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Scientific Article

Salvage Prostate Stereotactic Body Radiation Therapy After Definitive Cryoablation

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Abstract

Purpose: Whole gland cryoablation is a guideline-approved definitive treatment for localized prostate cancer, and is being explored for partial gland ablation. However, there is limited data regarding management of cryoablation failures. Stereotactic body radiation therapy (SBRT) is a well-established method of primary treatment for prostate cancer. Here we review salvage SBRT after cryoablation failures.

Methods and Materials: A large database of patients treated with definitive SBRT was interrogated to identify those who underwent primary cryoablation. All patients were determined to have progressive disease based on a rising prostate specific antigen and/or postcryoablation biopsy. All patients were treated with SBRT over 5 treatment fractions using a robotic radiosurgical platform. Baseline cryoablation characteristics and pre- and posttreatment Expanded Prostate Cancer Index Composite questionnaires were analyzed. Acute and late toxicity was evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Cancer outcomes after salvage SBRT were stratified by disease and treatment characteristics.

Results: A total of 51 patients were identified who underwent cryoablation followed by salvage SBRT. The majority (47%) were found to have intermediate-risk disease at the time of SBRT salvage and most commonly were treated with 3500 cGy in 5 fractions to the prostate and seminal vesicles. Only 1 grade 3+ toxicity was identified. Patient-reported quality of life metrics after SBRT salvage followed prior patterns observed in the de novo SBRT setting. With a median follow-up of 40 months, 76% of the cohort demonstrated disease control. Median time to prostate cancer recurrence was 57.5 months, and recurrence was predominantly seen in patients with underlying high-risk disease.

Conclusions: This is the largest cohort of patients treated with any radiation therapy salvage after cryoablation and the first institution to report SBRT as a modality of salvage. Salvage SBRT after cryoablation results in low rates of high-grade toxicity, acceptable changes in patient-reported quality of life, and durable rates of long-term oncologic control.

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All authors contributed to revising and giving final approval to the manuscript. All authors agree to be accountable for all aspects of the work, including its accuracy and integrity.

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Cryoablation finds its historical roots nearly 2 centuries ago in 1851. The first application of cryoablation in the treatment of prostate cancer was reported in 1964 by Gonder et al, which unfortunately yielded severe toxicity.[1] Limitations in precise delivery resulted in significant rates of urinary incontinence and rectourethral fistulas.[1,2] Advancements in image guidance, miniaturization of cryo-applicators, and the development of modern delivery systems brought cryoablation again into the medical forefront in the 1990s and 2000s.[3] The terms cryoablation, cryoablation, and cryoablation are often used synonymously.[3] Fundamentally, cryoablation destroys tumor cells by exposure to extremely low temperatures (e.g., −40°C to −50°C) and involves freeze-thaw cycles to optimize tumor cell kill.[4-6] The pathophysiology of cell death involves several major pathways. First, direct cellular injury occurs via extra- and subsequently intracellular ice formation, which leads to dramatic disequilibrium in osmotic processes and destruction of the cell membrane and intracellular organelles.[3,6,7] Second, microcirculatory failure occurs as a consequence of endothelial cellar ice damage, and after reperfusion a vascular stasis ensues as thrombocytes promote thrombosis of this damaged microvasculature.[3,5,6] Subsequent ischemia resultant from vascular damage is thought to be the main driver of cell death.[6] Finally, apoptosis is observed primarily at the periphery of the cryogenic target, where the first 2 pathways of cell death are less pronounced.[6]

Prostate cryoablation can be broadly separated into 2 categories: (1) primary treatment; and (2) salvage therapy after radio-recurrence. Within each subset, the volume treated falls into either whole gland or focal lesion-directed therapy. Two prospective randomized trials have been reported comparing external beam radiation therapy with whole gland cryoablation. However, both failed to show noninferiority to radiation, and in fact 1 demonstrated worse patient-reported sexual function with cryoablation.[8-10] As such, cryoablation is not currently recommended as a standard primary treatment approach by the National Comprehensive Cancer Network guidelines, although it is by the American Urological Association guidelines. In contrast, salvage cryoablation has emerged as a reasonable treatment option for patients who develop recurrence after definitive radiation therapy, which may occur in up to 20% to 30% of patients.[11] National Comprehensive Cancer Network guidelines list cryoablation along with observation, prostatectomy, and brachytherapy all as category 2A treatment options for men with local recurrence following definitive radiation. Focal cryoablation can yield an ∼50% 5-year biochemical relapse-free survival in this setting based on 2 reports.[12,13]

Modern data suggest a rapid increase in the utilization of focal cryoablation in the up-front setting; however, data regarding management of local cryoablation failures are scant.[14-17] It is unclear whether definitive cryoablation in the de novo setting results in overlapping toxicity with salvage radiation therapy. For those patients who opt to be treated with up-front cryoablation, there are very few data evaluating the role of radiation in a salvage setting and only 1 study from the present institution specifically using stereotactic body radiation therapy (SBRT). We report the role of prostate SBRT for local failures after cryoablation.

