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TARGETED CRYOABLATION OF THE PROSTATE: 7-YEAR OUTCOMES IN THE PRIMARY TREATMENT OF PROSTATE CANCER

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ABSTRACT

The efficacy and safety of the long-term experience with targeted cryoablation of prostate cancer (TCAP) at a community hospital is retrospectively reviewed. A series of 590 consecutive patients who underwent TCAP as primary therapy with curative intent for localized or locally advanced prostate cancer from March 1993 to September 2001 were identified. Patients were stratified into 3 risk groups according to clinical characteristics. Biochemical disease-free survival (bDFS), post-TCAP biopsy results, and post-TCAP morbidity were calculated and presented. The mean follow-up time for all patients was 5.43 years. The percentages of patients in the low-, medium-, and high-risk groups were 15.9%, 30.3%, and 53.7%, respectively. Using a prostate-specific antigen (PSA)-based definition of biochemical failure of 0.5 ng/mL, results were as follows: (1) the 7-year actuarial bDFS for low-, medium-, and high-risk patients were 61%, 68%, and 61%, respectively; (2) the bDFS probabilities for a PSA cutoff of 1.0 ng/mL for low-, medium-, and high-risk patients were 87%, 79%, and 71%, respectively; and (3) the bDFS probabilities for low-, medium-, and high-risk patients using the American Society for Therapeutic Radiology and Oncology (ASTRO) definition of biochemical failure (3 successive increases of PSA level) were 92%, 89%, and 89%, respectively. The rate of positive biopsy was 13%. After a positive biopsy, 32 patients underwent repeat cryoablation. For those patients who underwent repeat cryoablation, 68%, 72%, and 91% remain bDFS using definitions of 0.5 ng/mL, 1.0 ng/mL, and the ASTRO criteria, respectively, after a mean follow-up time since repeat cryoablation of 63 months. The rates of morbidity were modest, and no serious complications were observed. TCAP was shown to equal or surpass the outcome data of external-beam radiation, 3-dimensional conformal radiation, and brachytherapy. These 7-year outcome data provide compelling validation of TCAP as an efficacious treatment modality for locally confined and locally advanced prostatic carcinoma. UROLOGY **60** (Suppl 2A): 3–11, 2002. © 2002, Elsevier Science Inc.

Prostate carcinoma represents a serious health hazard. The American Cancer Society[1] estimated 198,100 new cases of diagnosed prostate cancer and 31,500 deaths in the United States in 2001. After skin cancer, prostate cancer has become the most commonly diagnosed cancer in US men and it is the second most common cause of cancer death in men after lung cancer.[2,3] With the advent of widespread prostate-specific antigen (PSA) screening in the past decade, many more men are being diagnosed in the early stages of the disease, when local cure is possible.[4]

Radical prostatectomy and radiation therapy are considered the "gold standard" treatment for localized prostate cancer. However, there is compelling evidence that both treatments provide less than optimal efficacy in the treatment of disease that is characterized by locally advanced stage,[5–8] poorly differentiated tumor,[9–11] or medium-to-high pretreatment PSA level.[12–15] Additionally, both treatments can result in significant morbidity,[16–20] adversely affecting the quality of life of the patient. The shortcomings of these treatments have

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prompted the development of alternative approaches in the treatment of prostate cancer. Cryoablation is such an approach.

Cryoablation was first used to treat prostate cancer in the late 1960s by Soanes and Gonder.[21] An open perineal approach was used, and although the survival rates approached those for radical prostatectomy, the approach was abandoned because of the unacceptably high morbidity.[22] Cryoablation was reintroduced in 1993 by Onik *et al.*,[23] who pioneered the use of transrectal ultrasound and incorporated advances in interventional radiology technology with the procedure. Recently, advances in technology and standardization of method have led to more widespread application of the procedure, with corresponding improvements in efficacy and safety.[24] In this article, we present the 7-year follow-up data from a series of 590 consecutive patients who received targeted cryoablation of the prostate (TCAP) as primary treatment for their prostate cancer at a community hospital.

MATERIAL AND METHODS

Patient Selection

Between March 1993 and September 2001, 590 consecutive patients were treated at Crittenton Hospital in Rochester, Michigan. Patients were eligible for inclusion if they exhibited localized or locally advanced disease (TNM stage T1 to T3).

