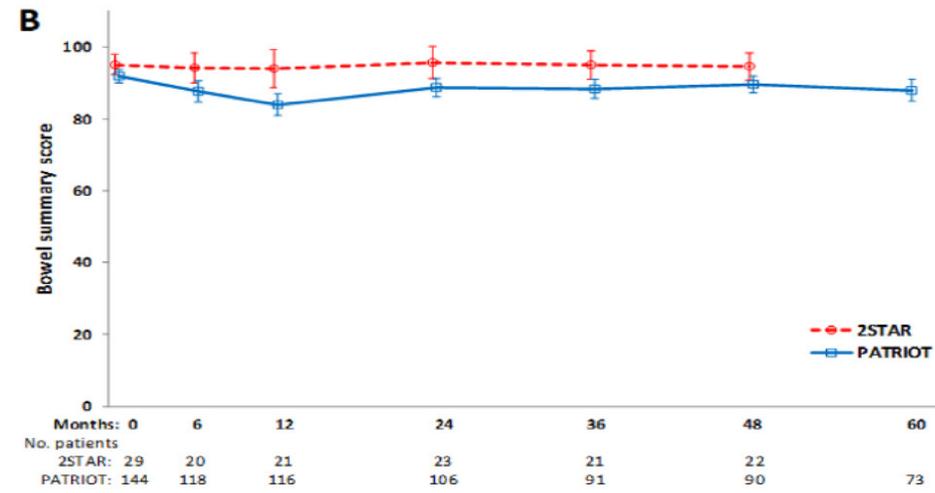
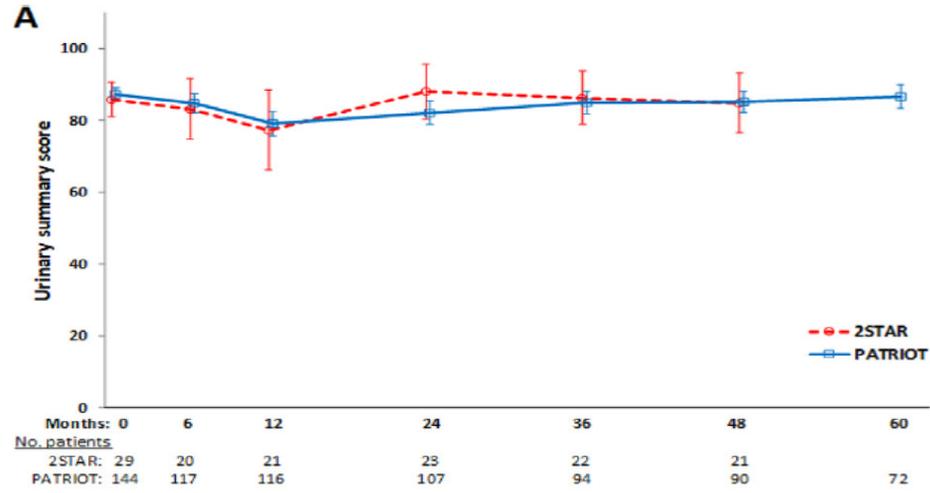


Fig. 1. Mean (+/- standard deviation) quality of life over time.

# ONE SHOT - single shot radiotherapy for localized prostate cancer: study protocol of a single arm, multicenter phase I/II trial



Zilli et al. *Radiation Oncology* (2018) 13:166

Thomas Zilli<sup>1,2\*</sup> , Marta Scorsetti<sup>3,4</sup>, Daniel Zwahlen<sup>5</sup>, Ciro Franzese<sup>4</sup>, Robert Förster<sup>6</sup>, Niccolò Gaj-Levra<sup>7</sup>, Nikolaos Koustouvelis<sup>1</sup>, Aurelie Bertaut<sup>8</sup>, Michel Zimmermann<sup>5</sup>, Giuseppe Roberto D'Agostino<sup>4</sup>, Filippo Alongi<sup>7,9</sup>, Matthias Guckenberger<sup>6</sup> and Raymond Miralbell<sup>1,2</sup>

## Phase I, safety evaluation

The main objective of the phase I trial is to determine if a single fraction SBRT, with a dose of 19 Gy, is safe and well tolerated by assessing the occurrence of Grade  $\geq 3$  acute adverse events (AE) during the first 3 months.

