Treatment of Prostate Cancer Local Recurrence After Whole-Gland Cryosurgery With Frameless Robotic Stereotactic Body Radiotherapy: Initial Experience

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Abstract

Frameless robotic stereotactic body radiotherapy has not been investigated for use in patients who failed primary cryosurgery treatment. We present a small case series of one institution's initial experience with CyberKnife in patients for salvage therapy. Analysis of results indicates that robotic stereotactic body radiotherapy is a viable option in these patients. The patients had minimal morbidity with significant reduction in prostate-specific antigen levels.

Background: The use of frameless robotic stereotactic body radiotherapy has not been investigated in patients whose primary cryosurgery treatment failed. The aim of this series was to present initial experiences with frameless robotic radiosurgery in the treatment of local prostate recurrence after cryotherapy. **Methods:** We reviewed the outcome of frameless robotic radiosurgery in 4 patients for biopsy-proven local recurrent prostate cancer after cryotherapy. The patients underwent stereotactic body radiation therapy (SBRT) at Winthrop University Hospital, Mineola, New York. **Results:** The patients' ages ranged from 66 to 75 years old. The average follow-up was more than 4 months. Presalvage prostate-specific antigen (PSA) levels were 7.3, 11.9, 6.1, and 20.9 ng/mL for the four patients. Presalvage Gleason scores were 7, 7, 9, and 8 respectively. One patient had insufficient follow-up for inclusion. The 3 remaining patients showed reduction of PSA levels after SBRT. Follow-up post-SBRT PSA levels were 2.2, 0.19, and 2.0 ng/mL. The average PSA reduction was 7.0 ng/mL. Morbidity at 3-week follow-up included urinary urgency, dysuria, and constipation. There was no change in international prostate symptom score or The International Consultation on Incontinence Questionnaire-Short Form scores after SBRT. One patient experienced erectile dysfunction from SBRT. **Conclusions:** Initial results indicate that robotic SBRT is a viable option for patients who have failed initial cryosurgery therapy measures. The patients had minimal morbidity with significant reduction in PSA levels.

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Introduction

Cryosurgery as a primary therapy has been shown to have biochemical failure-free rates of 73% to 77%.[1] Patients with refractory prostate cancer after cryoablation have few options for salvage therapy. Patients who choose cryoablation as a primary therapy are often patients who are poor surgical candidates to begin with; therefore, although salvage prostatectomy may be an option for some patients, it cannot be advised for all patients. Other accepted salvage treatment options include cryosurgery, brachytherapy, and high-intensity focused ultrasound.

Hypofractionation radiation has become increasingly popular as an alternative to traditional external-beam radiation. Extreme hypofractionation radiotherapy (RT) schedules substantially reduce the number of treatment visits for patients compared with traditional external-beam protocols by increasing the standard fractionation from approximately 2 Gy per fraction to >35 Gy per fraction. In addition, the fractionation sensitivity differential (tumor/normal tissue) for prostate cancer has been found to favor the hypofractionated RT over traditional fractionation

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schemes.[2] Hypofractionation has shown a favorable toxicity profile in other prostate cancer salvage settings such as patients after prostatectomy. Early results report no late grade 3 or 4 toxicities among study participants.[3] Robotic stereotactic radiosurgery (CyberKnife; Sunnyvale, CA) is a minimally invasive technique that delivers large doses of ionizing radiation to a well-defined target in hypofractionation schedules. This technique minimizes the radiation dose to surrounding tissues while maintaining therapeutic doses to the area of interest. Studies that evaluated the use of the CyberKnife in the primary treatment of prostate cancer showed a 4-year biochemical failure–free survival rate of 94%.[4] Adverse events were rare, with no grade 4 toxicities. Bladder toxicities, dysuria, and rectal toxicities were the most common associated morbidities.[4] To our knowledge, there have not been any reports on the use of CyberKnife in the setting of primary cryosurgery failure. In this report, we present 4 cases of cryotherapy failure and subsequent CyberKnife treatment.

