Advances in Radiation Oncology (2023) 8, 101143

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Preliminary Analysis of a Phase II Trial of Stereotactic Body Radiation Therapy for Prostate Cancer With High-Risk Features After Radical Prostatectomy

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Received 3 October 2022; accepted 30 November 2022

Abstract

Purpose: There are limited data regarding using stereotactic body radiation therapy (SBRT) in the postprostatectomy setting. Here, we present a preliminary analysis of a prospective phase II trial that aimed to evaluate the safety and efficacy of postprostatectomy SBRT for adjuvant or early salvage therapy.

Materials and Methods: Between May 2018 and May 2020, 41 patients fulfilled inclusion criteria and were stratified into 3 groups: group I (adjuvant), prostate-specific antigen (PSA) < 0.2 ng/mL with high-risk features including positive surgical margins, seminal vesicle invasion, or extracapsular extension; group II (salvage), with PSA ≥ 0.2 ng/mL but < 2 ng/mL; or group III (oligometastatic), with PSA ≥ 0.2 ng/mL but < 2 ng/mL and up to 3 sites of nodal or bone metastases. Androgen deprivation therapy was not offered to group I. Androgen deprivation therapy was offered for 6 months for group II and 18 months for group III patients. SBRT dose to the prostate bed was 30 to 32 Gy in 5 fractions. Baseline-adjusted physician reported toxicities (Common Terminology Criteria for Adverse Events), patient reported quality-of-life (Expanded Prostate Index Composite, Patient-Reported Outcome Measurement Information System), and American Urologic Association scores were evaluated for all patients.

Results: The median follow-up was 23 months (range, 10-37). SBRT was adjuvant in 8 (20%) patients, salvage in 28 (68%), and salvage with the presence of oligometastases in 5 (12%) patients. Urinary, bowel, and sexual quality of life domains remained high after SBRT. Patients tolerated SBRT with no grade 3 or higher (3+) gastrointestinal or genitourinary toxicities. The baseline adjusted acute and late toxicity grade 2 genitourinary (urinary incontinence) rate was 2.4% (1/41) and 12.2% (5/41). At 2 years, clinical disease control was 95%, and biochemical control was 73%. Among the 2 clinical failures, 1 was a regional node and the other a bone metastasis. Oligometastatic sites were salvaged successfully with SBRT. There were no in-target failures.

Sources of support: This work had no specific funding.

Disclosures: Steven E. Schild is a writer and editor for UptoDate. The other authors declare that they have no competing interests.

Data sharing statement: The data sets generated during the current study are not publicly available due to restricted access to institutional repository but can be available from the corresponding author on reasonable request.

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https://doi.org/10.1016/j.adro.2022.101143

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Conclusions: Postprostatectomy SBRT was very well tolerated in this prospective cohort, with no significant effect on quality of life metrics postirradiation, while providing excellent clinical disease control.
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Introduction

Radiation therapy (RT) may be used after radical prostatectomy in men with localized prostate cancer. Adjuvant therapy may be offered when patients present with high-risk pathologic features such as seminal vesicle invasion (SVI), extracapsular extension (ECE), and positive margins. On the other hand, salvage therapy is delivered when postsurgical serum prostate-specific antigen (PSA) has risen above a certain threshold. Several phase III randomized clinical trials have indicated that postprostatectomy RT improves overall and progression-free survival, either as adjuvant or early salvage. However, these studies have employed conventionally fractionated RT regimens delivered over 6 to 7 weeks.[1–5]

The relatively long duration of this treatment increases the total cost of care. It strains the system by growing demand for treatment machine time and personnel utilization in RT departments, limiting access to care. Brenner and Hall[6] postulated that relatively high doses of radiation were necessary to maximize prostate tumor control with conventional fractionation. Similarly, higher radiation doses have been demonstrated to improve outcomes in the postprostatectomy setting.[7,8] Hypofractionated regimens and ultrahypofractionated regimens, such as stereotactic body radiation therapy (SBRT), are novel solutions that deliver high biologic equivalent doses to the target in a much shorter overall treatment duration. Because of the low α/β of prostate cancer compared with the surrounding tissue, there is a theoretical improvement in the therapeutic ratio through these hypofractionated regimens. SBRT is a desirable option because fewer RT fractions with high biologic equivalent doses can decrease equipment utilization, improve access to care, and increase patient convenience. Although SBRT has demonstrated noninferiority to moderately hypofractionated RT for treatment of intact prostate, high-level clinical evidence on the role of SBRT for postprostatectomy RT is emerging.[9,10] Here, we present a preliminary analysis from a prospective phase II clinical trial evaluating the efficacy and safety of SBRT in the postprostatectomy setting.