Materials and Methods

Patient eligibility

This single institutional review of patients treated with SBRT for prostate cancer was approved by the local institutional review board (study #00001269). All patients were evaluated by a radiation oncologist and deemed appropriate for definitive SBRT salvage. All patients underwent pretreatment diagnostic tests including clinical examination, prostate specific antigen (PSA), and often transrectal ultrasound-guided biopsy. Patients were categorized into D'Amico risk group classifications. All patients underwent placement of fiducial markers in the prostate approximately 1 week before simulation. Fiducial markers were used for inter- and intrafractional image guidance. We reviewed and compared the demographic, cancer, and treatment-related data for patients who did and did not undergo up-front cryoablation.

Cryotherapy

All patients were initially treated with primary cryoablation. Cryotherapy was used in the upfront setting due to localized disease and patient preference. The type of cryoablation was categorized as partial gland, whole gland, or unknown. In some cases, patients were treated with more than 1 session of cryoablation as delineated in Table 1. Patients were subsequently determined to have a cryoablation failure if they demonstrated a progressive rise in PSA and/or a postcryoablation biopsy confirming disease. Pathologic grading of the biopsy specimen was performed in many cases. Of note, these biopsies often were magnetic resonance imaging (MRI) directed toward Prostate Imaging Reporting and Data System lesions, and did not necessarily reflect postcryoablation characteristics after partial gland treatment. Restaging workup before SBRT was negative for metastatic disease. All patients received SBRT as salvage radiation therapy after cryoablation failure.

Simulation, planning, and treatment delivery

All patients underwent computed tomography (CT)-based radiation treatment planning simulation using the Optima 580 CT scanner (GE Healthcare). An MRI of the prostate was also obtained in the majority of cases at the time of simulation and fused with the primary simulation CT scan at the level of the fiducials to assist in target volume delineation. Patients were recommended enema usage before simulation and delivery of each treatment fraction. Target volume contours were generated using previously described definitions. Nodal radiation was incorporated for those patients deemed to be at high risk for nodal involvement. Organs at risk were contoured and included rectosigmoid, bladder, penile bulb, small bowel, and femoral heads.

Table 1 Patient tumor and characteristics

	Cryotherapy		No Cryotherapy		
	Patient no.	Percentage	Patient no.	Percentage	*P* value
Age					< .001
<60 y	2	4	772	17	
60-70 y	13	25	2098	47	
>70 y	36	71	1579	36	
Prostate specific antigen (mg/mL)					.57
<10	29	57	3463	78	
10-20	15	29	760	17	
>20	7	14	226	5	
American Joint Committee on Cancer, 8th ed stage					< .001
TX	18	35	105	2	
T1	23	45	3541	80	
T2	5	10	762	17	
T3-T4	5	10	41	1	
Grade Group					< .001
1	8	16	1392	31	
2	14	27	1524	34	
3	11	22	878	20	
4	9	17.5	438	10	
5	9	17.5	217	5	
Risk group					< .001
Low	4	8	1130	25	
Intermediate	24	47	2531	57	
High	23	45	788	18	
Type of cryoablation					
Whole gland	13	26			
Partial gland	21	41			
Unknown	17	33			
Partial gland laterality					
Right	11	50			
Left	11	50			
Rounds of cryoablation pre-stereotactic body radiation therapy					
1	46	90			
2	5	10			

Clinical target volume included the entire prostate and proximal seminal vesicles. A 5 mm isometric expansion of the clinical target volume was created with a tighter, 3 mm, posterior margin to create the planning target volume. Dose calculations and planning optimization were performed using MultiPlan software (Accuray). Dosimetric constraints for the aforementioned normal structures were used based on institutional standards. Of note, uniform implementation of urethral dose constraints was not used during this era of treatment. All patients were treated using SBRT delivered over 5 treatment fractions. Treatments were delivered using a robotic radiosurgical platform with prostate motion accounted for in the x-, y-, and z-plane.

Follow-up

Toxicity was reported using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Patients were followed using serial PSA and clinical examination commonly at 3- to 6-month intervals. Biochemical progression was defined in accordance with the Phoenix definition. Toxicity was measured from completion of SBRT. Patients who underwent Expanded Prostate Cancer Index Composite (EPIC) questionnaires pre- and post-SBRT were reviewed for health-related quality of life (HRQOL). The multi-item scale scores were transformed linearly to the 0 to 100 scale. Health-related quality of life data for the urinary, bowel, and sexual domains were reviewed and included each domain-specific subscale. Patients who completed post-SBRT EPIC questionnaires were aggregated into follow-up at 1, 3 to 4, and 6 to 9 months due to variations in specific follow-up schedules. Changes in baseline summary and subscales were evaluated. Minimally important difference (MID) was used to determine the clinical relevance of HRQOL changes from baseline and was set at half a standard deviation, similar to prior publications.[18,19]

Statistical analysis

Statistical analysis was performed using SPSS, version 24 (IBM). The cryoablation and noncryoablation cohort demographic, cancer, and treatment data were compared using χ^2 analysis.