Procedure

The methodology used in cryosurgical ablation of the prostate has evolved significantly since its reintroduction by Onik *et al.*[23] in 1993. The modern procedure has used the following advances: 2 freeze cycles, use of US Food and Drug Administration (FDA)–approved urethral catheter warming devices, 6 to 8 cryoprobes, and the development of argon-based cryomachines. However, this treatment protocol represents the current state of the art of cryoablation treatment and was not used for all patients reported in this series. As one of the first centers performing TCAP, the patients we have treated, whom we report on in this article, have experienced the evolution of the procedure. It was not until 1996 that the procedure had matured to its current state of the art. Although all patients in our series were treated with 2 complete freeze-thaw cycles using a target temperature of −40°C, the first 350 patients were treated with a liquid nitrogen cryomachine, which we have shown to yield inferior results compared with the argon-based cryomachine we now use.[25] Once the target temperature is reached, the ice ball is maintained at a static size for up to 10 minutes if possible without endangering the rectal wall. The freeze rate of the first cycle tends to be slower than the second because of the decreased thermal capacity of the previously frozen tissue. There was a period between 1994 and 1995 that the FDA temporarily restricted the use of the preferred urethral warming system consisting of a pump, warmer, and catheter. We continued to use the same catheter with a modified pump and warming system, whereas most other centers used a completely different system consisting of a different warming and pump system and a modified Foley catheter to replace the warming catheter.

The TCAP procedure, previously described in detail by Lee *et al.*,[25] uses 3.4-mm diameter cryoprobes (Endocare, Inc., Irvine, CA) inserted transperineally into the prostate under guidance of transrectal ultrasound. Temperature probes are also guided transperineally to strategic locations within and around the prostate to evaluate the extent of the freezing injury. Temperature probes are placed in the right and left neurovascular bundles and the apex of the gland to ensure that the margins of the gland reach temperatures sufficient for efficacious treatment. Temperature probes are also placed in the Denonvilliers fascia and the external sphincter and are used to minimize complications by ensuring that the sensitive anatomy adjacent to the prostate is not frozen. A urethral warming catheter is used during the procedure to maintain the integrity of the urethra by not allowing it to be frozen. Androgen ablation therapy was given to 91.5% of the sample before treatment to downsize the gland and consisted of luteinizing hormone–releasing hormone, combined with an antiandrogen agent 3 months to 1 year before cryoablation. Hormonal therapy was not continued on any patient after cryoablation.

Patients were seen at regular intervals 3 and 6 months after the procedure and every 6 months thereafter. During these visits, PSA levels were determined. Prostate biopsies were performed routinely 6 and 12 months, 2 years, and 5 years after treatment and/or on suspicious PSA findings. An advantage of TCAP is that it can be repeated without increased morbidity, and an adjuvant TCAP procedure was performed on the finding of a positive biopsy if the patient so elected.

Statistical Analysis

Patients were separated into 3 risk groups based on likelihood of disease relapse. The low-risk group contained patients with disease at stage T2a or less, a PSA level ≤10 ng/mL, and a Gleason score of ≤6. The moderate-risk group contained patients with any 1 of the following: (1) disease at stage T2b or greater, (2) a PSA level of >10 ng/mL, or (3) a Gleason score >7. Patients in the high-risk group were characterized as having 2 or 3 of the above risk factors at the time of the procedure. Kaplan-Meier curves were generated for the PSA level >1 ng/mL and PSA >0.5 ng/mL stratified by risk group. The log-rank test was used to determine differences in the survival curves among risk groups.

RESULTS

Retrospective analysis of 590 consecutive patients who underwent TCAP procedures with curative intent between March 1994 and September 2001 was performed. The mean age of the sample was 70.76 years, with the median age being 71.13 years. Mean follow-up time was 5.43 years, and the median follow-up time was 5.72 years.

In all, 16.4% of the sample had a presurgery PSA level <4 ng/mL, 58.9% had a PSA level of 4 to 10 ng/mL, and 24.5% had a PSA level >10 ng/mL; 41.5% of the sample had a Gleason score <7, 52.5% had a Gleason score of 7, and 6% had a Gleason score >7; 1.8% of the sample were clinically staged T1, 78.1% were staged T2, 17.6% were staged T3, and 2.0% of the sample were staged T4. Of 590 patients, 15.9% were in the low-risk category, 30.3% were in the medium-risk category, and 53.7% were in the high-risk category. Table I summarizes the clinical characteristics of the sample.

