Salvage Cryosurgery for Recurrent Prostate Cancer After Radiation Therapy: A Seven-Year Follow-up

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Abstract

Cryosurgery of the prostate presents as an efficient therapy following failed radiation therapy. We report on a 7-year retrospective analysis evaluating the morbidity and biochemical disease-free survival (bDFS) of this therapy. Between 1993 and 2001, 59 patients who had been previously treated with radiation therapy and had rising serum prostate-specific antigen (PSA) values underwent salvage cryoablation of the prostate for localized, histologically proven, recurrent prostate cancer. Serial serum PSA testing was performed, and biopsies were taken at 6, 12, and 24 months, and again at 5 years, and any time the PSA rose above 0.5 ng/mL. Patients were stratified along clinical parameters. The combined postsalvage bDFS rate using a PSA cutoff of 0.5 ng/mL was 59% and 69% with a 1.0 ng/mL PSA cutoff. Using a PSA threshold of 0.5 ng/mL as evidence of biochemical recurrence, 61%, 62%, and 50% of patients with < 4 ng/mL, 4-10 ng/mL, and > 10 ng/mL PSA, respectively, remain biochemically relapse free at 7 years. A threshold of 1.0 ng/mL yielded a disease-free status of 78%, 74%, and 46%, respectively. Patient biopsies showed no evidence of residual or recurrent disease. Improved survival rates and no known latent complications indicate cryosurgery is a promising form of treatment for radiation-resistant prostate cancer. This 7-year analysis shows a promising validation of cryosurgery as an efficacious treatment modality for locally confined T1-T3 prostate cancer following primary radiation therapy failure.

Introduction

With prostate cancer being the second-leading cause of cancer death in American men, it is important to pay special attention to improving the safety and effectiveness of primary and salvage treatment options.[1-3] Radiation therapy is widely used to treat localized prostate cancer; however, recurrence and residual disease have been recorded in 25%-93% of radiation cases and the procedure cannot be repeated.[4] Salvage radical prostatectomy following radiation therapy failure can be performed with curative intent but is associated with significant morbidity.[5] Hormonal therapy (androgen deprivation) may reduce tumor size and slow growth but ultimately is not curative. Considering the limitations of these treatments, an alternative approach to cure recurrent prostate cancer with minimal morbidity is needed. Cryoablation is one such means.

The compounded difficulty of treating radiation-effected tissue via radical prostatectomy in radiation-resistant disease prompted interest in the development of an alternative salvage treatment for prostate cancer.[6] Salvage cryoablation was initiated shortly after the procedural technique was reintroduced in 1993 by Onik et al,[7] who pioneered the use of tran-

Table 1 Patient Characteristics Before Cryosurgery

Characteristic	Patients (n = 59)
Gleason Score	
Median (range)	7 (5-9)
< 7	10 (17%)
7	32 (54%)
> 7	17 (29%)
Missing	0
Prostate-Specific Antigen	
Median, ng/mL (range)	5.6 (0.01-57)
< 4 ng/mL	21 (36%)
4-10 ng/mL	24 (41%)
> 10 ng/mL	14 (24%)
Missing	0
Stage	
T2	41 (69%)
T2a	11
T2b	18
T2c	12
T3	16 (27%)
T3a	2
T3b	1
T3c	13
T4	1 (2%)
T4a	0
T4b	1
T4c	0
Missing	1 (2%)

srectal ultrasound and incorporated advances in interventional radiology technology.[8] Recent advances in technology and standardization of method have led to more widespread application of the procedure, with corresponding improvements in efficacy and safety.[9] In this article, we present the 7-year follow-up analysis from a series of 59 patients who received targeted cryoablation of the prostate (TCAP) as salvage therapy for radiation-resistant disease.