## Phase II, efficacy evaluation

The main objective of the phase II trial is to determine if a single fraction SBRT, with a dose of 19 Gy, is an effective treatment option by assessing bRFS at 3 years.

# 19 Gy in 1 fraction

# Safety and Efficacy of Virtual Prostatectomy With Single-Dose Radiotherapy in Patients With Intermediate-Risk Prostate Cancer Results From the PROSINT Phase 2 Randomized Clinical Trial

JAMA Oncol. 2021;7(5):700-708.

Carlo Greco, MD; Oriol Pares, MD; Nuno Pimentel, MD; Vasco Louro, MD; Inês Santiago, MD; Sandra Vieira, PhD; Joep Stroom, PhD; Dalila Mateus; Ana Soares; João Marques; Elda Freitas; Graça Coelho; Manuela Seixas; Antonio Lopez-Beltran, MD; Zvi Fuks, MD

**DESIGN, SETTING, AND PARTICIPANTS** The PROSINT single-institution phase 2 randomized clinical trial accrued, between September 2015 and January 2017, 30 participants with intermediate-risk prostate cancer to receive SDRT or extreme hypofractionated SBRT. Androgen deprivation therapy was not permitted. Data were analyzed from March to May 2020.

**INTERVENTIONS** Patients were randomized in a 1:1 ratio to receive 5 × 9 Gy SBRT (control arm) or 24 Gy SDRT (test arm).

**MAIN OUTCOMES AND MEASURES** The primary end point was toxic effects; the secondary end points were PSA response, PSA relapse-free survival, and patient-reported quality of life measured with the International Prostate Symptom Score (IPSS) and Expanded Prostate Cancer Index Composite (EPIC)-26 questionnaires.

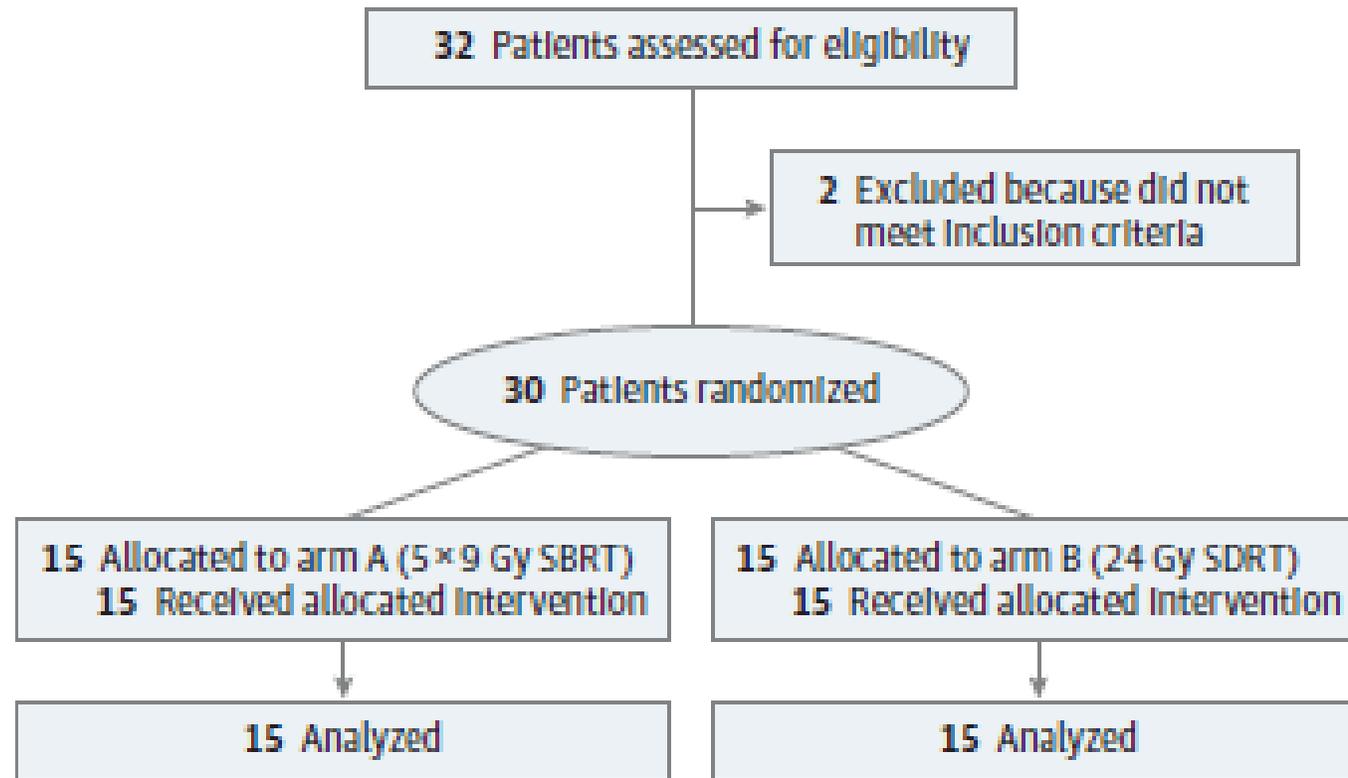
**RESULTS** A total of 30 men were randomized; median (interquartile range) age was 66.3

