Cryoablation as Primary Treatment for Localized Prostate Cancer Followed by Penile Rehabilitation

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OBJECTIVES   To determine the medium term efficacy and morbidity of patients who underwent cryoablation as primary therapy for localized prostate cancer followed by a penile rehabilitation regimen.

METHODS   Patients were treated with whole gland cryoablation. Those potent at intervention were encouraged to use a vacuum erection device regularly after treatment. Incontinence was defined as any leakage of urine. Potency was defined as the ability to achieve an erection sufficient to complete intercourse with or without oral pharmaceutical agents. Biochemical failure was defined as three successive rises in prostate-specific antigen, with a final value greater than 1.0 ng/mL.

RESULTS   A total of 416 consecutive patients were treated. The mean patient age was 69.4 years, mean prostate-specific antigen level was 8.7 ng/mL, median Gleason score was 6, and median stage was T1c. The mean follow-up of the entire population was 20.4 ± 14.7 months. Of those continent before treatment, 4.0% were incontinent at 6 months but only 2 (0.6%) used any absorbent pads. Kaplan-Meier analysis demonstrated progressive recovery of sexual function of preoperatively potent men, with $41.4\% \pm 4.3\%$ and $51.3\% \pm 5.9\%$ potent 1 and 4 years after treatment, respectively. No patients had rectal fistula. The actuarial probability of remaining biochemically disease free at 4 years was $79.6\% \pm 2.4\%$, with a mean time to failure of 4.2 months. After therapy, 168 patients underwent biopsy; 17 had positive findings (10.1%). The positive biopsy rate for the entire population was 4.1% (17 of 416).

CONCLUSIONS   The results of our study have indicated that cryoablation as a primary treatment of localized prostate cancer is effective with acceptable morbidity. The use of a penile rehabilitation regimen after treatment appeared to substantially increase postcryoablation potency.   UROLOGY 69: 306–310, 2007. © 2007 Elsevier Inc.

Prostate cancer is the most commonly diagnosed malignancy in American men and is responsible for approximately 30,000 deaths annually.[1] Although cryoablation was first studied in the 1960s, it has only recently been accepted as definitive treatment for prostate cancer.[2] This has resulted, in large part, from technical advances in the procedure that have made it safer and consistently efficacious.[3]

Both ultrasound[4] and temperature[5] monitoring are now used to monitor the procedure, and the development of argon-based technology improved the consistency of the cryoprobe performance.[6,7] A greater understanding of cryobiology, as well as animal and human investigations, have led to the definition of clinical endpoints for effective ablation and treatment planning.[6,8,9] Also, consis-

tent use of an approved urethral warmer has decreased the urethral complications, including sloughing and incontinence.[10] Finally, the use of two posterior-medial cryoprobes, rather than a single posterior-central cryoprobe, has reduced the fistula rate to less than 0.5%.[11–13]

We report on a consecutive series of patients who underwent modern prostate cryoablation by a single surgeon as the primary therapy for localized prostate cancer. Those patients who were potent at intervention were encouraged to regularly use penile vacuum therapy after treatment in the hope of preserving or recovering erectile function.

MATERIAL AND METHODS

Patients with biopsy-proven prostate cancer without evidence of metastasis were offered cryoablation as one of several definitive treatment options, including radical prostatectomy and radiotherapy. The preoperative assessment included evaluation of stage, prostate-specific antigen (PSA), and Gleason score. Bone scans were performed for patients who presented with a PSA level greater than 10 ng/mL or a Gleason score greater than 7.

All procedures were performed with the Cryocare System (Endocare, Irvine, Calif), which exploits the Joule-Thompson effect to freeze and thaw tissue by expanding inert gas within cryoprobes that are placed within the prostate. Up to eight cryoprobes can be simultaneously operated, yet controlled independently. A transrectal ultrasound probe (B-K Medical, Copenhagen, Denmark) with biplane 5.0 and 7.5-MHz transducers was used to guide cryoprobe placement and monitor ice formation. Temperatures in and around the gland were monitored with strategically placed thermosensors (Endocare). To protect the urethra and adjacent structures such as the bladder neck and external sphincter, a flexible urethral warming catheter (Endocare) was used.