Patients and Methods

Patient Selection

Our institutional review board approved the salvage cryoablation protocol used in this study. Between March 1993 and September 2001, 59 patients with rising prostate-specific antigen (PSA) levels who had previous radiation therapy treatment and were eligible for cryotherapy completed external beam radiation therapy or brachytherapy ≥ 24 months before evaluation. Patients had biopsies performed at regular intervals if their PSA level rose 0.5 ng/mL above nadir. Transrectal ultrasound and biopsies of the prostate and seminal vesicles were performed. To be eligible for salvage cryoablation, patients were required to have biopsy-proven recurrent prostate cancer without evidence of distant metastasis. Patients with gland volume > 40 mL, a Gleason grade ≥ 7, or stage ≥ T2b cancer received 3 months of combined hormonal therapy before cryotherapy. No patient continued with adjuvant androgen deprivation after cryotherapy.

Procedure

The cryoablation technique used was similar to those described by Onik et al[7] and Donnelly and Saliken.[10] Cryoablation of the prostate was performed using 2 freeze-thaw cycles of argon and helium gases. All patients had a US Food and Drug Administration–approved warming catheter placed in the urethra during the procedure to maintain its integrity. The number of probes varied between 4 and 6, depending on the prostate volume. At least 2 freeze cycles, separated by a complete thaw, were performed in which the prostate was encompassed in ice. Freezing was routinely extended into the bladder base and urogenital diaphragm. Patients were discharged home within 24 hours of the procedure. The first 10 patients received suprapubic catheters, the remaining had a Foley catheter. Catheters were removed 2-3 weeks after the procedure.

Patient Follow-up

Postoperative protocol included serial serum PSA testing performed every 3 months for 1 year and then twice a year. Patients were considered to have a biochemical recurrence if they had an increase in PSA of ≥ 0.5 ng/mL. In addition, sextant and extra core biopsies from cancer sites were taken at 6 months, 12 months, 2 years, and 5 years after treatment when a rise in PSA level was experienced and anytime PSA > 0.5 ng/mL. Patients received no other form of treatment for prostate cancer after salvage cryotherapy.

Statistical Analysis

Univariate analysis was performed using the χ^2 test and Kaplan-Meier survival analysis. The Cox proportional hazard regression model was used to carry out multivariate analysis. The time to recurrence was defined as the time from surgery to PSA recurrence or as time from cryosurgery to the last follow-up visit for those who did not experience biochemical recurrence.

Results

A retrospective analysis of 59 patients who underwent salvage TCAP after failed radiation therapy between March 1993 and February 2001 was performed. The mean and median age of the sample was 67.5 years. Mean and median length of follow-up after salvage cryoablation was 72.5 and 82.32 months, respectively. Presurgery clinical characteristics are summarized in Table 1.

Kaplan-Meier survival curves for 7-year actuarial biochemical disease-free survival (bDFS) by PSA cutoffs of 0.5 ng/mL and 1.0 ng/mL are shown in Figures 1A and 1B. The 0.5 ng/mL combined-risk group percentage was 59%. The combined-risk group percentage using the 1.0 ng/mL PSA cutoff of was 69%.

Figure 1 | Survival Curves for 7-Year Actuarial Biochemical Disease-Free Survival