Materials and Methods

The patients were treated with cryosurgery at Columbia University Medical Center, New York, a tertiary care academic US center that uses Endocare (Endocare Inc, Austin, TX) or the Galil cryotherapy surgical system (Galil Medical Inc, St Paul, MN). Before both treatment modalities, the patients had a negative metastatic evaluation, including nodal imaging of the abdomen and pelvis. The transrectal ultrasound (TRUS) guided percutaneous cryosurgery procedure was used as previously described.[5] The patients were treated with whole-gland cryosurgery.

Salvage treatment was conducted at Winthrop University Hospital, Mineola, New York. The CyberKnife system was used to deliver fiducial-based image-guided stereotactic body radiation therapy (SBRT) as described previously.[6-8] Four gold fiducials were placed in the prostate via TRUS. A noncontrast computed tomography was obtained, and anatomical contouring of the prostate, seminal vesicles, rectum, bladder penile bulb, femoral heads, and testes were conducted. The course of RT consisted of 5 fractions of 7 Gy for a total dose of 35 Gy, with a prescription dose coverage of 95% of the planning target volume. The planning target volume was the prostate gross tumor volume expanded by 5 mm, except for a 3-mm expansion posteriorly by the rectum. A range of 140 to 170 beams was used prescribed to the 83% to 87% isodose with multiple collimators. The rectal dose-volume goals were <5% of the rectum receiving 1.08% of the prescribed dose, <25% receiving 97% of the dose, <40% receiving 83% of the dose, and <60% receiving 55% of the dose. The bladder dose-volume goals were <5% of the bladder receiving 1.08% of the prescribed dose and <50% receiving 50% of the dose. The treatments were given over 5 consecutive days for each patient.

The International Consultation on Incontinence Questionnaire-Short Form was used to assess incontinence.[9] The American Urological Association International Prostate Symptom Score (IPSS) was used to assess urinary symptoms.[10] The SHIM (sexual health inventory for men) was used to assess erectile dysfunction.[11]

Results

Patient A

Patient A was a 75-year-old man with a significant medical history of aortic stenosis, coronary artery disease, and hyperlipidemia. He initially presented with a precryotherapy PSA level of 7.6 ng/mL and a Gleason score of 7 (4 + 3). The patient had erectile dysfunction before presentation. In February of 2010, he underwent cryosurgery as primary treatment for prostate cancer. His postcryosurgery PSA level nadir was 4.1 ng/mL. His PSA level climbed to 7.3 ng/mL by July 2011, at which time he underwent a TRUS biopsy. Three of 12 biopsy cores were found to be positive, with a Gleason score of 7 (3 + 4). The patient had SBRT in October of 2011. At a 3-week follow-up, the patient completed a morbidity assessment in which he only noted 1+ urinary urgency according to Radiation Therapy Oncology Group toxicity scales.[12] Four months after SBRT, the patient's PSA level was 2.2 ng/mL (PSA level reduction of 5.1 ng/mL [70%]), and the patient was asymptomatic.

Patient B

Patient B was a 73-year-old man with a significant medical history of hypertension and previous coronary artery bypass graft. He initially presented with a precryotherapy PSA level of 10.02 ng/mL and a Gleason score of 8 (4 + 4). In February of 2006, he underwent primary cryosurgery. His postcryosurgery PSA level nadir was 2 ng/mL. He was started on hormonal therapy. His PSA level climbed to 11.9 ng/mL by August 2011, at which time he underwent a TRUS biopsy. Two of 12 biopsy cores were found to be have a positive Gleason score of 9 (4 + 5). The patient had SBRT in November of 2011. At the 3-week follow-up, the patient completed a morbidity assessment in which he noted 1+ dysuria and 1+ constipation.[12] Two months after SBRT, the patient's PSA level was 0.19 ng/mL (PSA level reduction of 11.7 ng/mL [98%]), and, 4 months after SBRT, the patient's PSA level remained constant, at 0.18 ng/mL. The patient experienced erectile dysfunction after SBRT. His pre-SBRT SHIM was 21 and his post-SBRT SHIM was 1.