Cryoablations were performed at either the United States Medical Development Hospital (Arlington, Tex), Arlington Memorial Hospital (Arlington, Tex), or Baylor Medical Center (Coppell, Tex) by a single urologist (D.S.E.). Preoperative management, positioning, preparing, and suprapubic catheter placement techniques have already been described in detail.[14] The details of our surgical technique, as well as the endpoints, have also been previously described.[15]

Patients were discharged the day of cryoablation or, rarely, the following morning, with a suprapubic catheter. Patients attempted voiding per urethra 6 to 7 days postoperatively. The catheter was removed when the postvoid residual volume was consistently less than 100 mL. Patients potent at intervention were strongly encouraged to use a vacuum therapy device without the constriction ring to create and maintain an erection for 5 minutes at least once daily beginning 6 weeks after cryoablation and continuing until spontaneous erections returned. They were also instructed to take an oral erectile dysfunction pharmaceutical agent once every other day beginning 6 months after cryoablation and until the return of satisfactory erections, and then as necessary for intercourse.

Patients returned for follow-up at 6 weeks, 3, 6, 9, and 12 months, and every 6 months thereafter. The PSA level was measured at every visit. Beginning at 6 months, incontinence and impotence were assessed by physician interview.

For the purposes of this study, incontinence was defined as any leakage of urine regardless of the number of pads worn (if any) 6 months after cryoablation. Incontinence was further stratified as total, requiring the use of any pads, and stress, not requiring any pads. Potency, evaluated every 6 months, was defined as the ability to achieve an erection sufficient for intercourse with or without oral pharmaceutical assistance. Patients using a vacuum device for intercourse were not considered potent. Only those patients continent and potent, respectively, at intervention were included in the posttreatment potency and continence analysis.

For the efficacy analysis, patients were stratified according to risk group for biochemical nadir and survival. Three risk factors were considered: PSA level, Gleason score, and stage. If all the following were true, the disease was considered low risk: PSA less than 10 ng/mL, Gleason score less than 7, and stage less than Stage T2b. If one of these criteria were not true, the disease was considered moderate risk. If two or more were not true, the disease was considered high risk.

The biochemical disease-free survival (BDFS) was determined using a modified American Society of Therapeutic Radiation Oncology definition[16] of three successive rises in PSA level with a final value greater than 1.0 ng/mL. The time to biochemical failure was the interval from treatment until the midway point between the two PSA rises constituting the first

Table 1. Patient demographics before cryoablation	
Age (yr)	
Mean	69.4 ± 6.1
Median	70.0
PSA (ng/mL)	
Mean	8.7 ± 8.6
<10	75.4%
≥10	24.6%
Gleason score	
Mean	6.5 ± 0.8
Median	6
3–6	55.9%
7	33.1%
8–10	11.0%
Stage	
Median	T1c
≤T2a	78.6%
≥T2b	21.4%
Risk group (%)	
Low	39.5
Moderate	39.5
High	21.0

PSA = prostate-specific antigen.

of the three rises indicating failure. We have reported the scientific time to failure, as defined above, as well as the time at which the failure became clinically evident (when the third rise was observed). To determine biochemical survival, a minimum of four posttreatment PSA measurements were needed. Only patients with sufficient follow-up were included in the biochemical survival analysis. Kaplan-Meier analysis was performed with the commercially available statistics software MedCalc (Mariakerke, Belgium).

All patients treated in the first 12 months of our experience (n = 93) underwent a 12-core biopsy 1 year after treatment. Subsequent to this, because of the very high negative biopsy rate of this group,[15] patients underwent biopsy if their PSA level exceeded 1.0 ng/mL. If the biopsy findings in those patients were negative, a bone scan was performed.