45Gy in 5 fractions versus 24Gy in one fraction

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Figure 1. CONSORT Diagram

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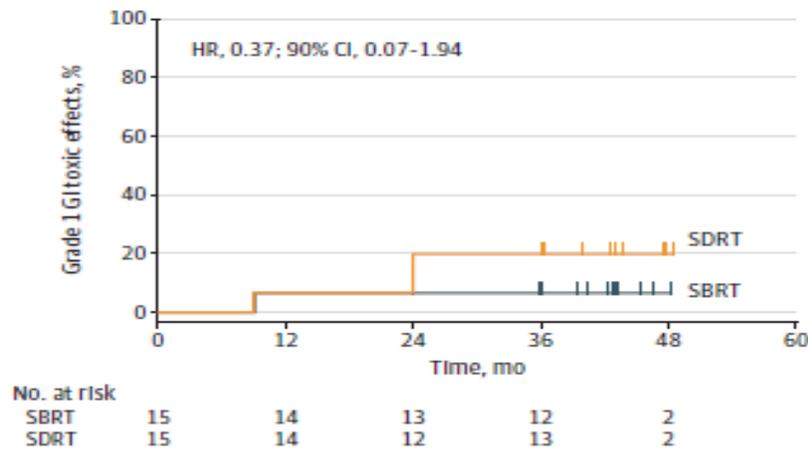
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SBRT indicates stereotactic body radiotherapy; SDRT, single-dose radiotherapy.

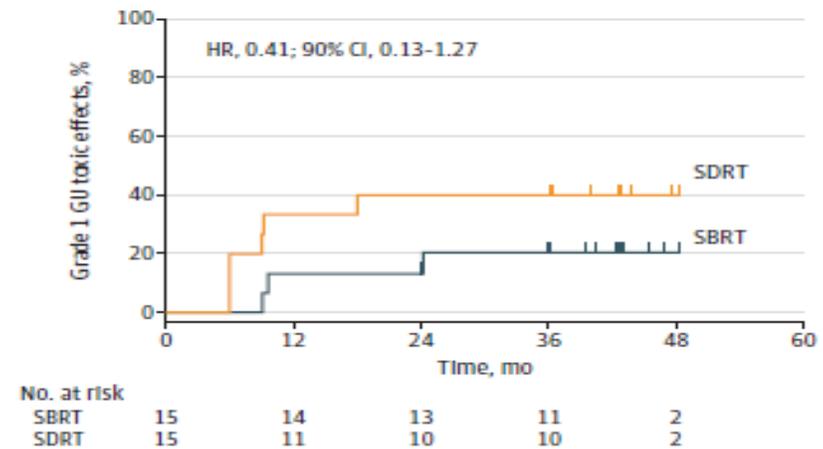
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**Figure 2. Clinical Outcomes of Stereotactic Body Radiotherapy (SBRT) vs Single-Dose Radiotherapy (SDRT) Stratified by Treatment Arm**