Results

Patient, tumor, and cryoablation characteristics

We reviewed our institutional database of patients from 2006 to 2020 to identify all patients who underwent primary cryoablation and were subsequently diagnosed with progressive disease requiring salvage treatment. A total of 51 patients were identified who underwent salvage SBRT after up-front cryoablation. A small number of patients (n = 5; 10%) underwent a second round of cryoablation before salvage SBRT. The median age at the time of SBRT salvage was 75 years (range, 58-86 years) and the following distribution of prostate risk group classification was observed: low (n = 4; 8%); intermediate (n = 24; 47%); and high (n = 23; 45%). Of note, those patients with pre-SBRT biopsy data (n = 43) were found to have relatively high-volume disease with a median of 42% of biopsy cores involved with carcinoma. For those patients with cryoablation specifics available, the majority (n = 21) were initially treated with partial gland treatment, and gland laterality was evenly distributed.

Clinical characteristics between the previously cryoablated cohort (n = 51) and the pretreatment-naïve patients were analyzed (n = 4749). Relative to the de novo SBRT treated cohort, the cryoablation group was composed of significantly older patients (median age 75 vs 67 years, $P < 0.001$) who were diagnosed more commonly with Grade Group 4 and 5 disease (35% vs 15%, $P < 0.001$). Interestingly, the pre-SBRT PSA values were not significantly different between the cryoablation and noncryoablation groups. However, the overall cryoablation group was composed of significantly more patients with high-risk disease (45% vs 18%, $P < 0.001$). Patient, tumor, and cryoablation characteristics are illustrated in Table 1.

Radiation treatment and dosimetric characteristics

All patients received SBRT as salvage radiation therapy after cryoablation failure. The time from cryoablation to SBRT salvage for those patients with data available (n = 34) was a median of 40 months. The majority of patients (n = 43; 84%) were treated to the prostate and proximal seminal vesicles alone. The remainder of patients (n = 8; 16%) received pelvic nodal irradiation followed by an SBRT boost to the prostate and seminal vesicles. Of those who did not receive nodal irradiation, 39 patients (77%) received a total dose of 3500 cGy to the prostate and proximal seminal vesicles, with the remaining patients receiving 3625 cGy in 5 fractions (n = 4; 8%).

For those who were treated with pelvic nodal irradiation, 4500 cGy was delivered to the pelvic lymph node basin followed by a prostate and seminal vesicle boost to 2100 (n = 7) or 1950 cGy (n = 1) in 3 fractions. A minority of patients (n = 18; 35%) received androgen deprivation therapy (ADT) and there was no significant difference in overall use of ADT between the cryoablation and noncryoablation

Table 2 Treatment and dosimetry results

	Cryotherapy		No Cryotherapy		
	Patient no.	Percentage	Patient no.	Percentage	*P* value
Androgen deprivation therapy					.12
Yes	18	35	989	22	
No	33	65	3460	78	
Radiation total dose in 5 fractions					.23
3500	39	76.47	3247	72.98	
3625	4	7.84	619	13.91	
Whole pelvis					.61
4500/25 + 2100/3	7	13.73	422	9.49	
4500/25 + 1950/3	1	1.96	103	2.32	
	Median	Mean	Median	Mean	
Clinical target volume	60.91	73.15	71.9	77.24	.23
Prescription isodose line (%)	85	84.8	84	84.28	.03

cohorts (P = .12). Median prescription isodose line for the nonpelvic nodal group was 85%. The vast majority of patients (n = 50) received amifostine (administered per rectum before each treatment fraction) as a rectal protectant, with the remaining patient undergoing placement of a pre-SBRT polyethylene glycol gel rectal spacer. Treatment and dosimetry characteristics are shown in Table 2.

Oncologic outcomes after SBRT salvage

After a median follow-up of 40 months, 12 patients (24%) were found to have progressive disease after salvage SBRT. Ten of these failures were identified by the Phoenix definition and an additional 3 were found to have radiologic failures (e.g., MRI or positron emission tomography) alone prompted due to clinical suspicion by the treating oncologist. Only 1 patient who was treated to the pelvic lymph nodes developed progressive disease. Median time to any failure was 57.5 months (4.8 years). Failures after salvage SBRT were most commonly seen in patients with high-risk disease (n = 9; 75%). Similarly, failure rate stratified by prostate cancer Gleason grade was most commonly observed in patients with Grade Group 4 or 5 cancer (n = 8; 67%). Although detailed cryoablation reports were not available for the entire cohort, there were nominally more SBRT salvage failures if a patient underwent up-front partial versus whole gland treatment (n = 5). Although only 5 patients underwent multiple rounds of cryoablation before SBRT, 2 of these patients went on to develope SBRT salvage failures. Salvage SBRT oncologic outcomes are shown in Table 3 and illustrated in Figure 1.

Toxicity outcomes

Overall, the toxicity of prostate SBRT as salvage treatment after cryoablation was minimal. A total of 15 patients (30%) developed any grade toxicity at a median of 30 months (range, 13-68 months) after radiation. Only 1 grade 3 toxicity (2% of total cohort) was observed in a patient who underwent transurethral prostatectomy at 51 months for bladder outlet obstruction. A total of 6 grade 2 toxicities (12% of total cohort) were identified and were evenly distributed between urinary frequency and erectile dysfunction, both requiring medication management. The median time to grade 2 or higher toxicity was 35 months after SBRT. Eight additional grade 1 toxicities were observed, which included the following: urinary frequency (n = 5); hematuria (n = 2); and fecal incontinence (n = 1).