RESULTS

From December 2000 to 2005, 416 consecutive patients underwent cryoablation as the primary therapy for localized prostate cancer. The patient demographics are summarized in Table 1. Of the 395 patients whose continence status was known before cryoablation, 384 (97.1%) were continent. The potency status was known for 325 patients before cryoablation, 127 (39.1%) of whom were potent. The mean follow-up of all patients was 20.4 ± 14.7 months (range 1.5 to 60, median 60). Sufficient follow-up data to determine biochemical survival were available for 291 patients, with a mean follow-up of 25.9 ± 13.1 months (range 9 to 60, median 25).

The procedure was well tolerated, with no postoperative deaths and no rectal fistula development. Of the 384 patients continent at treatment, 327 had 6 months of follow-up with known continence status. Of these 327 patients, 13 (4.0%) were incontinent. Stratifying by severity, 2 patients (0.6%) had total incontinence (requiring the use of absorbent pads) and 11 (3.4%) had stress
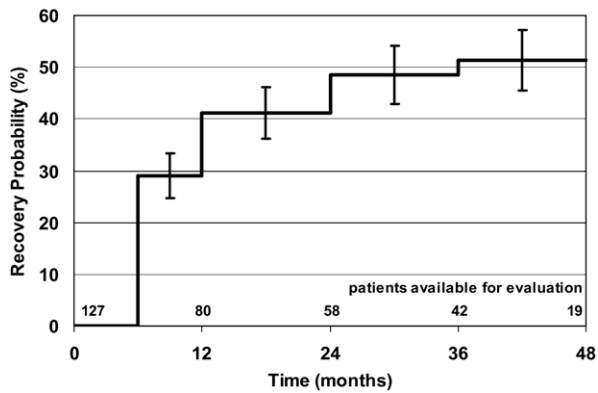
Figure 1. Kaplan-Meier prediction of potency recovery.

Figure 2. Kaplan-Meier survival curve of biochemical survival for **(A)** all patients and **(B)** patients stratified by risk group.

incontinence. All patients were impotent immediately after cryoablation. The Kaplan-Meier analysis demonstrating the time-dependent return to potency is shown in Figure 1. At 1, 2, and 4 years, the probability that a patient who was potent at intervention would regain his ability to have intercourse with or without oral pharmaceutical assistance was 29.1% ± 4.3%, 48.5% ± 5.0%, and 51.3% ± 5.9%, respectfully.

The mean and median PSA nadir was 0.45 and 0.1 ng/mL, respectively. A PSA nadir of less than 0.4 ng/mL was achieved by 79.7% of the population. Kaplan-Meier analysis revealed a 4-year BDFS rate of 79.6% ± 2.4% for the entire population (Fig. 2A). When stratified by risk group, 83.6% ± 3.8%, 82.3% ± 3.6%, and 69.1% ± 5.5% of low, moderate, and high-risk patients, respectively, remained disease free at 4 years (Fig. 2B). The mean time to biochemical failure according to the scientific definition was 4.2 months, with a mean time to being clinically evident of 14.2 months. After therapy, 168 patients underwent biopsy, and 17 (10.1%) had positive findings at a mean of 10.2 months after treatment, for a positive biopsy rate for the entire population of 4.1% (17 of 416).

COMMENT

There is a glaring lack of randomized prospective trials comparing definitive prostate cancer therapies.[17] As such, determining the efficacy of cryoablation in relation to other therapies is limited to comparisons of published patient series. Although this method is inherently flawed owing to differences in patient populations and BDFS definitions, it does have merit, and consistent trends have emerged.[3] Several investigators have compared their results with those in the published reports for radical prostatectomy and radiotherapy (including brachytherapy) and have consistently concluded that cryoablation appears to be at least equivalent in terms of efficacy.[12,13,18] The results of this study, although with a shorter follow-up, have also substantiated this claim, because the outcomes are comparable with those of other reports of cryoablation efficacy.