Materials and Methods

Study design and patient selection

This study was an institutional multicenter, open-label, nonrandomized phase II clinical trial approved by the institutional review board of the sponsoring institution. This trial was registered at the National Institute of Health clinical trial registry (NCT03570827), available on the ClinicalTrials.gov website. All participants signed informed consent before participation.

The trial opened for accrual at 2 National Cancer Institute (NCI)-designated comprehensive cancer centers, Mayo Clinic Rochester and Mayo Clinic Arizona, and accrued participants between May 2018 and May 2020. Eligibility criteria included patients with histologically confirmed adenocarcinoma of the prostate who underwent radical prostatectomy and presented high-risk pathologic features such as positive surgical margins, ECE, or SVI, or fulfilled biochemical failure criteria defined by serum PSA $\geq$ 0.2 ng/mL, as suggested by the American Urologic Association. The study stratified patients into 3 different groups: (1) group I (adjuvant), defined as serum PSA $<$ 0.2 ng/mL with at least 1 pathologic high-risk feature (positive margins, ECE, or SVI); (2) group II (salvage), defined as having serum PSA $\geq$ 0.2 ng/mL but $<$ 2 ng/mL and no evidence of distant disease or positive lymph nodes (LN) on imaging studies or surgical pathology; and (3) group III (oligometastatic), defined as having serum PSA $\geq$ 0.2 ng/mL and positron emission tomography tracer-avid pelvic or abdominal LNs or bone lesions in up to 3 distinct areas. Prior androgen deprivation therapy (ADT) was allowed if the total duration at the time of accrual was less than 6 months. For patients undergoing ADT at the time of accrual, serum PSA had to be undetectable to be considered eligible. Additional requirements included Eastern Cooperative Oncology Group performance status 0 to 2 and International Prostate Symptom Score $<$ 25.

Ineligibility criteria included previous pelvic radiation; history of nonprostatic cancer within the past 5 years; prior or current ADT for longer than 6 months; active rectal diverticulitis or Crohn disease; prior systemic chemotherapy for prostate cancer; history of urethral stricture requiring dilatation; current anticoagulation with warfarin sodium, heparin, low-molecular-weight heparin, or clopidogrel bisulfate; or significant medical, addictive, or psychiatric illnesses.

Interventions

All patients received postprostatectomy SBRT to the prostate fossa. The total dose for the prostate fossa was 30 Gy (group I) or 32 Gy (group II-III) in 5 fractions. SBRT

fractions were delivered at least 36 hours apart, mostly every other day, and completed within 2 weeks. For oligometastatic patients from group III, pelvic or abdominal LNs were also treated with 30 Gy in 5 fractions, while bone metastases received 20 Gy in 1 fraction. Six months of ADT were provided for patients in group II. Eighteen months of ADT were provided for patients from group III. SBRT was delivered using intensity modulated RT, most frequently via volumetric modulated arc therapy. The clinical target volume was defined as the prostate fossa plus seminal vesicles bed per Radiation Therapy Oncology Group consensus guidelines. A 5-mm isotropic expansion was added to create the planning target volume (PTV). The dose was prescribed to the PTV, with 100% of the prescription dose to at least 95% of the PTV and 100% of the PTV receiving at least 90% of the prescription dose. Normal tissue constraints included rectum V30 < 15% (minor deviation V30 < 40%, major deviation V30 > 40%), bladder V33 < 8 cc and V30 < 50 cc, femoral heads V40 < 1 cc (minor deviation V40 < 2 cc, major deviation V40 ≥ 2 cc), small bowel D_{max} of 35 Gy, large bowel D_{max} of 38 Gy, and spinal cord D_{max} of 14 Gy. A planning computed tomography (CT) was performed with a high-resolution scanner with <2-mm cuts through the prostate fossa. Patients were immobilized for the treatment in a supine position, using an appropriate customized immobilization device. An inflatable rectal probe was inserted to displace the posterior rectal wall from the radiation beams and to decrease movement of the rectum. One hundred cc of saline was recommended to be used on a daily basis. Daily image guidance was performed with cone beam CT. SBRT was delivered on TrueBeam linear accelerators (Varian Medical Systems Inc, Palo Alto, CA).

Study endpoints and follow-up

The primary study endpoint was freedom from failure (FFF), defined as the first occurrence of clinical failure (local recurrence, regional recurrence, or distant metastasis), biochemical failure (serum PSA ≧ 0.5 ng/mL above the nadir serum PSA), or the start/restart of subsequent salvage therapy including ADT. Secondary endpoints included physician-reported grade 2 and 3 genitourinary (GU) and gastrointestinal (GI) toxicities, patient-reported quality of life (QoL), sexual function at 3 years, and survival outcomes. Patients were followed with clinic visits every 3 months with history and physical examination, toxicity assessment, and repeat PSA for the first year then subsequently at 6-month intervals. Toxicities were assessed according to the NCI-Common Terminology Criteria for Adverse Events (version 4). Acute toxicity was measured as occurring less than 3 months (90 days) from end of radiation. Late toxicity was measured as occurring greater than or equal to 3 months from end of radiation. QoL outcomes were measured according to the concept of health-related QoL through the Patient-Reported Outcome Measurement Information System-10, Expanded Prostate Index Composite (EPIC), Medical Outcomes Study SF-12, and American Urologic Association Symptom Index.