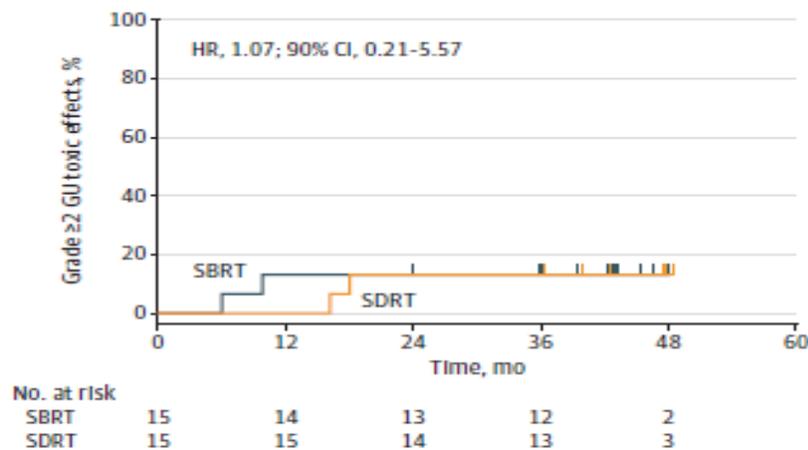
**A** Grade 1 rectal toxic effects by study arm



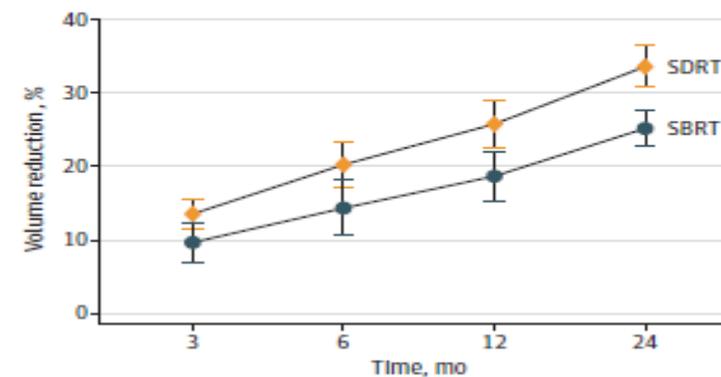
**B** Grade 1 urinary toxic effects by study arm



**C** Grade ≥2 urinary toxic effects by study arm



**D** Volume reduction on magnetic resonance imaging by study arm

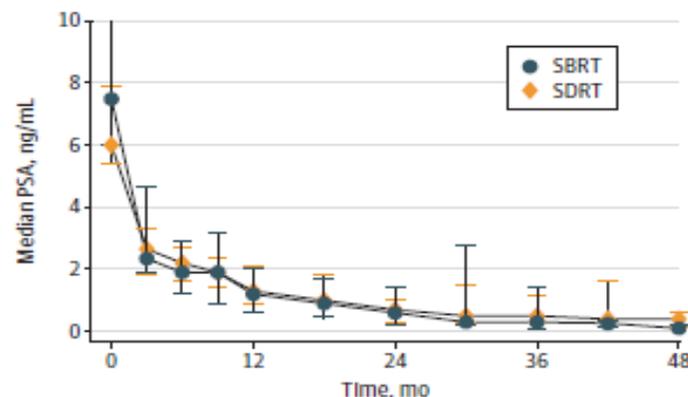


A, Cumulative incidence of bowel grade 1 gastrointestinal (GI) toxic effects. B, Cumulative incidence of genitourinary (GU) grade 1 toxic effects. C, Cumulative incidence of urinary grade ≥2 toxic effects. D, Percentage volume reductions

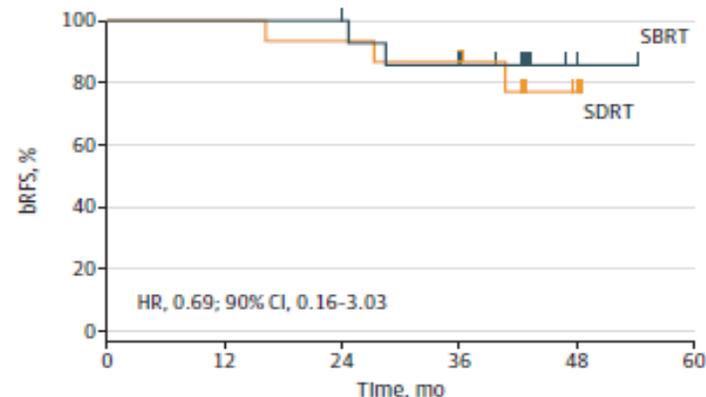
compared to baseline measured by magnetic resonance imaging. Error bars indicate SE; HR, hazard ratio.

