

SALVAGE CRYOTHERAPY FOR RECURRENT PROSTATE CANCER AFTER RADIATION THERAPY: THE COLUMBIA EXPERIENCE

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ABSTRACT

Objectives. Cryotherapy of the prostate represents a potential treatment for localized recurrent prostate cancer after radiation therapy. We report our experience and evaluate the predictive factors for prostate-specific antigen (PSA) recurrence.

Methods. Between October 1994 and April 1999, 43 patients underwent salvage cryoablation. All patients had biopsy-proven recurrent prostate cancer without seminal vesicle invasion, negative bone scans, and negative lymph node dissection. Patients had received 3 months of combined hormonal therapy before cryosurgery. Biochemical recurrence-free survival (bRFS) was defined as a PSA value less than 0.1 ng/mL.

Results. Complications included incontinence (9%), obstruction (5%), urethral stricture (5%), rectal pain (26%), urinary infection (9%), scrotal edema (12%), and hematuria (5%). The mean follow-up was 21.9 months (range 1.2 to 54). Twenty-six patients (60%) reached a serum PSA nadir less than 0.1 ng/mL, 16 (37%) had a PSA less than 4 ng/mL, and 1 (3%) had a PSA less than 10 ng/mL. The bRFS rate was 79% at 6 months and 66% at 12 months. The bRFS rate was higher for patients who had an undetectable postcryotherapy PSA than for patients who did not reach a PSA less than 0.1 ng/mL (73% versus 30%, $P = 0.0076$). Using multivariate analysis, a PSA nadir greater than 0.1 ng/mL was an independent predictor of PSA recurrence.

Conclusions. Current salvage cryotherapy of the prostate can result in undetectable serum PSA levels with low morbidity. Our data support the current safety and efficacy profile. We believe that cryotherapy is a viable option in the treatment of patients who have biopsy-proven local failure after radiation therapy for prostate cancer. Further refinements in technique and equipment may enhance cryosurgical results. UROLOGY 55: 79–84, 2000. © 2000, Elsevier Science Inc.

External beam radiation therapy and radioactive pellet brachytherapy have been widely used treatments for clinically localized prostate cancer. Biopsy and serum prostate-specific antigen (PSA) data after radiation therapy suggest a significant clinical failure rate in these patients. Recurrent and residual local disease has been reported to exist in 25% to 93% of these cases.^{1–7} It appears that clini-

cal failure, both local and distant, is correlated with biopsy status.^{3,4,8,9} In addition to biopsy data, the routine use of PSA has provided further information regarding the response to radiation therapy.

Considering the post-radiation biopsy results and PSA elevations, a substantial proportion of patients are at increased risk of clinical failure after radiation therapy. Some of these patients will be candidates for salvage therapy. The goal of this therapy is to improve local control and possibly impact long-term survival. Several series have reported on salvage prostatectomy or cystoprostatectomy. Short-term local control rates appear to be good, but the problems of incontinence, residual tumor, and other morbidities persist.^{10–13}

Recently, a renewed enthusiasm for cryotherapy ablation of the prostate, a potentially curative treatment, has developed because of the improvements

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in transrectal ultrasound and cryosurgical instrumentation.¹⁴⁻²² In this study, we retrospectively investigated the complication rates and biochemical recurrence rate after cryoablation of the prostate performed after radiation therapy failure.

MATERIAL AND METHODS

PATIENT SELECTION

Between October 1994 and April 1999, 43 patients underwent cryoablation of the prostate for localized recurrent prostate cancer after radiation therapy (60% of patients had Stage T1-T2 disease and 40% Stage T3 disease). The protocol was approved by our institutional review board. Patients eligible for cryotherapy had completed external beam radiation therapy at least 18 months before evaluation. Patients were required to have a rising serum PSA value. Transrectal ultrasound and biopsies of the prostate and seminal vesicles were performed. All patients had biopsy-proven recurrent prostate cancer without seminal vesicle invasion. All patients had negative bone scans. Patients underwent either a laparoscopic lymph node dissection or an open procedure; to be eligible for cryotherapy, there had to be no evidence of disease in the lymph nodes. All patients had received 3 months of combined hormonal therapy before cryotherapy and did not continue with adjuvant androgen deprivation after cryotherapy.

