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Scientific Article

Salvage image guided radiation therapy to the prostate after cryotherapy failure

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Abstract

Purpose: Cryotherapy is an option for the primary treatment of localized prostate cancer, along with radical prostatectomy, external beam radiation therapy, and brachytherapy. Although it is known that local recurrence can occur in >20% of patients treated with primary cryotherapy, unfortunately there is a paucity of data on later salvage treatments. The use of external beam radiation therapy is an attractive option after cryotherapy failure, but there is little data on its efficacy and toxicity. We evaluated the biochemical control and complication rates of salvage dose-escalated image guided intensity modulated radiation therapy (IG-IMRT) after cryotherapy failure.

Methods and materials: Patients who were treated at our institution from 2005 to 2016 were reviewed for those who underwent cryotherapy as initial treatment followed by salvage IGRT. Patients were treated with dose-escalated IG-IMRT using standard treatment margins of 3 mm posterior and 7 mm in all other directions and daily cone beam computed tomography or kv imaging to implanted fiducial markers. Biochemical progression was defined in accordance with the Phoenix consensus conference definition.

Results: Eight patients were identified as having received post-cryotherapy salvage radiation within the study period. The median total dose was 77.7 Gy (range, 75.6-81.0 Gy). Median follow-up was 55 months (range, 6-88 months). Six patients remained biochemically controlled at the latest follow-up. One patient developed distant metastases after 22 months and one experienced biochemical failure at 30 months with no evidence of distant metastases. No patients experienced acute gastrointestinal toxicities of grade 2 or higher. There were no cases of late gastrointestinal or genitourinary toxicity.

Conclusions: High-dose IG-IMRT results in high rates of salvage and extremely low rates of serious late toxicity for patients with locally recurrent prostate cancer after cryotherapy. Although the results are encouraging, given the small number of patients in this and other series, we remain cautious

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with regard to this treatment and believe the use of salvage radiation therapy after cryotherapy warrants further study.

Introduction

Cryotherapy is an option for the primary treatment of localized prostate cancer, along with radical prostatectomy, external beam radiation therapy (EBRT), and brachytherapy. Previous studies and meta-analyses have not found significant differences in the rates of failure between these primary treatments, although cryotherapy was associated with poorer sexual function posttreatment.[1,2] Early cryotherapy systems had significant genitourinary (GU) and gastrointestinal (GI) toxicities, but advances in transrectal ultrasound guidance, urethral warming, and third-generation cryotherapy and the use of focal cryotherapy have decreased treatment-associated side effects and increased rates of use.[3-5] A review of the national Cryo On-Line Database Registry found a > 1000-fold increase in the use of focal cryotherapy between 1997 and 2007.[6] As the number of patients undergoing primary cryotherapy increases, so too will the number of local recurrences that require salvage treatment.

Although it is known that local recurrence can occur in >20% of patients treated with primary cryotherapy, there is a paucity of data on salvage treatments after failure.[5,7-9] Salvage prostatectomy after cryotherapy has been noted to be extremely difficult because of tissue reaction and fibrosis.[10] Repeat cryotherapy as a salvage treatment has also been associated with increased rates of complications and toxicity.[11] EBRT as an option for salvage treatment has been little evaluated in the literature.[5,7-9] Of those reports that have been published, the majority have focused on the use of 3-dimensional conformal radiation therapy (CRT) with 2 studies combining 3-dimensional CRT with intensity modulated radiation therapy (IMRT). Recent advances in image guided radiation therapy using IMRT (IG-IMRT) have been shown to decrease the rates of toxicities in comparison with non–IG-IMRT at the same dose level in the primary treatment of prostate cancer.[12] This case series attempts to evaluate the biochemical control and complication rates of salvage dose-escalated IG-IMRT after cryotherapy failure.

Methods and materials

Patients receiving salvage radiation therapy postcryotherapy were retrospectively identified by a keyword search of the electronic medical record of all patients who received radiation therapy to the prostate at our facilities between 2005 and 2016. Cryotherapy was reported to be selected as the initial therapy due to a combination of patient preference and presentation with low-volume disease. All instances of recurrence were initially identified by rising prostate-specific antigen (PSA) and subsequently confirmed by biopsy. Staging at the time of recurrence was performed with computed tomography (CT) of the abdomen and pelvis and a bone scan. In this group of patients, radiation therapy was selected as salvage therapy in the context of recurrence, with imaging suggesting local extension into the seminal vesicles, bladder, or rectal wall, as well as recurrence after attempted salvage cryotherapy and patient preference after PSA recurrence.