Statistical analysis

This phase II study was designed to determine whether 5-year FFF after SBRT was comparable to previous major published results using conventional fractionation in the adjuvant and salvage setting. As appropriate, patient characteristics were summarized using means, medians, ranges, and proportions. Logistic regression models were employed for binary outcomes analysis. Groups I/II were evaluated separately from group III in this analysis.

Success was defined as FFF at 5 years. The most significant success proportion where the proposed treatment regimen would be considered ineffective in this population was ≤61% for groups I/II and ≤20% for group III, while the smallest success proportion that would warrant subsequent studies with the proposed regimen would be 80% for groups I/II and 47.5% for group III. Simon's optimum design was used to test the null hypothesis that the proportion of successes was equal to or higher than the previously mentioned thresholds by patient groups.

This was a preliminary analysis reporting physician-scored toxicity and patient-reported QoL outcomes of patients receiving postprostatectomy SBRT. Repeated measures mixed modeling was used to determine whether there were any differences in patient-reported QoL or physician-scored toxicity at baseline, end of treatment, 3 months, 1 year, and years 2, 3, 4, and 5 after radiation delivery. The Kaplan-Meier method was used to present rates over time for clinical outcomes such as FFF. Time-to-event outcomes were calculated starting from the date of the last radiation treatment. All statistical tests performed were 2-sided with an α level of 0.05, and these analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Between May 2018 and May 2020, 41 patients were consented to and treated in the study. The median follow-up was 23 months (range, 10.0-37.0). The median age at the time of SBRT was 70.0 years (range, 56.0-81.6). Upon study stratification, group I (adjuvant) had 8 (20%) patients, group II (salvage) had 28 (68%) patients, and group III (oligometastatic) had 5 (12%) patients. Among the 5 group III patients, 5 received SBRT to pelvic LNs, 1 to para-aortic LNs, and 1 to bone metastases. Further patient and treatment characteristics are demonstrated in Table 1.

Table 1 Patient characteristics

Characteristic	Group I N (%)	Group II N (%)	Group III N (%)	Total N (%)
No. of patients	8 (19.5)	28 (68.3)	5 (12.2)	41 (100.0)
Age at RT				
Mean (SD)	69.0 (7.3)	68.6 (6.4)	72.0 (5.6)	69.1 (6.4); $P = .575$
Median (range)	69.0 (57.7-81.6)	69.2 (56-80.2)	73.1 (62.3-76.7)	70 (56-81.6)
Race				
American Indian or Alaska native	0 (0.0)	1 (3.6)	0 (0.0)	1 (2.4)
Black or African American	0 (0.0)	1 (3.6)	0 (0.0)	1 (2.4)
White	8 (100.0)	26 (92.9)	5 (100.0)	39 (95.1)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ECOG				
Median (range)	0 (0-0)	0 (0-1)	0 (0-1)	0 (0-1)
Prior ADT				
Yes	1 (12.5)	4 (14.3)	2 (40.0)	7 (17.1)
No	7 (87.5)	24 (85.7)	3 (60.0)	34 (82.9)
Gleason grade				
I	0 (0.0)	1 (3.6)	0 (0.0)	1 (2.4)
II	5 (62.5)	12 (42.9)	1 (20.0)	18 (43.9)
III	3 (37.5)	8 (28.6)	2 (40.0)	13 (31.7)
IV	0 (0.0)	4 (14.3)	0 (0.0)	4 (9.8)
V	0 (0.0)	3 (10.7)	2 (40.0)	5 (12.2)
Pathologic T stage				
pT2	2 (25.0)	17 (60.7)	2 (40.0)	21 (51.2)
pT3a	4 (50.0)	9 (32.1)	3 (60.0)	16 (39.0)
pT3b	2 (25.0)	2 (7.1)	0 (0.0)	4 (9.8)
Pathologic N stage				
pNX	1 (12.5)	3 (10.7)	1 (20.0)	5 (12.2)
pN0	7 (87.5)	25 (89.3)	4 (80.0)	36 (87.8)
pN1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ECE				
Yes	4 (50.0)	11 (39.3)	3 (60.0)	18 (43.9)
No	4 (50.0)	17 (60.7)	2 (40.0)	23 (56.1)
SVI				
Yes	2 (25.0)	3 (10.7)	0 (0.0)	5 (12.2)
No	6 (75.0)	25 (89.3)	5 (100.0)	36 (87.8)
PNI				
Yes	7 (87.5)	14 (50.0)	5 (100.0)	26 (63.4)
No	1 (12.5)	14 (50.0)	0 (0.0)	15 (36.6)
LVSI				
Yes	1 (12.5)	3 (10.7)	0 (0.0)	4 (9.8)
No	7 (87.5)	25 (89.3)	5 (100.0)	37 (90.2)