The vast majority of patients (n = 13; 87%) who developed toxicity were treated with the most common dose of 3500 cGy in 5 fractions prescribed to an isodose line between 83% and 86%. All patients who developed toxicity were diagnosed with either intermediate- (n = 11; 73%) or high-risk disease (n = 4; 27%). Usage of ADT was not prevalent among patients who developed any toxicity (n = 3). Counterintuitively, only 2 patients (13%) who developed toxicity received prior whole gland cryoablation, with the remainder receiving either partial gland (n = 7; 47%) treatment or unknown. In addition, of the 5 patients who received 2 rounds of cryoablation, 2 went on to develop toxicity.

Patients who developed CTCAE renal and urinary toxicity were found to have cohort-median bladder mean and maximum doses of 1849 cGy (range, 826-1967 cGy) and 3774 cGy (range, 2353-3832 cGy), respectively. Bladder mean and maximum doses for those cryoablation

Table 3 Salvage stereotactic body radiation therapy oncologic outcomes

Total failures	No. 12	% 100
Phoenix/Phoenix + Prostate Imaging Reporting and Data System	9	75
Prostate Imaging Reporting and Data System alone	3	25
Failure risk group		
Low	0	0
Intermediate	3	25
High	9	75
Failure Grade Group		
1	0	0
2	3	25
3	1	8.33
4	3	25
5	5	41.67
Failure initial prostate specific antigen (ng/mL)		
<10	5	42
10-20	3	25
>20	4	33
Prior rounds of cryoablation		
1	4	33
2	2	17
Unknown	6	50
Gland treatment		
Whole	1	8
Partial	5	42
Unknown	6	50

patients who did and did not develop renal and urinary toxicity were not significantly different (P = .27 and P = .59, respectively). Table 4 details salvage SBRT toxicity outcomes.

EPIC quality of life outcomes

Patient quality of life data were reviewed for those who completed pre-SBRT EPIC quality of life questionnaires, which included nearly half of the cryoablation cohort. A total of 23, 22, and 24 patients had completed evaluable pre-SBRT EPIC questionnaires for urinary, bowel, and sexual domains, respectively. Nevertheless, notable attrition was observed in questionnaire completion after treatment. Baseline mean EPIC summary scores were found to be 89 ± 10, 93 ± 7, and 40 ± 24, in the urinary, bowel, and sexual domains, respectively. Supplementary Tables E1 to E3 depict detailed EPIC HRQOL outcomes.

Baseline EPIC urinary summary scores demonstrated a clinically significant decline (MID = 5) at 1 month after treatment (mean change from baseline, −10). This mean decline improved at 3 to 4 months (mean change from baseline, −8) and again at 6 to 9 months (mean change from baseline, −6), though its clinical significance persisted. All urinary domain-specific HRQOL subscales (ie, function, bother, and irritative/obstructive) also demonstrated a clinically significant decline at 1 month post SBRT with the exception of incontinence. Furthermore, all urinary domain-specific HRQOL subscales demonstrated improvements by 6 to 9 months, again with the exception of incontinence, which remained relatively unchanged. In fact, urinary bother no longer registered as clinically significance by 6 to 9 months, indicating patient symptom acclimation.

Baseline EPIC bowel summary scores demonstrated a clinically significant decline (MID = 3.5) at 1 month after treatment (mean change from baseline, −17). This mean decline rapidly improved at 3 to 4 months (mean change