Radiation therapy was performed with either IMRT or volumetric modulated arc therapy. Dose prescription, volumes treated, and the use of androgen deprivation therapy (ADT) were at the discretion of the treating physician. Doses between 75.6 and 81 Gy were prescribed in 1.8 Gy fractions. Generally, when seminal vesicles and the prostate were treated, planning target volume margins of 7 mm were prescribed in all directions except for posteriorly, where a margin of 3 to 5 mm was applied. Image guidance was done in all cases with either daily cone beam CT or kv imaging with matching of implanted fiducials. Variables extracted from each patient's electronic medical record for evaluation included PSA values, Gleason scores, TNM staging, use of neoadjuvant ADT, follow-up information, progression-free survival, and acute and late toxicities. Toxicities were scored in accordance with the Common Terminology Criteria for Adverse Events, Version 4.03 for GU and GI toxicities, including diarrhea, rectal hemorrhaging, rectal fistulas, hematuria, urinary obstruction, urinary incontinence, and erectile dysfunction. Dysuria and increases in nocturia were evaluated in accordance with the Radiation Therapy Oncology Group (RTOG) criteria for additional clarity. Biochemical progression was defined in accordance with the RTOG and American Society for Therapeutic Radiology and Oncology Phoenix consensus conference definition.[13]

Results

Eight eligible patients were identified as having received primary whole gland cryotherapy and salvage radiation between 2008 and 2016. Whole-gland cryotherapy was performed with standard published techniques.[14] Mean age at the time of salvage radiation therapy was 74 years (range, 62-83 years). Prior to cryotherapy, 3 patients had a Gleason score of 6, 4 patients had a score of 7, and 1 patient had a score of 8.

Table 1 Patient characteristics and outcomes

Patient	Age at RT	Precryo GS	Precryo PSA (ng/mL)	Cryo-RT Interval (mo)	Pre-RT GS	Pre-RT PSA (ng/mL)	ADT	Total Dose (Gy)	Follow up Post-RT (mo)	Post-RT PSA nadir (ng/mL)	Outcome
1	78	6	—	97	7	4.41	Y	77.4	58	10.53	Met
2	62	6	21.5	25	6	13.83	N	76.0	88	0.148	BC
3	69	7	9.5	36	8	5.23	Y	78.0	6	0.206	BC
4	65	7	25.24	61	7	14.38	Y	75.6	87	0.01	BC
5	80	6	6	74	7	4.2	N	81.0	52	0.15	BC
6	77	7	21	30	8	11.44	Y	75.6	57	0.01	BF
7	83	8	4.94	84	8	5.28	Y	79.2	15	0.01	BC
8	76	7	—	195	7	8.6	Y	79.2	13	0.04	BC

ADT, androgen deprivation therapy; BC, biochemical control; BF, biochemical failure; GS, Gleason score; Met, distant metastases; PSA, prostate-specific antigen; RT, radiation therapy.

Mean precryotherapy PSA was 14.7 ng/mL (range, 6.0-25.24 ng/mL) in the 6 patients for whom data were available. After cryotherapy, 3 patients had moderate urinary symptoms consisting of frequency and nocturia that was more prominent than their precryotherapy baseline, which were maintained until salvage treatment. One of these patients required regular α-antagonist treatment. The remaining patients were noted to have minimal urinary symptoms consisting of frequency and/or nocturia that was similar to their baseline prior to cryotherapy. All patients had some level of erectile dysfunction after cryotherapy and before salvage radiation therapy, which ranged from not requiring medication to complete dysfunction.

Radiation therapy was the first treatment for postcryotherapy recurrence in 4 patients, and hormone therapy alone was administered after cryotherapy and before radiation in the other 4 patients. Two patients had repeat cryotherapy procedures after initial biochemical failure prior to radiation therapy. The median interval between cryotherapy and salvage radiation therapy was 68 months (range, 25-195 months). All patients had biopsy-proven local recurrence prior to salvage, including 1 patient with a Gleason score of 6; the other patients had a Gleason score of 7 (n = 4) or 8 (n = 3).