Abbreviations: ADT = androgen deprivation therapy; ECE = extracapsular extension; ECOG = Eastern Cooperative Oncology Group; LVSI = lymphovascular invasion; No. = number; PNI = perineural invasion; RT = radiation therapy; SD = standard deviation; SVI = seminal vesicles invasion.

Outcomes

All consented participants were evaluable on the last follow-up. In total, 30 (73%) patients were free from failures at the previous assessment. Of the 11 (27%) patients who developed progression, 4 (36%) were in group I, 6 (55%) in group II, and 1 (9%) in group III. Eight (73%) failures were due to rising serum PSA, 1 (9%) was due to regional failure in pelvic LNs, and 1 (9%) was due to axial skeleton bony metastasis. The freedom from biochemical failure was 50% in group I, 78.5% in group II, and 80% in group III. By the end of the follow-up period, 1 failure was a patient's death due to metastatic disease to the liver and brain of neuroendocrine differentiation, presumed pulmonary in origin. Of the 11 patients who experienced failure, 4 were started on intermittent ADT. The 2 patients with nodal or bone failures were salvaged successfully with SBRT. There were no failures in the prostate bed or other radiated sites. All other patients remained free from progressive clinical disease. Figure 1 presents the Kaplan-Meier curves for overall survival (OS) (A) and freedom from progression (B).

Toxicities

SBRT was well tolerated after radical prostatectomy (Table 2). There were no grade 3 or greater (3+) toxicities. Ten patients had grade 2 GU adverse events: 2 (4.8%) in group I, 6 (14.6%) in group II, and 2 (4.8%) in group III. Six patients had baseline adjusted related grade 2 GU toxicities: 2 (4.8%) in group I, 3 (7.3%) in group II, and 1 (5%) in group III. The baseline adjusted acute and late toxicity grade 2 GU (urinary incontinence) rate was 2.4% (1/41) and 12.2% (5/41). There were no grade 2+ GI toxicities. All other treatment-related adverse events were graded as 0 or 1. Total urinary QoL scores remained high, with a median score of 91.3 (range, 42.3-97.9), 88.9 (range, 51.3-100), and 84.1 in group I, II, and III, respectively. The median total bowel QoL score was 97.3 (89.3-100), 96.4 (44-100), and 96.4 (73.2-100) across time in group I, II, and III. After SBRT, there was no statistically significant change ($P > .05$) in mean scores for EPIC urinary (Fig. 2A-J), bowel (Fig. 3A-F), and sexual function (Fig. 4A-F) domains at various time points. For patients who received ADT, lower scores were observed on the EPIC hormonal domain during the use period (Supplementary Material, Fig. 5A-F). In patients who received ADT for 6 months (group II), hormonal scores had recovered by 12 months (Supplementary Material, Fig. 5A-F). For patients treated with ADT for 18 months (group III), hormonal scores had recovered by 24 months (Supplementary Material, Fig. 5A-F). There were statistically significant differences in hormonal scores among group I, II, and III at 12 months ($P < .001$). Overall QoL remained high based on American Urologic Association Symptom Index and Patient-Reported Outcome Measurement Information System-10 mental and physical scores at the different follow-up timepoints (Supplementary Material, Fig. 6A-F).

Discussion

After radical prostatectomy, RT has traditionally been used in 2 scenarios. Adjuvant therapy is provided for patients with high-risk pathologic features such as positive margins, SVI, and ECE. In the salvage setting, prostate bed RT may be delivered when serum PSA persists or rises to detectable levels after surgery. Multiple randomized phase III trials have demonstrated the advantages of offering adjuvant/salvage RT after prostatectomy in the presence of such high-risk factors.[1-3] In Southwest