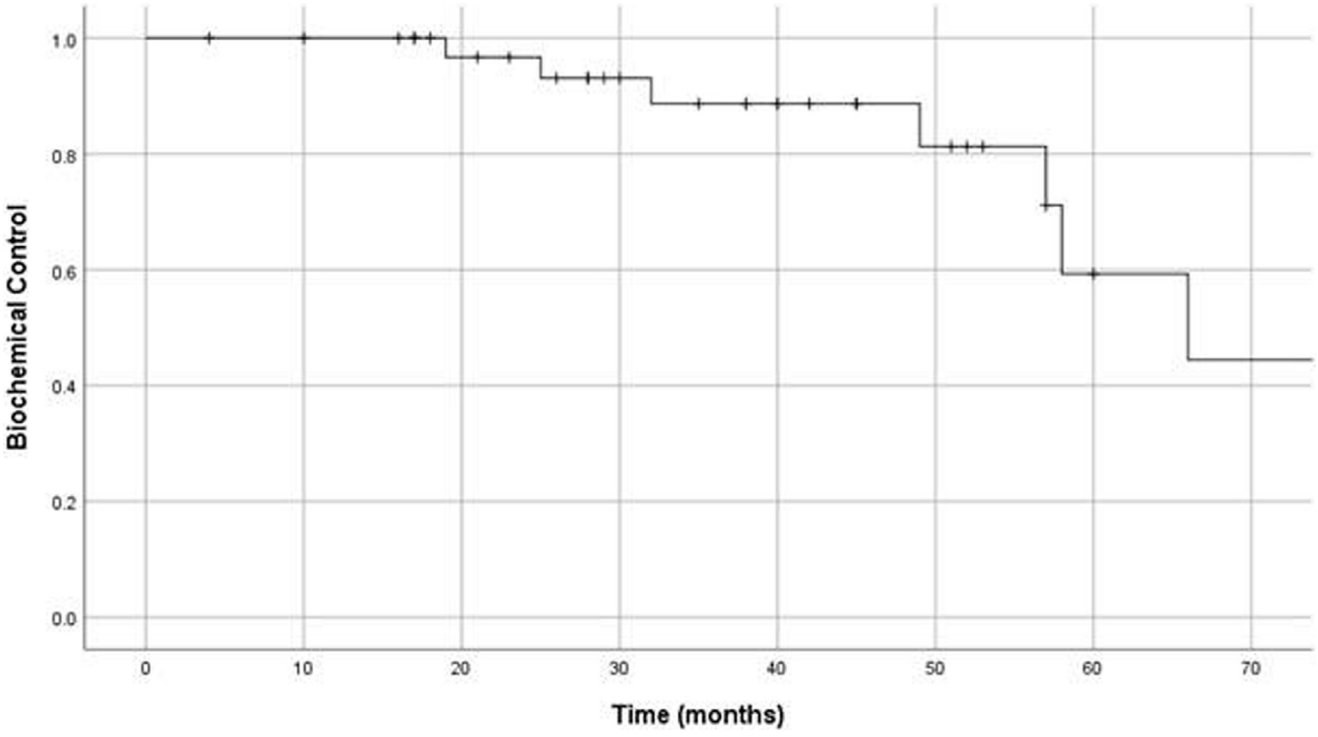

Fig. 1 Kaplan-Meier curve of biochemical control after stereotactic body radiation therapy salvage after primary cryotherapy failure.

from baseline, −8) and again at 6 to 9 months (mean change from baseline, −2), at which time it no longer demonstrated clinical significance. Both bowel domain-specific subscales (ie, function and bother) revealed a similar pattern of initial clinically significant decline with resolution at later time points. In contrast, baseline EPIC sexual summary scores (MID = 12) demonstrated no initial change after SBRT, but did reveal a gradual clinically significant decline at 3 to 4 months. Domain-specific sexual subscales reveal this gradual decline to be driven by worsening of sexual function over time with stability of sexual bother at later time points. EPIC urinary, bowel, and sexual summary score changes from baseline and the aforementioned 3 follow-up time points are illustrated in Figure 2A to 2C.

Discussion

The present study is the largest cohort of patients treated with any salvage radiation after cryoablation reported to date. It also contains the only institutional data demonstrating the efficacy of SBRT as a salvage radiation option after cryoablation.[20] Only 5 previously published manuscripts have reported the results of salvage radiation after up-front cryoablation in a combined total of 88 patients.[14-17,21] The vast majority of these patients were treated with 3-dimensional radiation therapy to a low median total radiation dose (ie, <66 Gy). Only 1 series, representing 8 patients, used exclusively modern image guided radiation therapy in delivery of salvage radiation.[21] Overall, there were extremely low rates of high-grade toxicity, with only 1 of 88 patients in these 5 reports developing grade 3+ toxicity (i.e. rectal bleeding requiring cauterization).[16] Our experience of 51 patients treated with salvage SBRT supports this low risk of salvage radiation after cryoablation failures, with only 1 grade 3+ CTCAE toxicity observed.

The most recent report on the use of radiation therapy after up-front cryoablation and that with the longest follow-up is from the Hopper et al, who identified a total of 8 patients undergoing salvage image guided radiation therapy after cryoablation.[21] Intensity modulated radiation therapy or arc therapy was used as the radiation salvage technique with a median total dose delivered of 77.7 Gy. After a median follow-up of 55 months, 6 patients maintained biochemical control, 1 patient developed biochemical failure, and 1 patient developed metastases. No patients experienced acute or late grade 3+ gastrointestinal or genitourinary toxicity, and worsening erectile dysfunction was not observed. In the present study, we identify CTCAE renal and urinary toxicity as the predominant toxicity domain, with the most common low-grade toxicity being urinary frequency. This toxicity did not seem to be associated with the dose fractionation schedule or bladder dosimetric parameters.