Patient C

Patient C was a 66-year-old man with a medical history of hypertension, hypercholesterolemia, and depression. He initially presented with a precryotherapy PSA level of 6.1 ng/mL and a Gleason score of 8 (4 + 4). In October of 2010, he underwent primary cryosurgery. His postcryosurgery PSA level nadir was 0.8 ng/mL. His PSA level climbed to 4.4 ng/mL by October 2011, at which time he underwent a TRUS biopsy. Four of 12 biopsy cores were found to be positive, with a Gleason score of 7 (3 + 4). The patient had SBRT in March of 2012. At a 3-week follow-up, the patient completed a morbidity assessment in which he denied urinary and erectile dysfunction. Two months after SBRT, the patient's PSA level was 2.0 ng/mL (PSA level reduction of 4.1 ng/mL [67%]), and the patient was asymptomatic.

Patient D

Patient D was a 69-year-old man who underwent primary cryosurgery in 2006. His PSA level reached 15 ng/mL in 2009, and he had a prostate biopsy, which was negative. In February of 2012, his PSA level was 20.9 ng/mL, at which point he had another biopsy, which was positive, with a Gleason score of 8 (4 + 4). The patient had SBRT and at time of manuscript preparation was only 2 weeks post treatment.

Discussion

To our knowledge, we present the first reported series of salvage SBRT treatment after disease recurrence after cryosurgery. Initial results are encouraging, all three patients showed reduction in PSA values after an average of 3-month follow-up (Table 1). The average

Table 1 Patient Profiles

	Patient A	Patient B	Patient C	Patient D
Age, y	75	73	66	69
BMI (kg/m^2)	23	36.6	24.4	25.8
Comorbidities	Aortic stenosis, cad, hld	Htn, cabg	Htn, hld, depression	None
Follow-Up, mo	7.5	6.5	2.5	0.5
Precryo PSA, ng/mL	7.6	10.02	6.1	NA
Precryo Gleason Score	7 (4 + 3)	8 (4 + 4)	8 (4 + 4)	NA
PSA Nadir After Cryo, ng/mL	4.1	2	0.8	NA
Time to Salvage Tx	1 y, 8 mo	5 y, 9 mo	1 y, 4 mo	6 y
PSA Presalvage Tx, ng/mL	7.3	11.9	6.1	20.9
Presalvage Gleason score	7 (3 + 4)	9 (4 + 5)	7 (3 + 4)	8 (4 + 4)
No. Positive Biopsy Cores Before Salvage	3	2	4	4
Bilateral positive cores	Yes	No	No	Yes
PSA Postsalvage Tx, ng/mL (Follow-Up Days)	2.2 (136)	0.19 (60); 0.18 (127)	2.0 (64)	NA
Lesion Size, mm^3	88.8	43.4	139.2	67.8
Planning Target Volume Mean, mm^3	3854	3781	3813	3784
% Coverage	96.8	95.3	97.9	96.0
Three-Wk Follow-Up Morbidities	1+ urgency	1+ dysuria; 1+ constipation	None	NA
IPSS Presalvage Tx	6	4	3	4
IPSS Postsalvage Tx	6	4	3	NA
ICIQ Presalvage Tx	0	1	0	0
ICIQ Postsalvage Tx	0	1	0	NA
SHIM Presalvage Tx	1	21	22	NA
SHIM Postsalvage Tx	1	1	22	NA

Abbreviations: BMI = body mass index; cabg = coronary artery bypass grafting; cad = coronary artery disease; cryo = cryosurgery; hld = hyperlipidemia; htn = hypertension; ICIQ = The International Consultation on Incontinence Questionnaire-Short Form; IPSS = International Prostate Symptom Score; NA = not available; PSA = prostate-specific antigen; SHIM = The sexual health inventory for men; Tx = treatment.