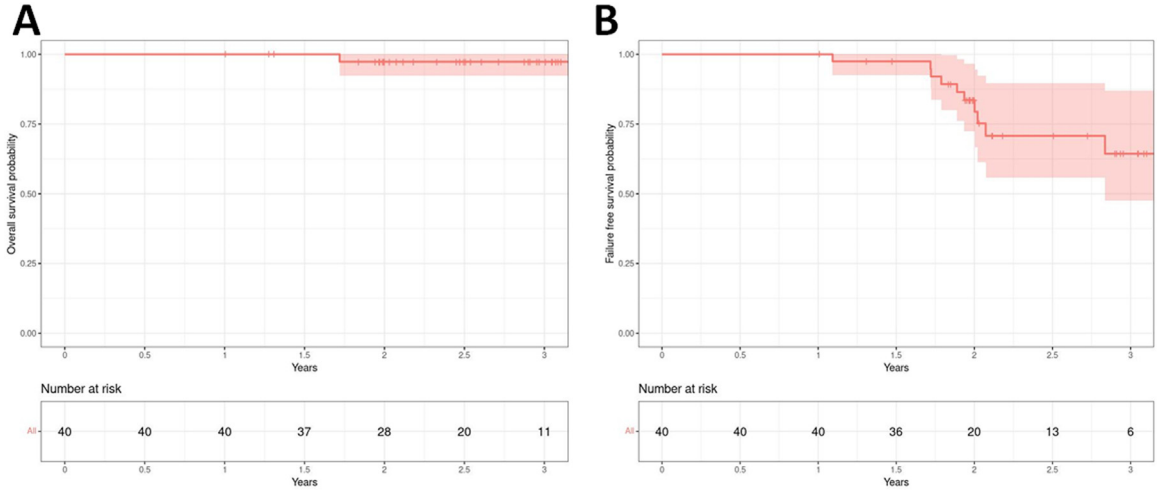

Figure 1 Overall survival (A) and freedom from failure (B) after stereotactic body radiation therapy (SBRT) postprostatectomy radiation.

Table 2 Toxicity outcomes after SBRT

Adverse events	Group I N (%)	Group II N (%)	Group III N (%)	Total N (%)
Any grade 2+				
Yes	2 (25.0)	6 (21.4)	2 (40.0%)	10 (24.4%)
No	6 (75.0)	22 (78.6)	3 (60.0%)	31 (75.6%)
Any grade 3+				
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	8 (100.0)	28 (100.0)	5 (100.0)	41 (100.0)
GU grade 2+				
Yes	2 (25.0)	6 (21.4)	2 (40.0)	10 (24.4)
No	6 (75.0)	22 (78.6)	3 (60.0)	31 (75.6)
GU grade 3+				
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	8 (100.0)	28 (100.0)	5 (100.0)	41 (100.0)
GI grade 2+				
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	8 (100.0)	28 (100.0)	5 (100.0)	41 (100.0)
GI grade 3+				
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	8 (100.0)	28 (100.0)	5 (100.0)	41 (100.0)
Other grade 2+				
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	8 (100.0)	28 (100.0)	5 (100.0)	41 (100.0)
Other grade 3+				
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	8 (100.0)	28 (100.0)	5 (100.0)	41 (100.0)

Abbreviations: GI = gastrointestinal; GU = genitourinary; SBRT = stereotactic body radiation therapy.

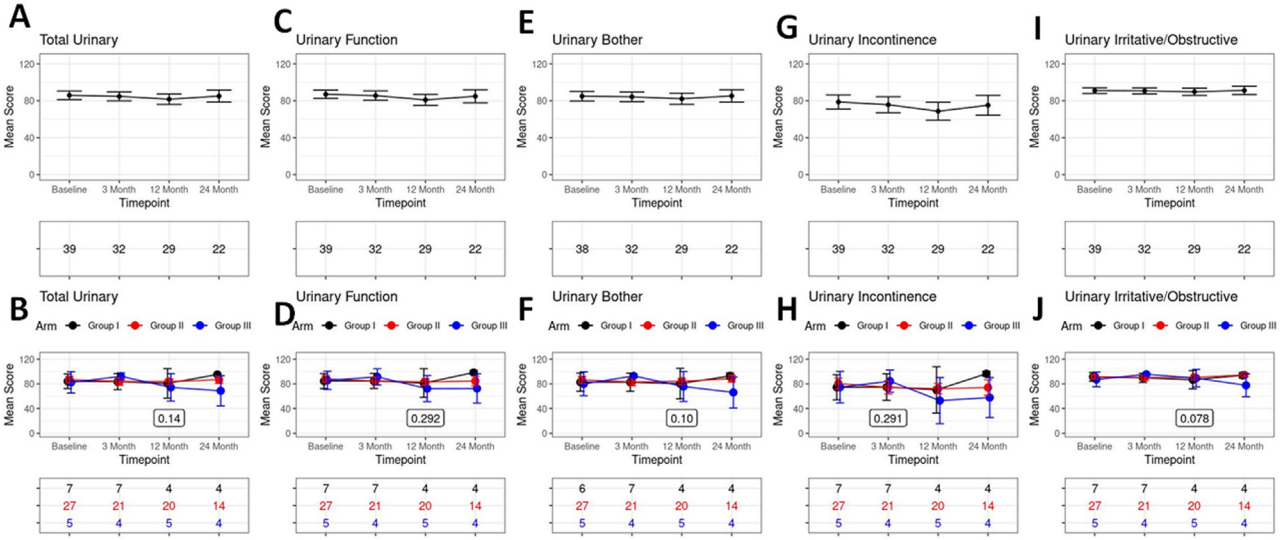

Figure 2 Urinary mean toxicity at timepoints after stereotactic body radiation therapy (SBRT) postprostatectomy radiation.