Mean PSA prior to radiation was 8.4 ng/mL (range, 4.2-14.38 ng/mL). Five patients received 6 months of neoadjuvant ADT, and another overlapped the end of a chronic course of Casodex with the first 30 days of radiation treatment. Two patients were noted as having evidence of local extension of the tumor prior to radiation, one into the bladder and another into the rectal wall. Radiation therapy treatment consisted of IMRT (n = 5) or volumetric arc therapy (n = 3) with either cone beam CT (n = 6) or kV imaging with implanted fiducial markers (n = 2) for guidance. The median total dose to the prostate was 77.7 Gy (range, 75.6-81.0 Gy). Six patients (Patients 1, 2, 3, 4, 7, and 8) were treated to both the prostate and the seminal vesicles, and 3 of these patients (Patients 1, 2, and 3) also received radiation to the whole pelvis.

After treatment, there was a median follow-up of 55 months (range, 6-88 months). Seven patients had a good PSA response postsalvage (PSA nadir ≤0.206 ng/mL), but 1 patient experienced an increase in PSA immediately post-treatment and subsequently developed distant metastases after 22 months. One patient who displayed an initial PSA response experienced biochemical failure 30 months after treatment, but at the time of this report, the patient has no evidence of distant metastases. Both patients with prior evidence of local invasion remained biochemically controlled at the latest follow-up. Individual Gleason scores, PSA values, and treatment timeline information are summarized in Table 1.

No patients experienced acute GI toxicities grade 2 or higher; 1 patient had acute GU toxicity that consisted of grade 2 dysuria and required pyridium. Two patients had grade 1 diarrhea, 4 patients had grade 1 dysuria, and 2 patients had a grade 1 increase in nocturia. There were no cases of late GI or GU toxicity. No patients were noted to have worsening erectile dysfunction after radiation therapy, but all patients had some level of erectile dysfunction prior to IG-IMRT, as previously noted. A summary of toxicities by patient can be found in Table 2.

Discussion

Cryotherapy as a primary treatment for prostate cancer is associated with significant rates of erectile dysfunction, incontinence, bladder outlet obstruction, and even fistula and is associated with rates of biochemical failure of >20% in most series.[9-11,14-17] There are understandable concerns with regard to any attempt at salvage after cryotherapy given the potential for compounding long-term toxicities. Salvage treatments such as repeat cryotherapy or prostatectomy have been associated with exacerbations of these toxicities, especially in earlier generations of cryotherapy, although this series and others have shown that EBRT as a salvage treatment for failure after

Table 2 Acute and late toxicities by patient

Patient	Acute GU	Acute GI	Late GU	Late GI
1	—	—	—	—
2	—	—	—	—
3	—	1—diarrhea	—	—
4	1—dysuria	1—diarrhea	—	—
5	1—dysuria	—	—	—
6	1—nocturia increase 2—dysuria	—	—	—
7	1—dysuria	—	—	—
8	1—dysuria 1—nocturia increase	—	—	—

GI, gastrointestinal; GU, genitourinary.

cryotherapy is associated with very low risks of severe late toxicity.[5,7,9,10,18]

Similar to the results observed in primary EBRT to the prostate, as radiation therapy techniques have advanced, it has become possible to dose escalate salvage EBRT while maintaining or improving the side effect profile.[5,7-9] We are aware of only 4 previously published series of salvage radiation therapy for recurrent prostate cancer after cryotherapy, totaling 67 patients, most of whom were treated with 3-dimensional CRT using doses lower than what would be considered standard today. In addition, the median follow-up was less than 3 years in all.

A series by Burton et al of 49 patients who were initially treated between 1990 and 1999 using 3-dimensional CRT showed a significant difference ($P = .024$) in biochemical control in those treated to ≥64 Gy compared with those treated to <64 Gy, with 2 patients experiencing late grade 2 toxicities that were treated conservatively.[7] There were no grade 3 toxicities in this report.