PSA level reduction was 7.0 ng/mL, which suggests significant reduction in disease burden. Two of 3 patients achieved post-SBRT treatment nadirs below their postcryosurgery nadirs. Given the short duration of follow-up, continued monitoring will be required to ensure that the results remain durable.

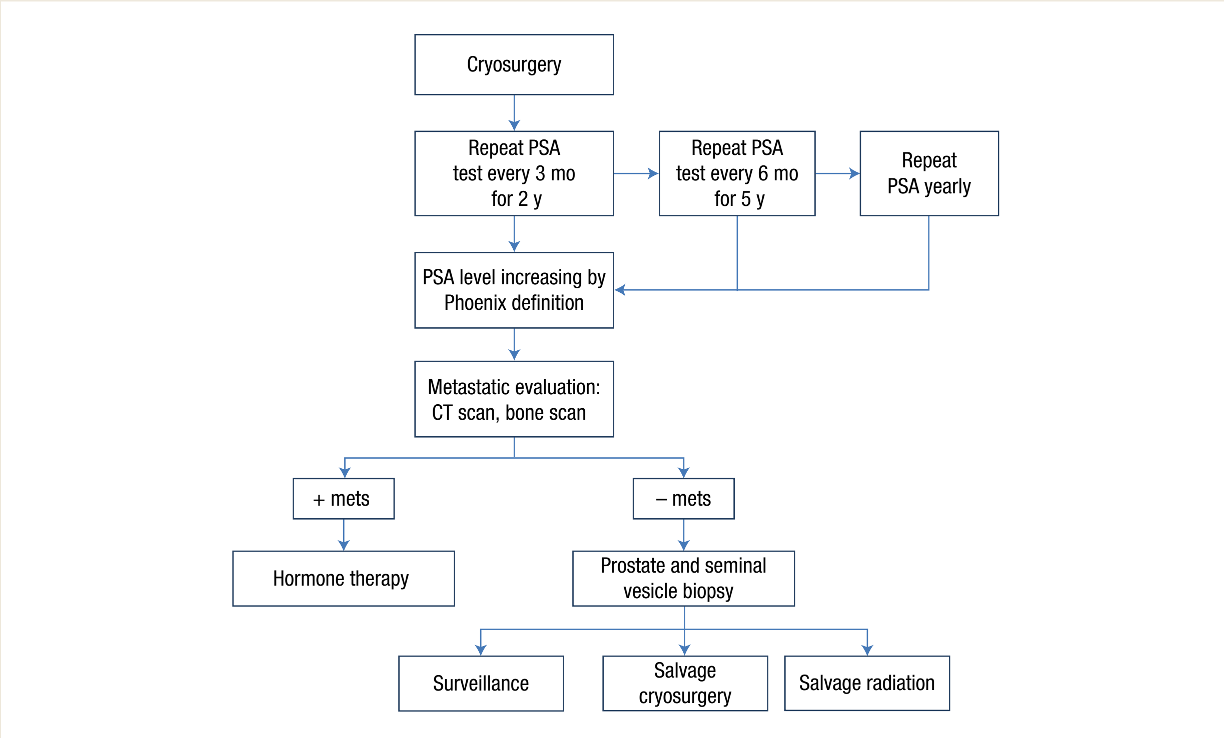
These patients had significant comorbidities that would potentially rule them out of surgical options. Salvage radical prostatectomy (SRP) is technically more challenging than primary prostatectomy.[13] Patients undergoing SRP have a mean operative time of 3.7 hours; robotic SRP times are significantly longer.[14] The long time under anesthesia for patients with multiple comorbidities likely increases the probability of adverse events perioperatively. Patients also require longer hospital stays for SRP procedures. These factors made these patients ideal candidates for salvage SBRT.

Patients with recurrent cancer after 1 treatment modality may benefit from alternative treatments. Cancer cells resistant to cryosurgery have evaded the cellular damage caused by expanding ice crystals and the microvascular damage of the thawing process.[15] These tissues may be inherently resistant to these processes and may benefit from alternative modes of cellular damage, such as SBRT.