CRYOTHERAPY PROCEDURE

All cryosurgeries were performed by a single surgeon (A.E.K.). The cryosurgical ablation technique used was that reported by Onik *et al.*²¹ and Pisters *et al.*¹⁷ In the first 25 cases, the CMS AccuProbe machine (Cryo-Medical Sciences, Rockville, Md), a liquid nitrogen-based system, was used. For the last 18 cases, cryoablation of the prostate was performed using the CryoCare Surgical System machine (Endocare, Irvine, Calif), which uses argon and helium gases to freeze and thaw, respectively. All patients had a urethral warming catheter placed during the procedure. The catheter was left in place for 2 hours after the procedure. The number of probes varied between three and six, depending on the prostate volume. A double freeze-thaw cycle involved two distinct freezing events in which the entire prostate gland was twice encompassed in an iceball, separated by a period of complete thawing. Freezing was routinely extended into the bladder base and urogenital diaphragm. Patients were discharged home within 24 hours of the procedure with a suprapubic catheter. The suprapubic catheter was removed 1 to 2 weeks after the procedure, depending on the postvoid residual urine volume.

PATIENT FOLLOW-UP

Patients underwent serial digital rectal examination and serum PSA testing 1 month after cryosurgery and then every 3 months for 18 months. At each consultation, patients were specifically questioned whether urine leaked with activities or leaked because of severe urgency. Incontinence was defined as the patient's reporting a lack of urinary control requiring one or more pads per day. Other complications (obstruction, urinary infection, edema, rectal pain) were assessed from the physician's perspective by chart review.

PSA nadir was defined as the lowest serum PSA measured at the follow-up consultations after cryotherapy. A PSA level of less than 0.1 ng/mL (Hybritech) was considered as undetectable. Patients were considered to have a biochemical recurrence if they had an increase in PSA of 0.2 ng/mL or more above their PSA nadir.

TABLE I. Patient characteristics

Number of patients	43
Mean age (yr)	69.4 (48.1-83.6)
Mean Gleason sum before radiation therapy	7.01 (4-7)
Mean serum PSA before radiation therapy (ng/mL)	16.7 (4.0-59)
Mean serum nadir PSA after radiation therapy (ng/mL)	3.08 (0.0-22.0)
Mean interval between radiation therapy and cryosurgery (yr)	3.9 (0.3-10.7)
Mean precryosurgery serum PSA (ng/mL)	7.07 (0.6-50)
Mean precryosurgery Gleason sum	7.3 (4-9)
Mean follow-up (mo)	21.9 (1.2-54)
PSA nadir after cryosurgery (n)	
≤0.1 ng/mL	26 (60%)
>0.1 to ≤4 ng/mL	16 (37%)
>4 to ≤10 ng/mL	1 (3%)

KEY: PSA = prostate-specific antigen.

Numbers in parentheses are the range, unless otherwise noted.

STATISTICAL ANALYSIS

The Statistical Analysis System, version 6.11 (SAS Institute, Cary, NC) software was used for the analysis, and all tests were performed at the 0.05 significance level. We summarized all data using mean and standard deviations for the continuous variables and frequency tables for the categorical variables. We performed univariate analysis by using the chi-square tests and Kaplan-Meier survival analysis. We used the Cox proportional-hazard regression model to carry out the multivariate analysis. We defined the time to recurrence as the time from surgery to PSA recurrence for those who experienced PSA recurrence and as time from cryosurgery to the last follow-up visit for those who did not experience biochemical recurrence.

RESULTS

PATIENT CHARACTERISTICS

The mean patient age was 69.4 years, with a mean serum PSA level of 7.07 ng/mL. Table I summarizes the patient characteristics. Of our 43 patients, 19 (44%) had a precryotherapy serum PSA less than 4.0 ng/mL, 18 (42%) between 4 and 10 ng/mL, and 6 (14%) greater than 10 ng/mL. The Gleason sum on presurgical procedure needle prostate biopsies was between 2 and 4 in 1 patient (2%), between 5 and 7 in 23 patients (53%), and between 8 and 10 in 19 patients (45%). The hospitalization stay was between 1 and 2 days. In some patients with no significant co-morbidity diseases, cryotherapy was performed as an outpatient procedure.