McDonough et al treated 6 patients with 3-dimensional CRT between 1993 and 1998 to a median dose of 66 Gy and had a 66% biochemical control rate, with 1 patient experiencing grade 3 rectal bleeding that required cauterization and transfusion and another with grade 2 rectal bleeding that resolved with suppositories.[8]

Hepel et al treated 16 patients from 1997 to 2007, including 3 patients who were treated adjuvantly and 13 with salvage after local failure, to a median dose of 73 Gy. The majority of patients were treated to the whole pelvis with 3-dimensional CRT to 45 Gy followed by an IMRT boost to the prostate gland to 73 Gy. Two patients had IMRT for the entire treatment.[5] No grade 3 toxicities were noted, although 1 case each of grade 2 rectal bleeding and urge incontinence were observed.

Choi et al treated 9 patients from 2008 to 2010; 7 were treated in a manner similar to that used by Hepel et al, with 45 Gy by 3-dimensional CRT to the prostate, seminal vesicles, and lymph nodes followed by an IMRT boost to the prostate for a median dose of 79.2 Gy, and 2 patients had all IMRT to 72 Gy.[9] Some patients were treated with daily image guidance using fiducial markers, but it is not clear how many. Other patients were treated with weekly port films. No late grade 3 or higher GU or GI toxicities were reported. A more detailed comparison of these studies and our results can be found in Table 3.

Ours is the first series to use modern radiation therapy techniques for all patients receiving dose-escalated IG-IMRT with daily image guidance. In addition, the 55-month median follow-up in our series is significantly longer than that in previously published reports. Using this technique, the crude rate of biochemical disease-free survival after salvage in our series is 75% at 5 years. There were no late grade 2 or 3 GI or GU toxicities.

As previously mentioned, alternatives to EBRT for salvage after cryotherapy failure are associated with significant toxicity and low efficacy. Koppie et al reported that

Table 3 Comparison with other salvage radiation therapy series

	# of patients	Mean precryo PSA (ng/mL)	Median interval	Mean pre-RT PSA (ng/mL)	Median dose (Gy)	Grade 3 toxicities	Median FU (months)	Treatment type
Burton	49	15.7	NR	2.4	64.8	0	32	3DCRT
McDonough	6	NR	36	2.3	66	1	34	3DCRT
Hepel	16	8.7	50	6	73	0	33	3D/IMRT
Choi	9	8.3	20.5	4.3	79.2	0	31	3D/IMRT
Our Study	8	14.7	68	8.4	77.7	0	55	IGRT

3D, 3-dimensional; 3DCRT, 3-dimensional conformal radiation therapy; FU, follow-up; IGRT, image guided radiation therapy; IMRT, intensity modulated radiation therapy; PSA, prostate-specific antigen; NR, not reported; RT, radiation therapy.

only 8 of 24 patients undergoing repeat cryotherapy as salvage treatment after primary cryotherapy failure had favorable PSA responses in addition to the increased number of complications already mentioned, while salvage prostatectomy is difficult due to fibrosis.[10,11,15] In conjunction with the studies mentioned, our results indicate that salvage IG-IMRT can be an effective treatment after cryotherapy failure. Concerns about high rates of GI or GU toxicities have not been reflected in these studies, even with increasing radiation doses.

In their case series, McDonough et al offered the theory that the sequence of cryotherapy and EBRT is the source of increased toxicity and that microvasculature changes after radiation enhance hypoxia and necrosis when cryotherapy is used as salvage after radiation failure but not in EBRT as salvage after cryotherapy.[8,19] Although it is unclear if this is the case and it is likely a multifactorial issue, recent reports on salvage cryotherapy after radiation have reported more serious side effects, such as rectourethral fistulas, urinary retention, and urge incontinence requiring pads, than the toxicities seen in these few case series on salvage EBRT after cryotherapy.[20,21]

Limitations of this study include its retrospective nature and the small study size. Although the median follow-up of this study is longer than that in similar studies, a full evaluation of late toxicities and biochemical control would be enhanced by longer follow-up.

Conclusion

High-dose IG-IMRT results in high rates of salvage and extremely low rates of serious late toxicity for patients with locally recurrent prostate cancer after cryotherapy. Although the results are encouraging, given the small number of patients in this and other series, we remain cautious with regard to this treatment and believe the use of salvage radiation therapy after cryotherapy warrants further study.

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