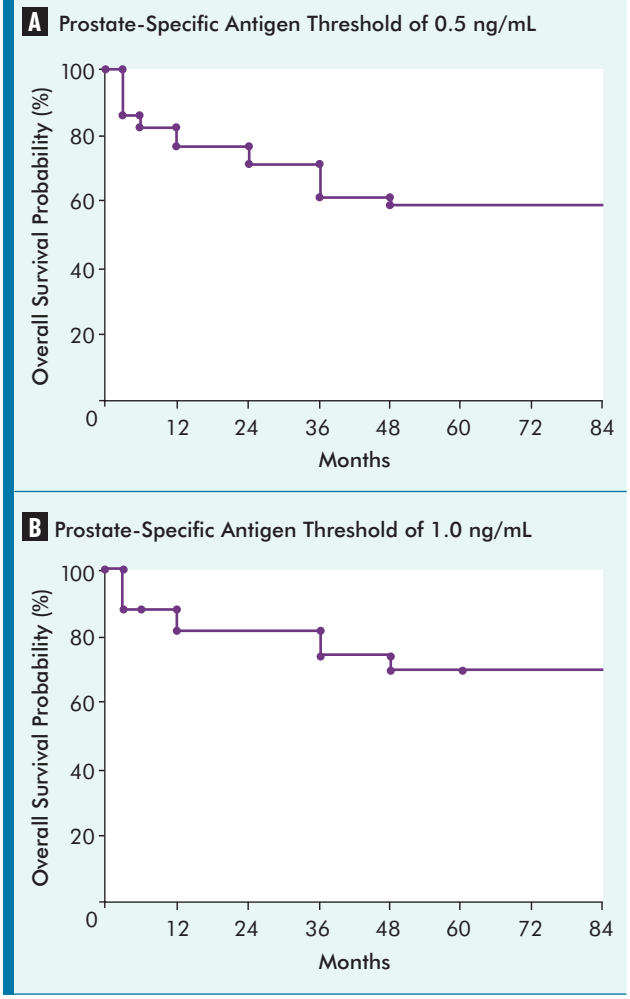

Table 2 | Stratified Actuarial Biochemical Disease-Free Rates

	Patients	PSA* ≤ 0.5 ng/mL	PSA* ≤ 1.0 ng/mL
Preoperative PSA			
< 4 ng/mL	20	60.8%	78.4%
4-10 ng/mL	25	62.0%	74.3%
> 10 ng/mL	14	50.0%	45.7%
Gleason Score			
3-6	10	50.0%	66.7%
7	32	65.8%	80.2%
8-9	17	52.3%	52.3%
T Stage			
T1-T2	42	66.5%	76.7%
T3-T4	17	41.2%	51.5%

*Post operative PSA.
Abbreviation: PSA = prostate-specific antigen

Stratified bDFS rate results are presented in Table 2. Of the 38 patients who underwent biopsy, none were positive for disease. The average time from salvage cryosurgery to the most recent biopsy was 20.7 months, with a median value of 24 months. Morbidities included 4.3% incontinence and rectal fistula formation in 3.4%.

Discussion

Radiation therapy, like radical prostatectomy, remains a gold-standard treatment for localized prostate cancer. Although it is a minimally invasive procedure with the potential of cure, there are multiple drawbacks. Once performed, the procedure cannot be repeated as it would place patients at an increased risk for radiation-induced complications in addition to the possible likelihood of radiation-resistant tumors.[11] It has also been suggested that recurrent prostate cancers are more biologically aggressive either because of cytologic evolution, perhaps induced by radiation, or due to the progression of an innately aggressive tumor already resistant to radiation.[12]

The unique characteristics of radiation-resistant prostate cancer leave patients with limited second-line options. The effect of primary radiation therapy is known to increase morbidity in salvage prostate cancer treatments. Salvage radical prostatectomy imparts its own challenges, including the complexity and risk involved in the procedure itself as well as an association with high comorbidity and extended hospitalization.[13] Furthermore, neither cytotoxic chemotherapy nor androgen ablation can be considered curative therapies for prostate cancer although they may have a role in abating metastasis.[14]

Historically, the use of cryosurgery has been limited to primary therapy for locally extensive prostate cancer for men who are too old or whose comorbidity is too extensive to be appropriate candidates for radical surgery. Advances in technology and techniques, however, have led to increases in efficacy and safety and an expanded role for cryoablation including the treatment of low- and medium-risk primary disease.

Since the mid-1990s, TCAP has met with success in treating early-detected, radiation–resistant prostate cancer.[15] The 7-year bDFS data from this report further support cryoablation as a safe and efficacious salvage treatment for radiation-resistant prostate cancer with durable results. Still, it is difficult to compare and contrast salvage cryosurgery and salvage radical prostatectomy because of (1) the retrospective, single-institution nature of most studies, (2) the nonuniform patient selection, and (3) the variations in the definition of biochemical failure.[16] Biopsy-proven and biochemical failure disease-free rates, stratified by matching sample subgroups on important dimensions such as clinical stage, degree of tumor differentiation, risk factors, and preoperative PSA levels, and a comparison of morbidities give an approximation of efficacy at least equivalent to salvage radical prostatectomy, salvage brachytherapy, and palliative salvage androgen ablation therapy.[6]