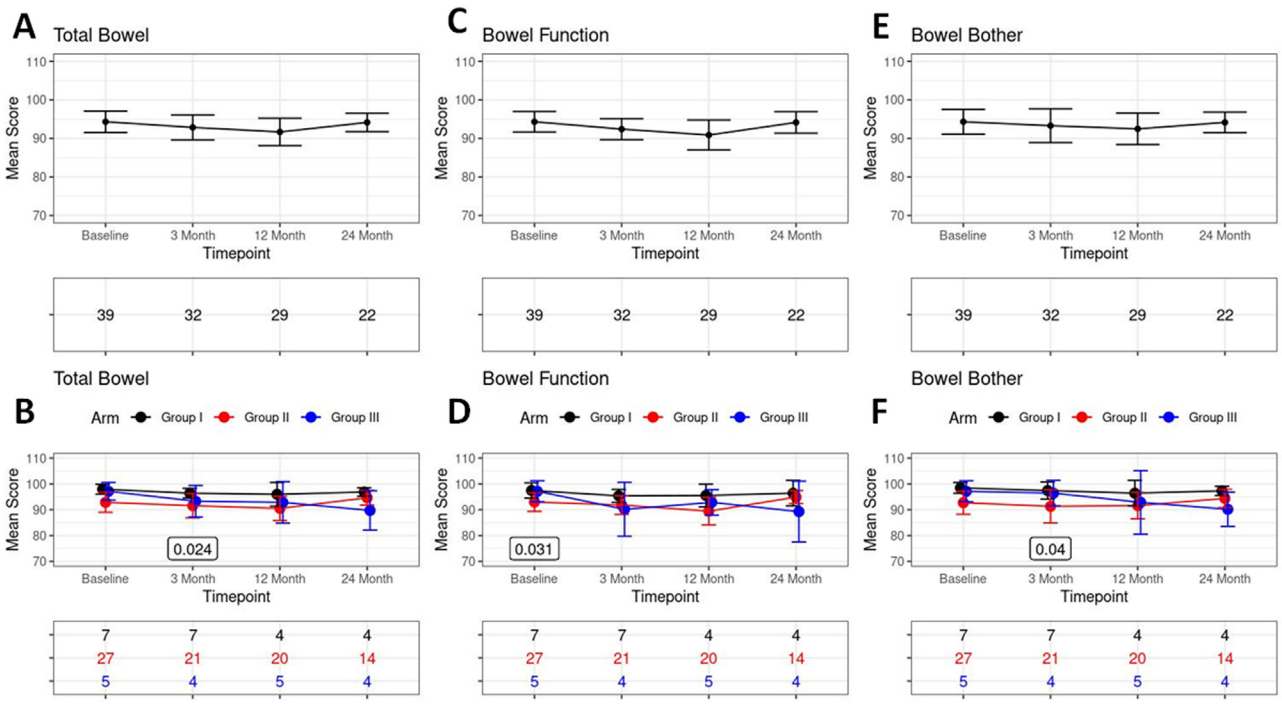

Figure 3 Gastrointestinal mean toxicity at timepoints after stereotactic body radiation therapy (SBRT) postprostatectomy radiation.

Oncology Group (SWOG) 8794, adjuvant RT demonstrated improved 10-year biochemical progression-free survival (BPFS) and OS in patients with high-risk pathologic features compared with a wait-and-see approach with delayed salvage therapy when PSA had risen to 0.5 ng/mL or higher after being undetectable postoperatively.[3] Similarly, European Organization for Research and Treatment of Cancer 22991 demonstrated improved 10-year BPFS with adjuvant RT but no difference in OS.[2] The exact timing of postprostatectomy radiation has also been extensively investigated.[9,11-13] The RADICALS trial evaluated conventionally fractionated