Similar to the results of Bahn *et al.*,[18] Kaplan-Meier
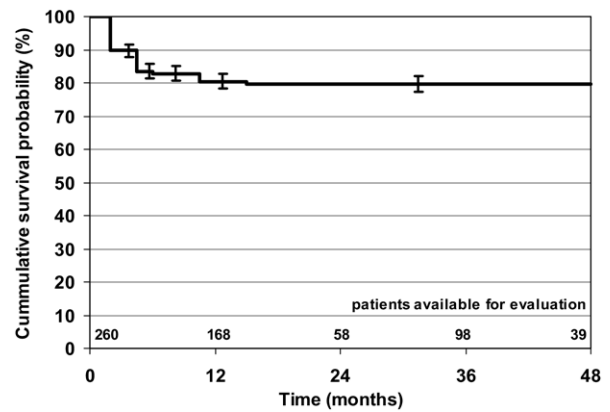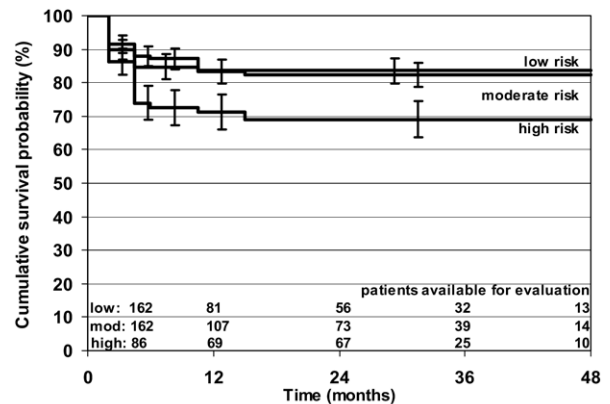
analysis showed flattening of the curve after about 15 months (Fig. 2A). This is indicative of the relatively short time to biochemical failure, which could be clinically advantageous. If cryoablation is not effective for a particular patient, it should be rapidly evident biochemically, prompting prompt biopsy. Additionally, the mean time to biopsy failure was also relatively brief (10.2 months). Early knowledge of treatment failure allows for pursuit of other treatment options while cure might still be possible. This can be contrasted with the PSA bounce phenomenon[19] and the indeterminate biopsy results observed after radiotherapy.[20] Either could mask recurrence, and the window for cure could be missed. The American Society of Therapeutic Radiation Oncology definition of failure also has limitations, including backdating, as was evident with the need to clarify the scientific and clinically apparent times to failure.[21]

Another similarity between the Kaplan-Meier curves of the present series and those presented by Bahn *et al.*[18] was the lack of difference in BDFS when the results were stratified by risk. This could have been because of the locally aggressive nature of tissue damage during cryoablation. Confluent necrosis has been observed in prostatic tissue after a double freeze-thaw cycle with an end temperature of −40°C or less.[9] This principally results from

platelet aggregation after the procedure that completely occludes the microvasculature, resulting in uniform ischemic necrosis.[8] If all the cancer is exposed to sufficiently cold temperatures, it will be ablated, irrespective of the aggressiveness of the individual cells.[9]

Past studies have shown that the incidence of incontinence, when modern cryotechnology is used, ranges from 1.3%[12] to 7.5%.[13] The 4.0% incontinence rate (0.6% total and 3.4% stress) in the present series fits well within previously recorded ranges. No rectourethral fistula occurred in our series. This was not surprising, because reports using argon-based cryoprobes have stressed (and we echo) that urethral fistulas are no longer a morbidity expected after cryoablation.[3]

What was different from previous cryoablation reports was the potency rate observed in the present series. Evaluating erectile function is difficult. Many methods are available to evaluate it, including physician interview, stamp tests,[22] rigidity scans,[23] and self-administered questionnaires.[24–27] Each has its own merits and limitations, and none are exact. However, we believe that an in-depth physician interview will yield reliable results. Impotence is expected immediately after cryoablation. However, for some patients, it proves to be transient, with recovery noted as far as 5 years after treatment.[12] In a prospective study, Robinson et al.[28] found recovery of erectile function with time. Within 3 years of the procedure, 47% of the men who were having intercourse before cryoablation had returned to intercourse with or without the use of oral or device erectile dysfunction aids.