Nuanced treatment-related toxicity was explored with pre- and post-SBRT EPIC patient-related quality of life questionnaires, although patient numbers and follow-up duration were limited. We observed baseline urinary and

Table 4 Salvage stereotactic body radiation therapy toxicity outcomes

Toxicity	Time to toxicity (mo)	Cryotherapy type	Androgen deprivation therapy	Total dose (cGy)	Prescription isodose line (%)	Bladder mean (cGy)	Bladder maximum dose (cGy)	Rectal maximum dose (cGy)
Renal and urinary								
Grade 3 urinary tract obstruction	51	Unknown	Yes	3625	87	1574	3774	3790
Grade 2 urinary frequency	40	Unknown	No	4500/2100	85	826	2352	2255
Grade 2 urinary frequency	30	Focal	No	3500	83	1967	3832	3782
Grade 2 urinary frequency	17	Whole	No	3500	85	1905	3743	3644
Grade 1 hematuria	68	Focal	No	3500	84	Unknown	Unknown	Unknown
Grade 1 urinary frequency	53	Unknown	No	3500	85	Unknown	Unknown	Unknown
Grade 1 urinary frequency	30	Focal	No	3500	83	1967	3832	3782
Grade 1 urinary frequency	29	Unknown	No	3500	84	1683	3757	3739
Grade 1 urinary frequency	17	Whole	No	3500	83	Unknown	Unknown	Unknown
Grade 1 urinary frequency	16	Focal	Yes	3500	85	1849	3828	3740
Grade 1 hematuria	13	Focal	Yes	3500	86	1849	3802	3739
Reproductive system								
Grade 2 erectile dysfunction	53	Unknown	No	3500	85	Unknown	Unknown	Unknown
Grade 2 erectile dysfunction	35	Focal	No	3500	84	1787	3348	3819
Grade 2 erectile dysfunction	29	Unknown	No	3500	85	1806	3741	3717
Gastrointestinal								
Grade 1 fecal incontinence	30	Focal	No	3500	83	1967	3832	3782
					Median	1849	3774	3740