RT is currently being used in the salvage setting for biochemical recurrence after radical prostatectomy. Stephenson et al[16] conducted a large multi-institutional retrospective analysis of 1540 patients and found a 6-year progression-free probability after salvage RT of 32%. However, a significant improvement in disease-free status was seen with lower PSA values at initiation of salvage RT, which suggests that priority be placed on prompt salvage treatment.[16] Similar findings have been reported at other institutions.[17-19] We present an algorithm (Figure 1) for follow-up after cryotherapy to decrease the time from disease recurrence to treatment.

Operative procedures before RT have been associated with increased urinary toxicities, which led the American Brachytherapy Society to list transurethral resection of the prostate (TURP) as a relative contraindication for brachytherapy.[20] Newer guidelines have modified this contraindication to only include patients with large or poorly healed TURP, which reflects recent evidence that brachytherapy does not significantly increase the risk of urinary problems.[21] Results of recent studies have shown that external-beam RT (EBRT) in patients with a history of TURP have an increased risk for acute and late urinary toxicities over patients with no history of TURP.[22,23] Urinary incontinence rates after

Figure 1 Winthrop University Hospital Algorithm for Following-up Patients After Cryosurgery



prostatectomy and savage RT, depending on the RT used, ranges from 7% to 14% at 5 years.[24] It remains to be seen if a history of cryotherapy increases the likelihood of urinary symptoms in patients who undergo SBRT. No patients in our series had increasing IPSS or The International Consultation on Incontinence Questionnaire-Short Form scores after SBRT.

One patient experienced decreased erectile function as a result of the SBRT. Alternative salvage modalities have very high rates of erectile dysfunction. Erectile dysfunction rates among patients who receive salvage cryosurgery after failed RT range from 70% to 90%.[25-29] In contrast, salvage radical prostatectomy after failed RT is associated with incontinence rates that range from 21% to 90%, and as many as 40% of patients experience urethral stricture formation.[30]

This study hints at future modes of prostate cancer treatment. A recent randomized control trial has shown the superiority of EBRT combined with high-dose brachytherapy boost over EBRT alone. Patients with high-dose brachytherapy boost have biochemical disease–free survival rates of 75% and 66% at 5 and 7 years, respectively, compared with EBRT-alone rates of 61% and 48%, respectively.[31] In this regard, combining focal cryosurgery and total-gland SBRT may allow lower-dose SBRT to be administered to achieve similar efficacy. Alternatively, the combination of full-dose SBRT and focal cryosurgery may yield significantly increased survival with a minimal increase in morbidity.

Conclusion

Initial results indicate that robotic SBRT is a viable option for patients who have failed initial cryosurgery therapy measures. The patients had minimal morbidity, with significant reduction in PSA levels. Further investigation is warranted to determine long-term recurrence rates and to identify the patient population that will benefit the most from SBRT.

Clinical Practice Points

- Increased use of cryosurgery for the treatment of prostate cancer will cause an increase in the number of patients who experience local recurrence of prostate cancer. Cryosurgery as a primary therapy has been shown to have biochemical failure–free rates of 73% to 77%.[1]
- Salvage prostatectomy is not a viable option for all patients with local recurrence. Less-invasive alternatives must be available for these patients. Other accepted salvage treatment options include cryosurgery, brachytherapy, and high-intensity focused ultrasound.
- Frameless robotic stereotactic radiosurgery (CyberKnife) is a minimally invasive technique that minimizes the radiation dose to surrounding tissues while maintaining therapeutic doses to the area of interest.
- Studies that evaluated the use of the CyberKnife in the primary treatment of prostate cancer have shown very promising results. Initial results presented here indicate that frameless robotic SBRT is a viable option for patients who had initial cryosurgery therapy that failed.
- These results raise the possibility of combining focal cryosurgery and total-gland SBRT, which may allow lower-dose SBRT to be

administered to achieve similar efficacy that mirrors the effect of EBRT combined with high-dose brachytherapy boost.

Disclosure

The authors have stated that they have no conflicts of interest.

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