Our series, which encouraged patients to engage in a penile rehabilitation effort with regular use of a vacuum erection device without the constriction ring, had a potency rate of 29.1% ± 4.3% at 1 year and 51.3% ± 5.9% at 4 years. This was substantially greater recovery than in any other series published to date and the return appeared to be expedited compared with that in the study by Robinson et al.[28]

This could be attributed to several factors. In contrast to most other cryoablation reports, we calculated impotence, taking into consideration only those patients potent at cryoablation. Including all patients in the denominator of the potency calculation, regardless of their pretreatment potency status, would artificially decrease the potency rate. It is inappropriate to attribute treatment as the cause of a man's impotence if he was impotent before the intervention. More importantly, we believe that the manner in which the procedure was presented to the patients, as well as the use of penile rehabilitation, was instrumental in helping our patients regain sexual function. Patients were told at the initial consultation and again immediately before treatment that (according to the results of Robinson et al.[28]), they would be impotent immediately after cryoablation, but it was not necessarily true that they would remain impotent. This could have created a hopeful atmosphere for

the patients, increasing their probability of regaining erectile function. This, we believe, in concert with the regular use of a vacuum device without a constriction ring in attempt to both oxygenate the penis and prevent atrophy, was responsible for the rapid and high rate of return of sexual function.

Brachytherapy has reported potency rates of 49% to 100%.[29] The results of this study have demonstrated that potency rates within the range of those after brachytherapy may be achieved after cryoablation. Previous cryoablation studies have resulted in potency rates as great as 78%,[30] but this occurred after focal cryoablation in which only one hemisphere of the prostate was frozen. In our study, all prostates were aggressively and completely treated with cryoablation.

CONCLUSIONS

Modern cryoablation as a primary intervention performed in a community hospital setting is an effective and safe primary therapy for localized prostate cancer. The effect of cryoablation on erectile function appears to be minimized when a patient is correctly informed that recovery of erectile function is possible. Also, the use of a penile rehabilitation program after cryoablation may expedite the return of erectile function.

References

1. American Cancer Society: Cancer facts and figures 2005. Bethesda, American Cancer Society, 2005.
2. Whyte JJ, Bagley GP, and Kang JL: The Health Care Financing Administration cryosurgery decision: a timely response to new data. J Urol **162:** 1386–1387, 1999.
3. Katz AE, and Rewcastle JC: The current and potential role of cryoablation as a primary therapy for localized prostate cancer. Curr Oncol Rep **5:** 231–238, 2003.
4. Onik GM, Cohen JK, Reyes GD, et al: Transrectal ultrasound-guided percutaneous radical cryosurgical ablation of the prostate. Cancer **72:** 1291–1299, 1993.
5. Wong WS, Chinn DO, Chinn M, et al: Cryosurgery as a treatment for prostate carcinoma: results and complications. Cancer **79:** 963–974, 1997.
6. Lee F, Bahn DK, Badalament RA, et al: Cryosurgery for prostate cancer: improved glandular ablation by use of 6 to 8 cryoprobes. Urology **54:** 135–140, 1999.
7. Rewcastle JC, Sandison GA, Saliken JC, et al: Considerations during clinical operation of two commercially available cryomachines. J Surg Oncol **71:** 106–111, 1999.
8. Hoffmann NE, and Bischof JC: The cryobiology of cryosurgical injury. Urology **60:** 40–49, 2002.
9. Larson TR, Robertson DW, Corica A, et al: In vivo interstitial temperature mapping of the human prostate during cryosurgery with correlation to histopathologic outcomes. Urology **55:** 547–552, 2000.
10. Saliken JC, Donnelly BJ, and Rewcastle JC: The evolution and state of modern technology for prostate cryosurgery. Urology **60:** 26–33, 2002.