The 7-year actuarial biochemical disease-free survival (bDFS) probabilities are shown in Figures 1 through 3. The sample is stratified according to

risk for biochemical relapse, and the definition of biochemical failure is provided as a PSA cutoff of 0.5 ng/mL and 1.0 ng/mL. Using a PSA threshold of 0.5 ng/mL as evidence of biochemical recurrence, 61%, 68%, and 61% of low-, medium-, and high-risk patients remain free from biochemical relapse at 7 years (Figure 1). The combined-risk group percentage, using the PSA cutoff of 0.5 ng/mL, was 62%. Analysis using a threshold of 1.0 ng/mL yielded 7-year disease-free status for 87%, 79%, and 71% of the low-, medium-, and high-risk patients, respectively (Figure 2). Using a PSA cutoff of 1.0 ng/mL, the rate of freedom from biochemical relapse for the combined-risk group was 76%. Using the American Society for Therapeutic Radiology and Oncology (ASTRO) definition of biochemical failure of 3 successive increases of PSA level, the low-, medium-, and high-risk group of patients maintained a rate of freedom from biochemical relapse of 92%, 89%, and 89%, respectively, with the combined-risk groups attaining a 89.5% disease-free status using the ASTRO definitions of biochemical recurrence (Figure 3). There was a significant downward trend in bDFS by risk group (log-rank test, $P = 0.028$) for the PSA threshold of 1.0 ng/mL. The number of patients undergoing biopsies at each time interval and the stratified results are presented in Tables II and III, respectively.

TABLE I. *Patient demographics*

Patient Demographics	Patients (n)
PSA (ng/mL)	
<4	97
4–10	348
>10	145
Total	590
Gleason Score	
3–6	241
7	310
8–9	35
Missing	4
Total	590
T stage	
T1	11
T2	461
T3	104
T4	12
Missing	2
Total	590

PSA = prostate-specific antigen.

Of the 547 patients who underwent ≥1 biopsy, the time from cryoablation to the most recent biopsy ranged from 3 to 96 months, with a median value of 24 months. After a positive biopsy, 32 patients chose to undergo repeat cryoablation. With a median time since repeat cryoablation of 63 months,