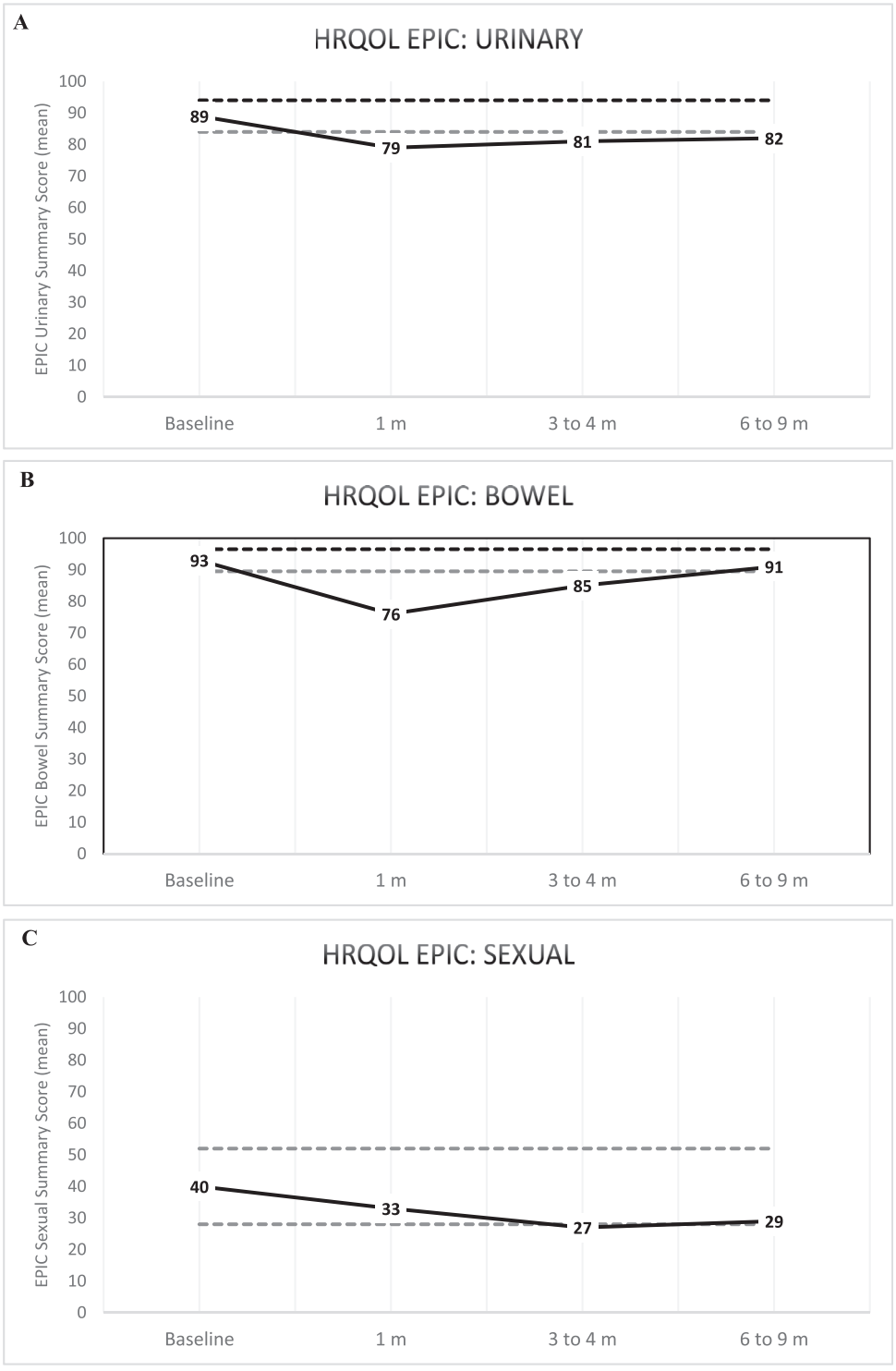

Fig. 2 (A) Expanded Prostate Cancer Index Composite urinary summary domain scores (mean) at baseline and post-stereotactic body radiation therapy. Dashed lines indicate minimally important difference upper and lower boundaries based on baseline summary score one-half standard deviation. (B) Expanded Prostate Cancer Index Composite bowel summary domain scores (mean) at baseline and post-stereotactic body radiation therapy. Dashed lines indicate minimally important difference upper and lower boundaries based on baseline summary score one-half standard deviation. (C) Expanded Prostate Cancer Index Composite sexual summary domain scores (mean) at baseline and post-stereotactic body radiation therapy. Dashed lines indicate minimally important difference upper and lower boundaries based on baseline summary score one-half standard deviation. *Abbreviations:* EPIC = Expanded Prostate Cancer Index Composite; HRQOL = health-related quality of life.

bowel scores nearly identical to those reported by King et al in a multi-institutional consortium.[22] In contrast, the baseline sexual domain for the present study was notably worse relative to that of King et al, which may reflect the median age being 6 years older in our cohort. We observed transient declines in HRQOL urinary and bowel domains, which showed improvements toward baseline at later time points. Although, urinary scores demonstrated gradual improvement, there was still a clinically meaningful decline in urinary summary score, whereas bowel decline no longer demonstrated clinical relevance at last EPIC evaluation. In contrast, HRQOL sexual domain showed a gradual decline with no similar rebound, which was driven by worsening sexual function. This mimics quality of life patterns previously reported for up-front SBRT for localized prostate cancer.[18-24] Our data support similar HRQOL trends for postcryoablation SBRT relative to the de novo setting, at least at early time points.

Interestingly, the mean pre-SBRT PSA was markedly higher in the present study (11.3 ng/mL) relative to the aforementioned 5 published reports (range, 2.4-8.4 ng/mL). Moreover, 92% of our cohort was diagnosed with intermediate- or high-risk disease just before salvage SBRT. Despite a higher presalvage PSA and aggressive risk grouping, our overall progression rate after salvage SBRT was the second lowest of the prior published studies. This is likely, in part, a function of the higher radiobiologic dose delivered in our series. That is, the equivalent dose in 2 Gy fractions of 35 Gy in 5 fractions is 79 to 85 Gy, assuming a prostate cancer α/β of 2 to 1.5, which is similar to or higher than the median doses used in prior publications. This is particularly impressive considering the minority of patients received ADT as a component of treatment. Dose is known to be associated with improved biochemical control in the de novo setting, and a similar dose response has been observed when radiation is applied as a salvage technique after cryoablation.[15] As such, the ablative potential of SBRT may be a crucial method to eradicate resistant prostate cancer clones that have survived cellular damaged inflicted by cryoablation.

The interplay of cryoablation and radiation therapy is nebulous and not well studied. In vitro data exploring tumor radiosensitivity with the application of hypothermia just before radiation have been mixed.[23-25] Pathophysiologically, it has been postulated that hypothermia could diminish tumor cell ability for sublethal damage repair.[25] Cryotherapy results in vascular alterations, which have an unclear radiobiologic effect when therapeutic radiation is delivered sequentially. It is interesting to note our postcryoablation cohort was predominantly high-risk with stratification driven by prostate cancer grade grouping rather than PSA. This likely reflects distinct normal gland destruction by cryoablation that leads to unique posttreatment PSA kinetics, which may have important implications for PSA surveillance after cryoablation and salvage radiation therapy. McDonough et al postulate that the sequence of delivery plays a crucial role in the development of toxicity, with cryoablation salvage after radiation yielding dramatically worse toxicity outcomes relative to the converse.[16] With very limited data, it is difficult to confirm this hypothesis; however, relative to the present study, the crude rates of toxicity seen in publications reporting cryoablation after definitive radiation therapy are much higher.[12,13,26]

Limitations of the present study include its retrospective nature, relatively short median follow-up, and limited number, albeit a consequence of the rarity of the clinical situation. In addition, we included patients who were treated with more than 1 round of cryoablation as well as those who received salvage pelvic nodal irradiation within our analysis, which makes uniform interpretation of clinical outcomes challenging. Moreover, given the distant history of some treatments, detailed cryoablation data were not immediately available. Finally, although quality of life data were collected for many patients, there were only partial posttreatment follow-up data, thus limiting its generalizability. Overall, this is the largest and most robust analysis of radiation therapy as a salvage treatment after up-front cryoablation.

Conclusions

Stereotactic body radiation therapy as salvage treatment after cryoablation failure leads to very low rates (2%) of high-grade toxicity. The most prevalent low-grade toxicities observed were urinary frequency and erectile dysfunction, and HRQOL metrics postsalvage followed those seen in the de novo SBRT setting. Despite initial cryoablation failure and aggressive baseline disease, durable control was observed with SBRT, with failures predominantly seen in patients with more aggressive high-risk disease.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.adro.2021.100849.