FOLLOW-UP

With a mean follow-up of 21.9 months, no patient died of prostate cancer or developed metastatic disease. Twenty-six patients (60%) reached a serum PSA nadir less than 0.1 ng/mL (undetect-

TABLE II. Salvage cryosurgery: follow-up

Study	Patients (n)	Follow-up (mo)	Biochemical Recurrence	Positive Prostate Biopsy
Pisters <i>et al.</i> , ¹⁷ 1997	150	13.5 (1.2–32.2)	—	25/110 (23%)
Lee <i>et al.</i> , ²⁰ 1997	43	—	—	At 3 mo 3/20 (15%) At 1 yr 7/20 (35%)
Miller <i>et al.</i> , ¹⁵ 1996	33	17.1 (4.1–34.3)	—	9/33 (27.3%)
Present study	43	21.9 (1.2–54)	79% bRFS at 6 mo 66% bRFS at 12 mo	3/8 (37%)

KEY: bRFS = biochemical recurrence-free survival (Kaplan-Meier curve analysis). Numbers in parentheses are the range.

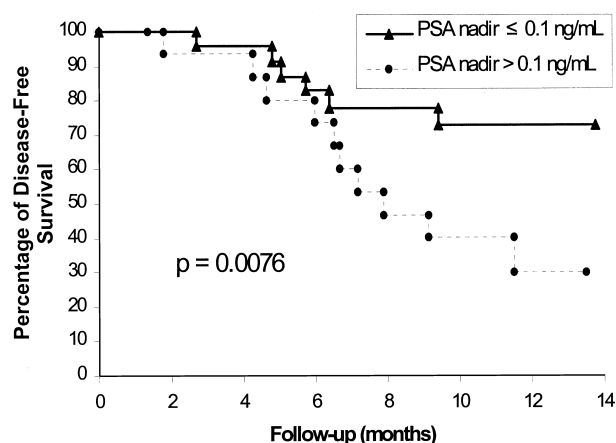


FIGURE 1. bRFS rate according to serum PSA nadir after cryotherapy.

able), 16 (37%) a PSA less than 4 ng/mL, and 1 (3%) a PSA less than 10 ng/mL.

The biochemical recurrence-free survival (bRFS) rate, estimated by Kaplan-Meier curve analysis, was 79% at 6 months and 66% at 12 months (Table II). Eight of our patients underwent subsequent needle prostate biopsy for increasing serum PSA levels: three of them had a local recurrence (37%).

We compared the bRFS rate between the two cryomachines and, to eliminate the learning curve, we also compared the bRFS rate of the two machines we used. Excluding the first 7 patients, two groups of 18 patients were considered. No statistical difference was observed between these groups.

We found that the bRFS rates differed between the group of patients who reached a PSA nadir less than 0.1 ng/mL (undetectable) and the group who did not reach an undetectable serum PSA (73% versus 30%, log rank = 7.11, $P = 0.0076$; Fig. 1).

Multivariate analysis was performed to determine the most independent prognostic factors of PSA recurrence after cryotherapy (Table III). In this analysis, we included preoperative parameters (serum PSA, Gleason sum on needle biopsy, and the interval between radiation therapy and cryo-

TABLE III. Multivariate analysis to define the independent predictors of PSA recurrence after cryosurgery

	Risk Ratio	P Value
Precryosurgery serum PSA	0.60 (0.17–2.13)	0.43
Precryosurgery Gleason sum	0.999 (0.35–2.82)	0.99
Interval between radiation therapy and cryotherapy	0.991 (0.96–1.02)	0.51
Freezes (n)	0.67 (0.26–1.76)	0.41
PSA nadir >0.1 ng/mL	2.98 (1.25–7.10)	0.01

KEY: PSA = prostate-specific antigen. Numbers in parentheses are the range.

therapy), the perioperative parameter (number of freezes), and the postoperative parameter (value of the PSA nadir). A PSA nadir greater than 0.1 ng/mL was an independent predictor of PSA recurrence after cryotherapy. Multivariate analysis was performed, including preradiation therapy parameters (preradiation therapy serum PSA, value of postradiation therapy PSA nadir, or preradiation therapy Gleason sum). These parameters did not independently predict biochemical recurrence after cryotherapy.