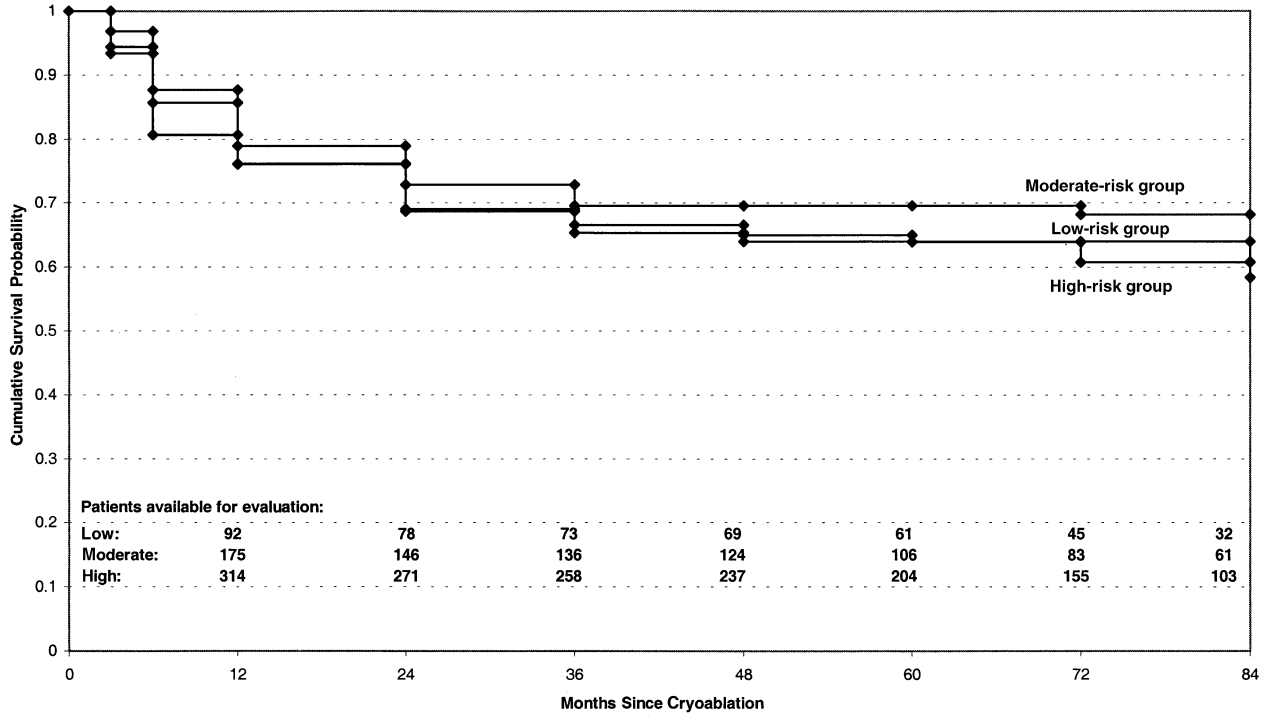

FIGURE 1. *Kaplan-Meier survival curve using a biochemical disease-free survival definition of a prostate-specific antigen threshold of 0.5 ng/mL.*

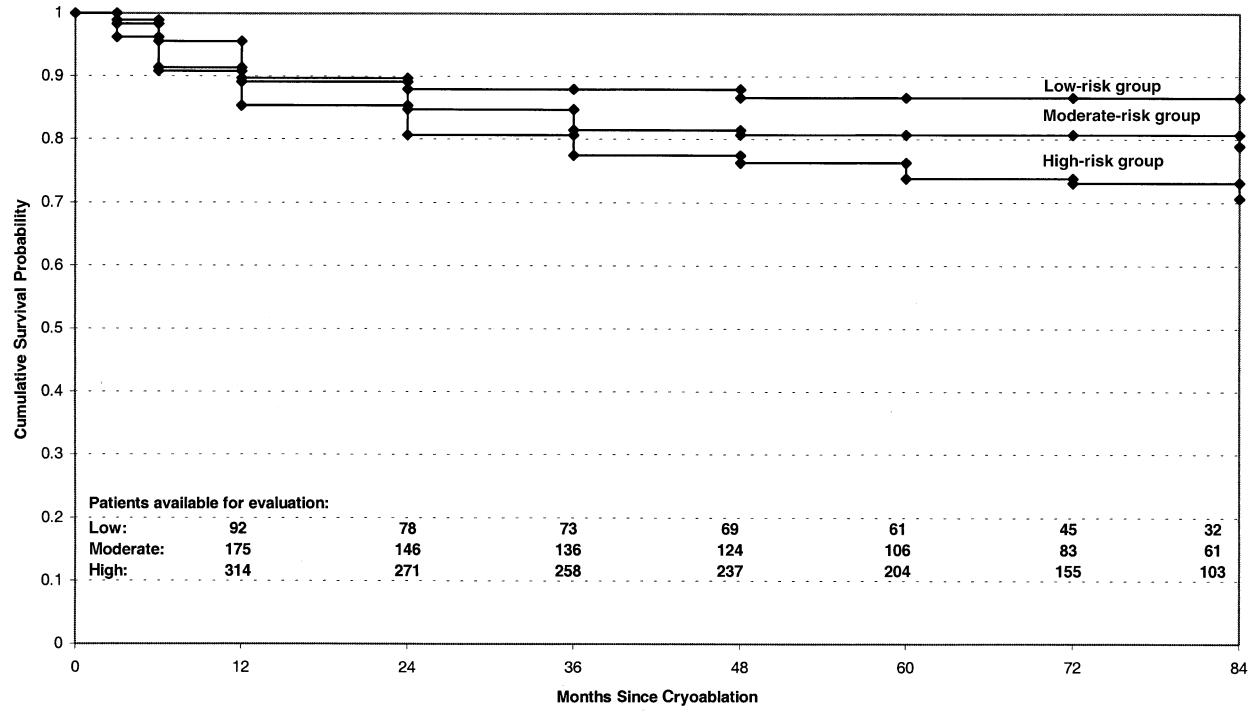

FIGURE 2. *Kaplan-Meier survival curve using a biochemical disease-free survival definition of a prostate-specific antigen threshold of 1.0 ng/mL.*