Local control of cancer is the goal of any definitive local therapy although the best method for detecting recurrent disease proves difficult to determine. Salvage cryoablation, like primary

radiation therapy, does not eradicate the entire gland, and definitions of biochemical relapse are imperfect. There are several reasons why PSA readings might be elevated despite no residual cancer, including (1) preservation of residual PSA-producing tissue such as normal glandular tissue (acini), (2) distant metastasis, or (3) a combination of the two. Postcryoablation multiple-biopsy results provide an accurate appraisal of bDFS, yet biopsy, too, can miss residual disease and does not detect metastatic disease.[5] Sextant biopsies, although improved with transrectal ultrasound guidance and advanced biopsy devices, are still limited to only a partial sample of the gland. Furthermore, as reported by Brawer,[17] biopsies performed after radiation therapy are some of the most difficult specimens to interpret for surgical pathologists because of radiation atypia, occult micrometastasis, and sampling errors. Using both biopsy and PSA methods to test for recurrence ensures both accurate correlation to other treatment modalities and rigorous patient observation.

In this series, the lack of evidence of positive biopsies suggests that failure was likely caused by micrometastatic disease overlooked in salvage therapy work-up. These micrometastatic cells, found most often in bone marrow or lymph nodes, spread concurrently with radiation treatment and, being outside of the prostatic capsule, remain beyond the realm of any salvage prostate cancer treatment. Several studies have correlated an elevated Gleason score in the primary tumor with an increased prevalence of micrometastatic cells.[18-20] Reverse-transcription polymerase chain reaction amplification of PSA messenger RNA has been proven to characterize metastatic cell proliferation.[21] Cher and colleagues have found an association between androgen ablation and a reduced prevalence of metastatic cells that could be useful in adjuvant primary therapies.[18] A phenotypic characterization assay performed in addition to standard bone scans would detect distant metastases earlier and improve treatment plans in patients likely to have micrometastatic bone marrow or lymphatic cancers. It is plausible that the PSA failures in this group of 59 men may have an etiology based on preexisting extracapsular or systemic cancers. With more careful screening and patient work-up, the success of cryosurgery to fully ablate localized radiation-resistant cancer may be greater than reported. Complication rate is similar to the primary cryotherapy group, except for 2 cases of rectal injury that were seen during our early learning curve experience. The incontinence rate was 8% in this cohort, which was higher than the primary cryosurgery group's rate of 4.3%.

Although there is no uniform definition of success between prostate cancer therapies, a definition of biochemical relapse limited to PSA levels is, perhaps, the most reasonable measure in trials involving cryoablation therapy. Similar to radiation therapy, prostatic tissue that may be PSA-producing is left intact in contrast to radical surgery. In cryoablation, there is some preservation of tissue surrounding the urethra. Akdas et al have shown that a PSA level of 0.4 ng/mL is not unexpected when 1 g of prostatic tissue has been preserved in patients free of prostate cancer.[22] Thus, a definition of biochemical failure that is just on the threshold of PSA detection may be unreasonable for cryoablation. Typically, a PSA threshold of either 0.5 ng/mL or 1.0 ng/mL, a series of PSA elevations, or failure to maintain PSA nadir serves as evidence of biochemical recurrence. Benign PSA-releasing tissue, antiandrogen treatment, and ongoing treatment effects after radiation therapy make each biochemical method a somewhat subjective test of cancer relapse.[17] Thus, our results using a 0.5 ng/mL threshold as evidence for biochemical relapse indicate a high, but reasonable, standard of efficacy.

Conclusion

We have found that salvage cryosurgery is a promising form of treatment for radiation-resistant prostate cancer. A 7-year retrospective analysis shows a success rate comparable with salvage radical prostatectomy and hormonal therapy. Favorable outcome is expected if cryoablation is performed when postradiation PSA is < 10 and tumor stage is T1-T2. There are minimal morbidity rates and no known latent complications involved with the procedure. In addition, the cryosurgery is minimally invasive, requiring a short hospital stay with most patients being able to be discharged within 24 hours.

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