References

1. Gonder MJ, Soanes WA, Smith V. Experimental prostate cryoablation. *Invest Urol*. 1964;1:610–619.
2. Langenhuijsen JF, Broers EMP, Vergunst H. Cryosurgery for prostate cancer: An update on clinical results of modern cryotechnology. *Eur Urol*. 2009;55:76–86.
3. Mahnken AH, König AM, Figiel JH. Current technique and application of percutaneous cryoablation. *Rofo*. 2018;190:836–846.
4. Hoffmann NE, Bischof JC. The cryobiology of cryosurgical injury. *Urology*. 2002;60(suppl 1):40–49.

5. Gage AA, Baust J. Mechanisms of tissue injury in cryoablation. *Cryobiology*. 1998;37:171–186.
6. Baust JG, Gage AA. The molecular basis of cryoablation. *BJU Int*. 2005;95:1187–1191.
7. Gage AA. History of cryoablation. *Semin Surg Oncol*. 1998;14:99–109.
8. Robinson JW, Donnelly BJ, Siever JE, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer: Quality of life outcomes. *Cancer*. 2009;115:4695–4704.
9. Donnelly BJ, Saliken JC, Brasher PMA, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer. *Cancer*. 2010;116:323–330.
10. Chin JL, Al-Zahrani AA, Autran-Gomez AM, Williams AK, Bauman G. Extended followup oncologic outcome of randomized trial between cryoablation and external beam therapy for locally advanced prostate cancer (T2c-T3b). *J Urol*. 2012;188:1170–1175.
11. Shinohara K, Rhee B, Presti JC, Carroll PR. Cryosurgical ablation of prostate cancer: Patterns of cancer recurrence. *J Urol*. 1997;158:2206–2209. [discussion 2209-2210].
12. de Castro Abreu AL, Bahn D, Leslie S, et al. Salvage focal and salvage total cryoablation for locally recurrent prostate cancer after primary radiation therapy. *BJU Int*. 2013;112:298–307.
13. Li Y-H, Elshafei A, Agarwal G, Ruckle H, Powsang J, Jones JS. Salvage focal prostate cryoablation for locally recurrent prostate cancer after radiotherapy: Initial results from the Cryo On-Line Data Registry. *Prostate*. 2015;75:1–7.
14. Hepel JT, MacAusland SG, Long JP, Wazer DE, DiPetrillo T. Intensity-modulated radiotherapy of the prostate after cryoablation: Initial experience. *Urology*. 2008;72:1310–1314.
15. Burton S, Brown DM, Colonias A, et al. Salvage radiotherapy for prostate cancer recurrence after cryosurgical ablation. *Urology*. 2000;56:833–838.
16. McDonough MJ, Feldmeier JJ, Parsai I, Dobelbower RR, Selman SH. Salvage external beam radiotherapy for clinical failure after cryoablation for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2001;51:624–627.
17. Choi M, Kim CR, Hung AY. Salvage intensity-modulated radiation therapy for locally recurrent prostate cancer after cryoablation. *Clin Genitourin Cancer*. 2013;11:85–88.
18. Bhattasali O, Chen LN, Woo J, et al. Patient-reported outcomes following stereotactic body radiation therapy for clinically localized prostate cancer. *Radiat Oncol*. 2014;9:52.
19. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: The remarkable universality of half a standard deviation. *Med Care*. 2003;41:582–592.
20. Quarrier S, Katz A, Haas J. Treatment of prostate cancer local recurrence after whole-gland cryoablation with frameless robotic stereotactic body radiotherapy: Initial experience. *Clin Genitourin Cancer*. 2013;11:89–93.
21. Hopper AB, Sandhu APS, Parsons JK, Rose B, Einck JP. Salvage image guided radiation therapy to the prostate after cryoablation failure. *Adv Radiat Oncol*. 2018;3:52–56.
22. King CR, Freeman D, Kaplan I, et al. Stereotactic body radiotherapy for localized prostate cancer: Pooled analysis from a multi-institutional consortium of prospective phase II trials. *Radiother Oncol*. 2013;109:217–221.
23. Johanson KJ, Wlodek D, Szumiel I. Effect of ionizing radiation and low temperature on L5178Y-R and L5178Y-S cells. II. Cell survival and DNA strand breaks after roentgen or gamma irradiation. *Acta Radiol Oncol*. 1983;22:71–76.
24. Holahan EV, Bushnell KM, Highfield DP, Dewey WC. The effect of cold storage of mitotic cells on hyperthermic killing and hyperthermic radiosensitization during G1 and S. *Radiat Res*. 1982;92:568–573.
25. Burton SA, Paljug WR, Kalnicki S, Werts ED. Hypothermia-enhanced human tumor cell radiosensitivity. *Cryobiology*. 1997;35:70–78.
26. Pisters LL, von Eschenbach AC, Scott SM, et al. The efficacy and complications of salvage cryoablation of the prostate. *J Urol*. 1997;157:921–925.