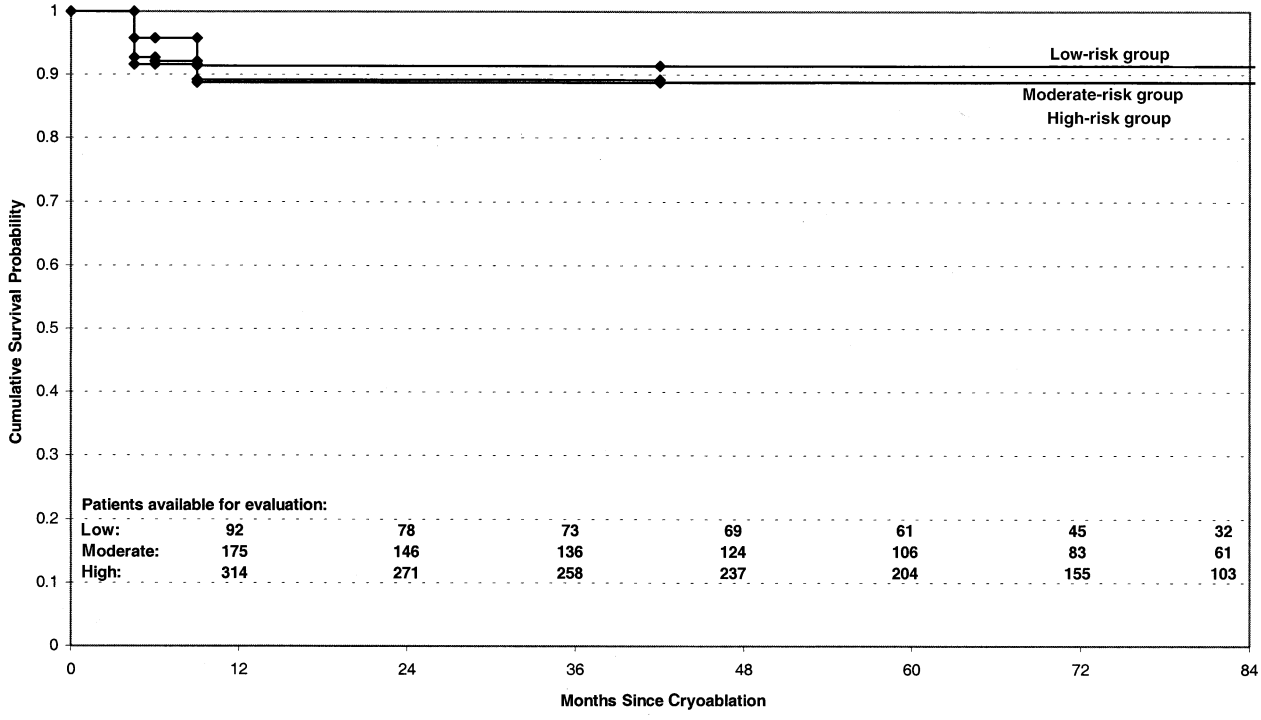

FIGURE 3. *Kaplan-Meier survival curve using the American Society for Therapeutic Radiology and Oncology (ASTRO) criteria for biochemical disease-free survival of 3 consecutive increases of prostate-specific antigen.*

22 (69%), 23 (72%), and 29 (91%) returned to bDFS using definitions of 0.5 ng/mL, 1.0 ng/mL, and the ASTRO criteria, respectively.

Of the 590 patients, 533 patients were continent and 373 were potent before the surgery. Of the 373 patients who were potent, 94.9% (354) were impotent after surgery; 5.1% (19) recovered their potency, with an average recovery time of 16.4

months. Of the 533 patients who were continent before surgery, 84.1% (448) regained continence after surgery with an average recovery time of 6.1 months. Altogether, 15.9% of patients were considered incontinent using the broad definition of any leakage (even a drop of urine), and 4.3% were considered incontinent if they used any pads. Fistula occurred in 2 (0.004%) patients, with both patients reporting fistula in the first 3 months. Both fistulas healed spontaneously with prolonged catheter drainage. Transurethral resection of the prostate occurred at a rate of 5.5%. Table IV illustrates the morbidity rates found among the sample.