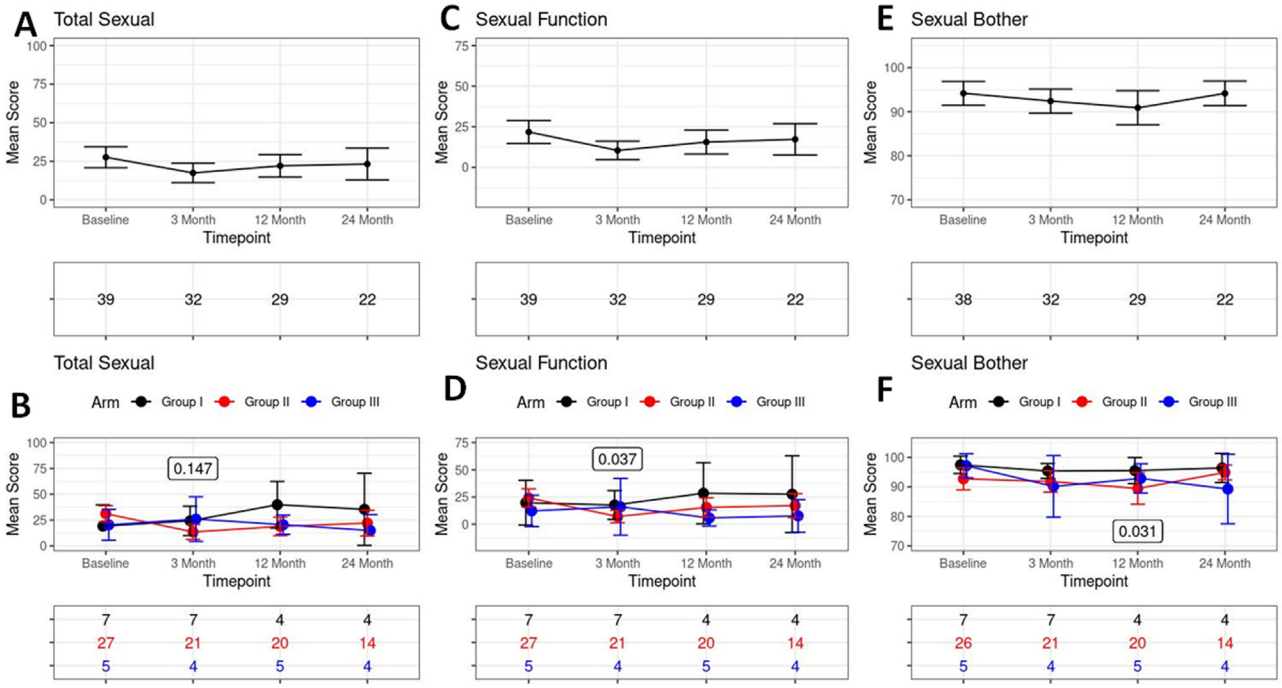

Figure 4 Sexual mean toxicity at timepoints after stereotactic body radiation therapy (SBRT) postprostatectomy radiation.

RT (66 Gy/33 fx) and hypofractionated RT (52.5 Gy/20 fx) in patients with high-risk factors after prostatectomy as adjuvant versus salvage therapy in the setting of PSA failure defined as >0.1 ng/mL or 3 consecutive PSA rises. No difference in BPFS between adjuvant RT and early salvage RT was observed.[14] Other important phase III trials have confirmed the equivalent outcomes of offering early salvage RT compared with adjuvant RT, including a recent large meta-analysis.[15-17]

More recently, phase II and III trials have started to evaluate the role of hypofractionated RT in the postprostatectomy setting.[18-20] Wages et al[18] performed a combined phase I/II study of 32 patients in which the shortest dose fractionation schedule with acceptable toxicity was 42.6 Gy in 10 fractions. Grade 3 GU and GI toxicity occurred in 3 (9.4%) patients and 1 patient (3%). At a median follow-up of 3.5 years, 34.3% of patients presented biochemical failure. The NRG GU003 trial evaluated toxicity outcomes between hypofractionated versus conventionally fractionated postprostatectomy RT, observing no significant changes in mean GU and GI toxicity at 6- and 12-months posttreatment, fulfilling the trial noninferiority.[20] However, patients treated with the hypofractionated regimen experienced higher acute GI toxicity.[20] In published series of hypofractionation delivered in the postprostatectomy setting, acute GU toxicity and GI toxicity has ranged between 9% to 13% and 9% to 18%, respectively.[19,21-23]

SBRT is a proven approach to managing intact prostate cancer. It is associated with similar biochemical control rates compared with more protracted regimens at the cost of higher acute toxicities.[24-26] However, there are little data regarding the efficacy and toxicity of ultrahypofractionated regimens such as SBRT in the postprostatectomy setting. One of the theoretical advantages of using SBRT in this scenario is based on the proposed α/β of 1.5 for prostate cancer, for which 30 Gy in 6 Gy fractions and 32 Gy in 6.4 Gy fractions (5 treatments) would be a dose equivalent in 2 Gy fractions of 64 and 72 Gy, respectively. Considering an estimated α/β of 3.5 for normal tissue, a dose equivalent in 2 Gy fractions of only 52 and 58 Gy would be delivered to the portions of the rectum or bladder receiving total prescription doses.[15-17,27-34] Beyond radiobiologic advantages, a much shorter treatment schedule offers patients convenience beyond being more cost-effective compared with other RT modalities.[35] Here, we presented a preliminary analysis of a phase II trial reporting toxicity outcomes of patients with prostate cancer treated with SBRT after radical prostatectomy.