Figure 3. Prostate-Specific Antigen (PSA) Response With Stereotactic Body Radiotherapy (SBRT) vs Single-Dose Radiotherapy (SDRT)

**A** PSA decline stratified by study arm

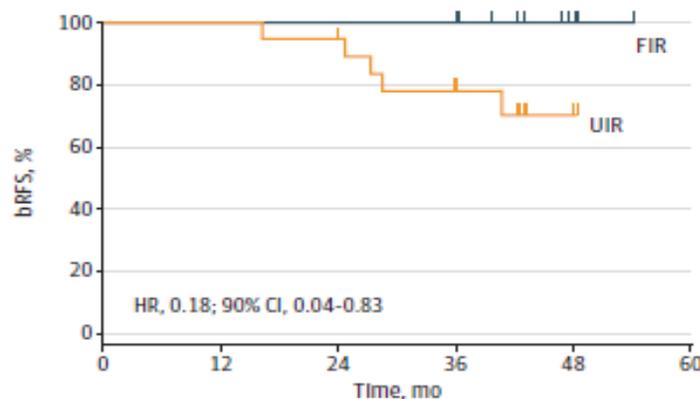


**B** Actuarial bRFS stratified by study arm



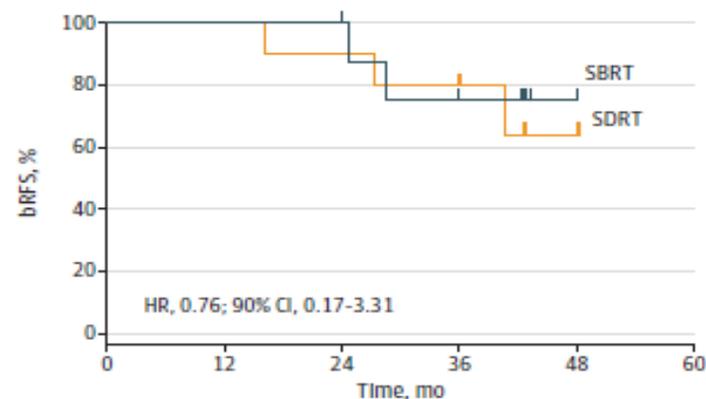
Time (mo)	0	12	24	36	48	60
SBRT	15	15	15	12	3	
SDRT	15	15	14	13	4	