DISCUSSION

Cryoablation treatment of prostate cancer is a technique that was originally introduced in the 1960s, but was abandoned because of excessive morbidity. Use of this approach was resurrected with the introduction by Onik *et al.*[23] in 1993 of a modern transrectal ultrasound–guided percutaneous method. The treatment itself has undergone an evolution, which has stemmed from recent developments in interventional radiology, has improved cryogenic technology, and has provided a better knowledge of cryobiology.[26,27] The mechanism of action of TCAP is complex. It has been proposed that cryoablation exerts its efficacious effect by: (1) the induction of protein denaturation by dehydration, (2) the rupture of cell membrane from ice crystal expansion, (3) the transfer of water from intracellular to extracellular spaces, (4) the vascular stasis, (5) the induced apoptosis, and (6) the toxic concentration of cellular contents or osmotic shock.[28,29]

Traditionally, proponents of TCAP as a primary therapy for prostate cancer have asserted that the procedure offers advantages over conventional treatment by allowing a noninvasive treatment of locally extensive cancer outside the gland in patients who are too old or have too much comorbidity to be appropriate candidates for radical surgery. However, refinement of the procedure has led to increases in efficacy and safety. The 7-year bDFS data from this report strongly indicate a broader role for cryoablation by demonstrating that cryoablation produces rates of efficacy that are highly competitive with all conventional forms of radiation therapy (external-beam radiation, 3-dimensional conformal radiation therapy, and brachytherapy). Head-to-head comparisons of different treatment modalities for prostate cancer are complicated by (1) the retrospective, single-institution nature of most studies, (2) the nonuniform patient selection, (3) the use of varying dosing procedures and techniques, and (4) the variations in the definition of biochemical failure.[24] However, an approximation of comparative efficacy can be attained by matching sample subgroups on important dimensions such as clinical stage, degree of tumor differentiation, risk factors, and preoperative PSA levels. Table V[30–33] compares the range of 7-year efficacy cited in the available literature of the 3 common radiation treatment modalities for localized prostate cancer and the results from this study.

There is no established uncontroversial definition of successful outcome for cryoablation or for any other treatment of localized prostate cancer. PSA level cutoffs of 0.2 to 0.4 ng/mL are often used in studies of radical surgery, whereas a PSA cutoff of 1.0 ng/mL is more often used in radiotherapy trials. The ASTRO definition of biochemical relapse, 3 consecutive elevations in PSA, is another widely used measure of radiotherapy treatment outcome. The ASTRO definition or a PSA cutoff of 1.0 ng/mL definition of biochemical relapse is, perhaps, the most reasonable measure in trials involving cryoablation therapy. Similar to radiotherapy, prostatic tissue that may be PSA-producing is left intact. This is in contrast to radical surgery, where the entire gland is removed, and with it, all PSA-producing tissue. In cryoablation, there is some preservation of tissue surrounding the urethra. Akdas *et al.*[34] have shown that a PSA level of 0.4 ng/mL is not unexpected when 1 g of prostatic tissue has been preserved in men free of prostate cancer. Thus, a PSA level of 0.5 ng/mL, which is just on the threshold of PSA detection, may be appropriate for radical surgery, but is reasonable for cryoablation. It should be noted that the ASTRO definition is not without limitation. It is not inconceivable that a patient may have 3 consecutive increases in PSA, all of which may be <0.5 ng/mL, before hitting a plateau under 0.5 ng/mL. In this situation, the patient would be exhibiting biochemical relapse under ASTRO criteria but would be free from biochemical failure using a PSA cutoff of 0.5 ng/mL. Conversely, a patient may have a 3-month PSA level of 0.1 ng/mL and a 6-month PSA level of 1.1 ng/mL, with no further reading. The patient would exhibit biochemical failure using 1.0 ng/mL as a cutoff but would be free from biochemical failure under ASTRO. It is intended that this patient series be used to correlate disease-specific survival with PSA evolution, hoping to determine the best definition of bDFS after cryoablation.