COMPLICATIONS

During the follow-up period, 6 patients (14%) had urinary problems, including two with urgency, which resolved with anticholinergic medication. Four patients (9%) had stress incontinence requiring one or more pads daily. Of these 4 patients, two required an artificial sphincter for severe incontinence.

Of the 43 patients who underwent cryoablation of the prostate, 2 patients had obstruction due to necrotic tissue and required transurethral resection of the prostate. Two patients developed a urethral stricture and were successfully treated by urethral dilation.

The most frequent complications we observed

TABLE IV. Overall incidence of complications for the 25 patients who underwent cryotherapy with the AccuProbe machine (machine 1) and the 18 patients who underwent cryotherapy with the CryoCare Surgical System machine (machine 2)

	Overall Complication Rate (n = 43)	Machine 1 Complication Rate (n = 25)	Machine 2 Complication Rate (n = 18)
Major complications			
Incontinence	4 (9)	2 (8)	2 (11)
Obstruction	2 (5)	2 (8)	0 (0)
Urethral dilation	2 (5)	2 (8)	0 (0)
Rectal fistula	0 (0)	0 (0)	0 (0)
Hydronephrosis	0 (0)	0 (0)	0 (0)
Renal failure	0 (0)	0 (0)	0 (0)
Death	0 (0)	0 (0)	0 (0)
Minor complications			
Rectal pain	11 (26)	4 (16)	7 (38)
Perineum swelling- scrotal edema	5 (12)	3 (12)	2 (11)
Lower tract infection	4 (9)	3 (12)	1 (6)
Hematuria	2 (5)	1 (4)	1 (6)

Numbers in parentheses are percentages.

TABLE V. Salvage cryosurgery for radiorecurrent prostate cancer: comparisons of the most frequent complications reported

Study	Patients (n)	Incontinence (%)	Impotence (%)	Obstruction/ Retention (%)	Prostate- Rectal Fistula (%)	Urethral Strictures (%)	Pain (%)	Hydronephrosis (%)
Pisters <i>et al.</i> , ¹⁷ 1997	150	60*	72 [‡]	43	1	0	NA	0
Lee <i>et al.</i> , ²⁰ 1997	46	8.7 [†]	NA	NA	8.7	NA	NA	NA
Miller <i>et al.</i> , ¹⁵ 1996	33	10.3*	NA	9	0	5.1	NA	0
Present study	43	9*	NA	4	0	0	24	0

KEY: NA = not available.

* Incontinence = need of ≥ 1 pad/day.

[†] Incontinence = any urinary trouble.

[‡] Preoperative potency not available.

were rectal pain and scrotal-perineal edema (Tables IV and V). In all cases, these minor complications disappeared within 3 months after cryotherapy. A comparison of complication rates between the two cryomachines is reported in Table IV. No statistical difference was observed between these two groups.

COMMENT

Cryosurgical technology has been applied in the past to a wide variety of neoplasms, including brain, cervix, skin, and liver.²³⁻²⁶ Within urology, cryosurgery has been applied to both renal and prostate cancers.^{14-22,27,28} The idea of introducing extremely cold temperatures to cancer cells has been applied to both localized and metastatic tumors. The cold environment that is created within a tumor or organ can destroy both cancerous and normal cells.

In the past, cryosurgical ablation of the prostate was performed using an open perineal incision. Owing to the pioneer work of Onik *et al.*,²¹ the procedure is now performed percutaneously. In addition, the entire procedure, including the placement of needles and cryoprobes and freezing, is performed under real-time transrectal ultrasound guidance. With accurate placement of the cryoprobes in the prostate, the iceball that is generated has a much greater chance of destroying the entire gland.