11. Bahn DK, Lee F, Silverman P, *et al:* Salvage cryosurgery for recurrent prostate cancer after radiation therapy: a seven-year follow-up. Clin Prostate Cancer **2:** 111–114, 2003.

12. Donnelly BJ, Saliken JC, Ernst DS, *et al:* Prospective trial of cryosurgical ablation of the prostate: five-year results. Urology **60:** 645–649, 2002.

13. Long JP, Bahn D, Lee F, *et al:* Five-year retrospective, multi-institutional pooled analysis of cancer-related outcomes after cryosurgical ablation of the prostate. Urology **57:** 518–523, 2001.

14. Donnelly BJ, and Saliken J: Salvage cryosurgery—how I do it. Rev Urol **4**(suppl 2): s24–s29, 2002.

15. Ellis DS: Cryosurgery as primary treatment for localized prostate cancer: a community hospital experience. Urology **60:** 34–39, 2002.

16. American Society for Therapeutic Radiology and Oncology Consensus Panel: Consensus statement: guidelines for PSA following radiation therapy. Int J Radiat Oncol Biol Phys **37:** 1035–1041, 1997.

17. Merrick GS, Wallner KE, and Butler WM: Prostate cryotherapy: more questions than answers. Urology **66:** 9–15, 2005.

18. Bahn DK, Lee F, Badalament R, *et al:* Targeted cryoablation of the prostate: 7-year outcomes in the primary treatment of prostate cancer. Urology **60:** 3–11, 2002.

19. Critz FA, Williams WH, Benton JB, *et al:* Prostate specific antigen bounce after radioactive seed implantation followed by external beam radiation for prostate cancer. J Urol **163:** 1085–1089, 2000.

20. Prestidge BR, Hoak DC, Grimm PD, *et al:* Posttreatment biopsy results following interstitial brachytherapy in early-stage prostate cancer. Int J Radiat Oncol Biol Phys **37:** 31–39, 1997.

21. Williams SG: Ambiguities within the ASTRO consensus definition of biochemical failure: never assume all is equal. Int J Radiat Oncol Biol Phys **58:** 1083–1092, 2004.

22. Carroll JL, Baltish MH, and Bagley DH: The use of PotenTest in the multidisciplinary evaluation of impotence: is it a reliable measure? J Sex Marital Ther **16:** 181–187, 1990.

23. Weinberg JJ, and Badlani GH: Utility of RigiScan and papaverine in diagnosis of erectile impotence. Urology **31:** 526–529, 1988.

24. Rosen RC, Riley A, Wagner G, *et al:* The International Index of Erectile Function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology **49:** 822–830, 1997.

25. Day D, Ambegaonkar A, Harriot K, *et al:* A new tool for predicting erectile dysfunction. Adv Ther **18:** 131–139, 2001.

26. Esper P, Mo F, Chodak G, *et al:* Measuring quality of life in men with prostate cancer using the Functional Assessment of Cancer Therapy-Prostate instrument. Urology **50:** 920–928, 1997.

27. Litwin MS, Nied RJ, and Dhanani N: Health-related quality of life in men with erectile dysfunction. J Gen Intern Med **13:** 159–166, 1998.

28. Robinson JW, Donnelly BJ, Saliken JC, *et al:* Quality of life and sexuality of men with prostate cancer 3 years after cryosurgery. Urology **60:** 12–18, 2002.

29. Incrocci L, Slob AK, and Levendag PC: Sexual (dys)function after radiotherapy for prostate cancer: a review. Int J Radiat Oncol Biol Phys **52:** 681–688, 2002.

30. Onik G, Narayan P, Vaughan D, *et al:* Focal "nerve-sparing" cryosurgery for treatment of primary prostate cancer: a new approach to preserving potency. Urology **60:** 109–114, 2002.