The use of multiple biopsy results after cryoablation provides an accurate appraisal of local control of cancer, which is the goal of cryoablation therapy. There are several reasons why PSA readings may be elevated despite multiple negative biopsy results, including (1) preservation of residual normal glandular tissue (acini), (2) incomplete ab-

TABLE II. *Stratified biopsy results*

Patient Characteristics	Patients (n)	Negative Biopsy	DFR (%)
PSA (ng/mL)			
<4	97	89	91.8
4–10	348	310	89.1
>10	145	115	79.3
Gleason Score			
3–6	241	221	91.7
7	310	262	84.5
8–9	35	28	80.0
T stage			
T1	11	11	100.0
T2	461	414	89.8
T3	104	77	74.0

DFR = disease-free rate; PSA = prostate-specific antigen.

TABLE III. *Number of patients who underwent biopsy at different time intervals*

Time Since TCAP (mo)	Patients Biopsied (n)
6	436
12	403
24	301
48	78
60	41

TCAP = targeted cryoablation of prostate cancer.

TABLE IV. *Postcryoablation morbidity*

Morbidity	Rates (%)
Incontinence*	4.3
Impotence†	94.9
TURP	5.5
Fistula	<0.1

TURP = transurethral resection of the prostate.
** Incontinence was defined as the use of pads.*
† Of men who were potent before cryoablation.

lation of cancer, (3) distant metastasis, or (4) a combination of these.

Table VI[33,35–42] compares the biopsy results of the current series with other studies in the literature. It is demonstrated that TCAP yields superior rates of negative biopsy results relative to other primary treatment modalities of prostate cancer. Although the Ragde *et al.*[33] study yielded a lower rate of positive findings, they also used a highly selected patient population that was characterized by low pretreatment PSA levels and slowly growing, relatively nonaggressive tumor that is in the early clinical stage. Additionally, the use of 1-time biopsy may lead to sampling error that may falsely elevate the disease-free rate. This is in contrast with the remainder of the studies (which are more representative of prostate cancer populations as a whole) and with the current series in particular, which comprises the full spectrum of clinical stage, with many patients exhibiting tumors that are moderately to poorly differentiated and subject to a greater degree of aggressive growth.

Although radiation therapy has the potential to cure or significantly delay the progression of locally confined prostatic tumors among selected patients, it may result in significant morbidity, potentially leading to lifestyle restriction and psychological distress in the patient. It is now widely recognized among urologists and radiation oncologists who treat prostate cancer that because the natural history of prostatic adenocarcinoma is often characterized by slow progression, concern for issues related to the quality of life for the patient after the intervention is amplified.

The quality of life of patients who have received primary treatment for localized prostate cancer is, to a large degree, influenced by adverse changes in bowel, urinary, and sexual function. There is wide variation in the literature on reported rates of complication from prostate cancer treatment. A likely reason for these discrepancies is that the study may use physician-derived or patient-derived information. An example of this discrepancy is the review of complications from the "nerve-sparing" (a surgical approach intended to retain presurgical potency) prostatectomy literature by McCammon *et al.*[43] who found that physician-reported studies arrived at 1-year postsurgery rates of potency of 54% to 71%, whereas patient-reported studies have reported potency rates that ranged from 2% to 32%.

A frequently occurring complication among TCAP patients is impotence. Immediate erectile dysfunction is probably inevitable if the operator aggressively freezes the apex of the gland and the periprostatic tissues, especially the neurovascular bundles. This area should be targeted because it is a probable area for conventional surgical or cryosurgical failure.[11] Because the neurons for erectile function are injured but not killed, subsequent axonal regeneration may lead to functional recovery. There is documented evidence that potency can return among some patients. Robinson *et al.*[44] studied the quality of life of 75 men who received TCAP as primary treatment for prostatic carcinoma. At 3 years after TCAP, 5 of the 38 patients who were having erections sufficient for intercourse at baseline had a return of consistent erectile function sufficient for intercourse. An additional 13 patients were able to achieve erections sufficient for intercourse with assistance. This brings the overall total to 18 of 38 (47%) patients being able to have intercourse at 3 years, and it