One additional technical advance in cryosurgery of the prostate has been Food and Drug Administration approval of a urethral-warming device. The urethral warmer has maintained the integrity of the mucosa, preventing urethral damage during freezing. This has resulted in a urethral slough rate that has dropped to very low percentages. At Columbia-Presbyterian Medical Center, we have found that

by maintaining the urethral warmer for an additional 2 hours in the recovery room after cryosurgery, the urethral slough rate is 0%.

During cryosurgery, cells can die by necrosis and apoptosis. There are a number of cellular events that occur during freezing that lead to cell death, including membrane disruption, release of lysosomal proteases, and the formation of intracellular ice. The degree of cell damage has been shown to correlate directly with the duration of the freeze, the number of freeze-thaw cycles, and the lowest temperature that is reached. Most cryosurgeons use a double freeze-thaw cycle technique.^{17,18} Although there are only a few published reports on the number of freezing cycles, evidence has been suggested that a double freeze technique will increase cell kill over a single freeze, without additional morbidity.¹⁸ The optimal timing and rapidity of thawing is unknown; however, most cryosurgeons believe that a quick freeze followed by a slow thaw will yield the maximal cell kill.

When consulting a patient for salvage therapy after radiation therapy, a number of factors should be considered. Currently, our algorithm consists of the Gleason grade of the tumor, the serum PSA, and the age and medical condition of the patient. When a patient presents with either a rising serum PSA or changes in the rectal examination (eg, a new nodule, induration, asymmetry, or firmness) after radiation, the first step in restaging should consist of a prostate and seminal vesicle ultrasound-guided biopsy. If the biopsy reveals seminal vesicle involvement, we do not recommend cryosurgery because of the possibility of freezing the bladder base or trigone and the high likelihood that these patients will not be cured by local therapy. In this case, patients should be counseled for hormonal therapy.

In most cases of radiation-recurrent cancers, the Gleason grade of the tumor will increase from the preradiation value.²⁹ For this reason, patients who are candidates for salvage cryoablation should undergo a metastatic evaluation, including a bone scan and laparoscopic lymph node dissection. If the pelvic nodes are negative, our patients receive 3 months of combined androgen deprivation before cryosurgery. Androgen deprivation was used in our study, as well as in published reports,¹⁴⁻²⁴ to decrease the prostate size to facilitate cryotherapy: the freeze will be faster, less gas will be required, and the potential side effects of freezing the bladder and sphincter will be lower. In our experience, hormonal therapy can also increase the distance between the base of the prostate and the anterior rectal wall. On transrectal ultrasound, there appears to be a thickening of Denonvilliers' fascia, allowing an increase in the safety zone for the cryosurgeon. The iceball can therefore be allowed to

extend beyond the posterior aspect of the prostate with greater confidence.

Current therapies for patients who present with a localized recurrence of prostate cancer after radiation therapy are salvage radical prostatectomy, hormonal therapy, salvage cryotherapy, and salvage brachytherapy.³⁰ The goal of these therapies is local control of the tumor. Cryotherapy may provide local control with lower morbidity than salvage radical prostatectomy. Our results confirmed the low rate of complications with cryotherapy. The side effects were gleaned from a review of patient charts, which could underreport the severity of some complications; however, the major complications, such as fistula, obstruction, or death were not underreported. Major complications such as prostate-rectal fistula, hydronephrosis, or renal failure that were reported in the first studies of cryoablation of the prostate did disappear because of the technical evolution of the cryoprobe and greater surgeon experience (Table V). The risk of urethral strictures decreased after 1997 when urethral warmers began to be used. The major risk remains incontinence, but this risk is lower than with salvage radical prostatectomy. The rate of local control of disease is similar between the different forms of therapy (Table II).

CONCLUSIONS

Salvage cryotherapy can impact local tumor control. Our data support the current safety and efficacy profile that cryotherapy is a viable option in the treatment of patients who have biopsy-proven local failure after radiation therapy for prostate cancer. Further refinements in technique and equipment may enhance cryosurgical results.

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