Our treatment population comprised patients with prostate cancer postprostatectomy treated with SBRT as adjuvant therapy, early salvage therapy, and oligometastatic state salvage. A significant concern for SBRT in the postprostatectomy setting is radiation-induced toxicity.[36] Two phase I studies have been performed to determine the maximum tolerated dose delivered via SBRT to the prostate fossa of patients with biochemical failure after radical prostatectomy.[36-38] Ballas et al[37] observed that SBRT with dose escalation up to 35.5 Gy in 5 fractions to the prostate fossa was tolerable, with no patients experiencing acute grade ≥3 GI or GU toxicity. About half of the patients treated at the highest dose level experienced acute grade 2 GI toxicity but improved at 10-week follow-up in most patients. Similarly, Sampath et al[38] performed a dose escalation phase I trial with 3 dose levels of 5 × 7, 5 × 8, and 5 × 9 Gy, reporting no dose-limiting acute toxicity up to the highest dose level. However, late grade ≥2 GU toxicities were observed with 40 Gy (38%) and 45 Gy (40%) regimens. The The Stereotactic Intensity Modulated Radiotherapy After Radical Prostatectomy Trial (SCIMITAR) multicenter phase 2 trial demonstrated that SBRT delivered with CT-guided RT and magnetic resonance guided RT lead to acute and late grade 2 GU toxicity of 9% and acute and late grade 2 GI toxicity of 5% and 0%, respectively.[10] In our study, we demonstrate higher acute and late GU toxicity, which was 22% (9/41) and 17% (7/41), respectively. However, the baseline adjusted acute and late toxicity grade 2 GU (urinary incontinence) rate was 2.4% (1/41) and 12.2% (4/41), which is very low. There were no grade 3 GU toxicities. There was no grade ≥2 GI toxicities experienced. In our study of postprostatectomy SBRT, there were low rates of acute and late toxicities observed.

Oligometastatic cancer is a disease state intermediary between localized and widely metastatic disease, and it has been hypothesized that long-term control of disease could potentially be achieved through radical treatment of all sites of macroscopic disease. In the seminal Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers (SABR-COMET) trial, the use of hypofractionated RT toward oligometastatic disease demonstrated higher rates of 5-year OS (42.3% vs 17.7%) and PFS (17.3% vs 0%) compared with standard palliative care.[39] Studies have found that the predominant pattern of failure for patients with prostate cancer was through nodal metastases, most commonly fulfilling the definition of oligometastatic disease, and that treatment of lymph node metastasis from prostate cancer with SBRT is safe and effective.[40-46] Moreover, results from the phase III SPPORT trial recently demonstrated that the addition of elective pelvic nodal irradiation might not offer significant advantages compared with salvage RT to the prostate bed plus ADT in patients with detectable serum PSA after radical prostatectomy.[47] Hence, a strong rationale exists for offering SBRT to patients who develop oligometastatic recurrence. Our study's analysis of patients treated in group III corroborated the excellent outcomes of other prospective trials on oligometastatic prostate cancer such as ORIOLE and STOMP.[48,49] After initial SBRT with or without ADT, 2 patients developed a subsequent clinical failure (1 regional recurrence in pelvic lymph nodes and 1 distant recurrence in axial skeleton). The 2 patients could

be salvaged successfully with another course of SBRT directed to these recurrences and remain free of disease. Given the positive effect of ablative therapy for the treatment of oligometastatic disease, as demonstrated in the SABR-COMET trial, it is suspected that these patients will have durable disease control.[39]

Our study had several limitations, including small sample size, the lack of randomization, a short follow-up time, the reliance on advanced radiation oncology technology and staff expertise, and the inherent potential for patient selection bias. Also, it involved a patient sample that may not be sufficiently representative of the general population. Longer follow-up is also necessary to assess survival outcomes and more late toxicities. To our knowledge, this study is the first prospective, multicenter phase II clinical trial exploring the role of SBRT after radical prostatectomy in the adjuvant, salvage, and oligometastatic settings using standardized health-related QoL metrics. A randomized phase III clinical trial is underway to compare SBRT versus moderately hypofractionated RT in the early salvage and oligometastatic setting.

Conclusions

In this preliminary analysis, postprostatectomy SBRT demonstrated low rates of GU and GI toxicities without a noticeable effect on patient-reported QoL measures. Future clinical trials are needed to evaluate different postprostatectomy SBRT fractionation schemes compared with conventionally fractionated and moderately hypofractionated regimens.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2022.101143.

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