**C** Actuarial bRFS stratified by FIR vs UIR



Time (mo)	0	12	24	36	48	60
FIR	11	11	11	11	4	
UIR	19	19	18	13	3	

**D** Actuarial bRFS for UIR group stratified by SBRT vs SDRT

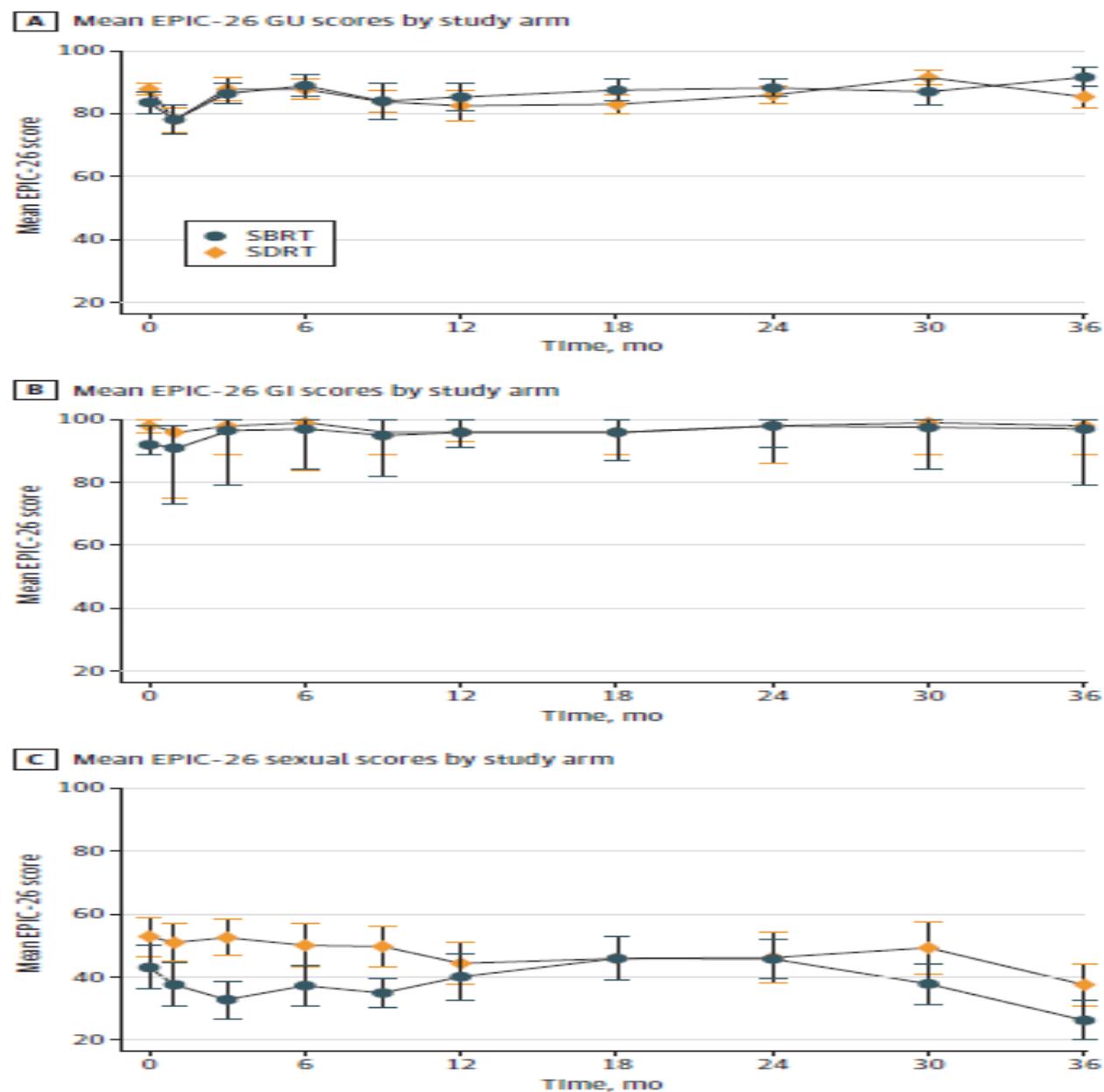


Time (mo)	0	12	24	36	48	60
SBRT	9	9	9	6	2	
SDRT	10	10	10	8	2	

A, Median PSA over time stratified by treatment arm; error bars indicate interquartile range. B, Actuarial PSA relapse-free survival (bRFS) stratified by treatment arm. C, Actuarial bRFS stratified by favorable intermediate-risk (FIR)

vs unfavorable intermediate-risk (UIR) categories. D, UIR actuarial bRFS stratified by treatment arm. HR indicates hazard ratio.

**Figure 4. EPIC-26 Patient-Reported Outcomes of Stereotactic Body Radiotherapy (SBRT) vs Single-Dose Radiotherapy (SDRT) Over Time Stratified by Treatment Arm**



# BED VALUES using an alpha beta of 2

- 40 Gy / 5 fractions      BED 200
- 38 Gy/ 4 fractions      BED 219
- 40 GY/ 3 fractions      BED 306
- 26 Gy/ 2 fraction      BED 195
- 19 Gy/ 1 fraction      BED 200
- 24 Gy/ 1 fraction      BED 312

# CONCLUSIONS

- Data from trials with short follow up support the efficacy and safety of 1-4 fraction regimens
- Concerns from the Four Rs of radiobiology do not seem to be an issue
- Perhaps BED is the most important issue in achieving cancer control
- Higher BED fractionation schemas cause greater gland shrinkage, hence more ablative
- More prospective randomized trials would be needed to shed light on the optimal fractionation