TABLE V. *Comparison of the current series with published 7-year follow-up reports with respect to biochemical survival after external-beam radiation therapy (XRT), 3-dimensional conformal radiation therapy (3D-CRT), and brachytherapy (brachy)*

Study	Therapy	n	Age (yr) median	PSA (%)		Gleason (%)			Clinical T Stage (%) ≤T2a→>T2b	7-yr Biochemical Disease-Free Survival (%)		
				≤10	>10	3–6	7	8–10		≤0.5	≤1.0	ASTRO
Martinez *et al.*[30]	XRT	225	73	100	0	100	0	0	Median T2a (T1a–T3c)			69
Kestin *et al.*[31]	XRT	871	73	47.4	44.5	63.1	18.8	13.5	T1 = 20,* T2 = 74.6,† T3 = 8.6‡			48
Hanks *et al.*[32]	3D-CRT	456	—	43.2	56.8	95.6§		4.4	≤T2a = 50.4, >T2b = 49.6			57
Ragde *et al.*[33]	Brachy	122	70	78.7	21.3	100	0	0	≤T2a = 85.3, >T2b = 14.7	79	87	89
Current series	Cryo	590	71	75.4	24.6	41.1	52.9	6	T1 = 1.9, T2 = 80, T3 = 18.1	62	76	90

ASTRO = American Society for Therapeutic Radiology and Oncology; Cryo = cryoablation; PSA = prostate-specific antigen.
* *Originally stratified as clinical stages T1a–T1c.*
† *Originally stratified as clinical stages T2a–T2c.*
‡ *Originally stratified as clinical stages T3a–T3c.*
§ *Originally stratified as Gleason 2–4, 5–7, and 8–10.*

TABLE VI. *Comparison of the current series' positive biopsy rates and those observed after brachytherapy (brachy), 3-D conformal radiation therapy (3D-CRT) and external-beam radiation therapy (XRT)*

Author	Tx	Pts (n)	Pretreatment PSA (ng/mL)	Gleason Stage	Clinical T Stage	Median Follow-up	% Positive Biopsy
Stock *et al.,* 1996[35]	Brachy	97	75% <20	82% <7	T1–T2	18 mo	26%
Ragde *et al.,* 1997[33]	Brachy	126	78.7% <10; median 5.0	2–6	T1–T2	7 yr	5%*
Ragde *et al.,* 1998[36]	Brachy	152	Median 11.0	91% <8	98% <T3	10 yr	15%
Zelefsky *et al.,* 1998[37]	3D-CRT	743	Median 15	81 <8	T1–T3	>30 mo	48%
Dinges *et al.,* 1998[38]	XRT	82	Median 14.0		T2–T3	24 mo	27%
Crook *et al.,* 1998[39]	XRT	102			T1–T3	40 mo	20%†
Babaian *et al.,* 1995[40]	XRT	31	70% >10		T1–T3	51 mo	71%
Laverdiere *et al.,* 1997[41]	XRT	120	Median 11.2	24.3% >6	T1–T3	24 mo	62%
Ljung *et al.,* 1995[42]	XRT	55		35% >6	T1–T3	6.8 yr	67%
Current series	TCAP	590	24.5% >10	58.4% >6	T1–T4	5.72 yr	13%

PSA = prostate-specific antigen; TCAP = targeted cryoablation of the prostate.
* *13% indeterminate.*
† *15% indeterminate.*

provides evidence that erections sufficient for intercourse can return over time.

CONCLUSION

We have shown that the 7-year efficacy rates of TCAP are comparable or superior to the rates of efficacy of all conventional radiation therapy modalities for prostate cancer. There are several other advantages to cryoablation treatment over conventional prostate cancer therapy. Cryoablation requires only a short hospital stay, with most patients being able to be discharged within 24 hours. The procedure can be applied in cases of locally advanced cancer because of the ability to extend the freezing margin well outside the glandular margin, including seminal vesicles, thus allowing the treatment of stage T3 disease. There are no known latent complications, and in an era where cost containment is a priority, the procedure is less expensive than competing treatments because it does not require the massive installation of radiotherapy equipment or the inhospital convalescence of prostatectomy.[45] We believe that these results will lead to a greater acceptance of TCAP as a viable treatment option for localized to locally advanced prostate cancer.

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