The Current and Potential Role of Cryoablation As a Primary Therapy for Localized Prostate Cancer

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Targeted cryoablation of the prostate has evolved significantly since its reintroduction in the early 1990s. This evolution stems from engineering advancements, procedural refinement, introduction of temperature monitoring, and greater understanding of cryobiology. Recent publications demonstrate durable efficacy for cryoablation, equivalent to other therapies for low-risk disease and possibly superior for moderate- and high-risk prostate cancer. Morbidity following the procedure is mild in comparison with other therapies, with the exception of sexual function impairment. However, longer-term quality-of-life studies show that a significant number of patients return to having intercourse, and late-onset morbidities are not observed. These results contrast with those for radiotherapy—specifically brachytherapy—for which several recent studies document a decline in sexual function, protracted morbidity, and the emergence of late-onset morbidity. Cryoablation is an effective therapy with acceptable morbidity that should be offered as a treatment option to all patients with localized prostate cancer. Furthermore, cryoablation has the potential ability to be tailored to an individual patient's disease. As diagnostic tools and methods continue to advance, it may become possible to target the less aggressive forms of prostate cancer. Focal cryoablation may prove to be an ideal treatment modality in this setting.

Introduction

Prostate cancer represents a serious health hazard for men. The American Cancer Society estimated that approximately 200,000 new cases of prostate cancer will be diagnosed each year and that over 30,000 lives will be claimed by the disease in the United States. After skin cancer, prostate cancer has become the most commonly diagnosed cancer in American men and is the second most common cause of cancer death in men, following lung cancer [1]. With the widespread introduction of prostate-specific antigen (PSA) screening for prostate cancer in the past decade, many more men are now diagnosed in the early stages of the disease, when local cure is possible. However, the optimal treatment for localized disease is unclear. Radical prostatectomy and external-beam radiotherapy are recognized as the conventional standards of care. Other treatments such as brachytherapy, cryosurgery, and high-intensity focused ultrasound are also used in the management of many patients.

The decision-making process that a prostate cancer patient goes through involves establishing a balance between the perceived risks and rewards associated with each treatment modality. No therapy is 100% effective and, unfortunately, no therapy can guarantee zero impact on a patient's quality of life (QOL). Many factors are involved in planning the treatment path, including the aggressiveness of the cancer, patient age, life expectancy, physical activity level, sexual activity level, and comorbidities. The treatment choice is a balance between the patient's acceptance of efficacy or cure probability, tolerance of potential treatment morbidity, and long-term QOL impact.

Randomized, prospective clinical trials comparing the efficacy of primary prostate cancer therapies are lacking. Comparisons of efficacy are difficult and rely on the results of well-controlled and documented clinical investigations comprised of case series by qualified experts. Direct comparisons of efficacy between treatments are necessarily estimates, but fortunately patient selection biases introduced in unrandomized trials are limited in well-conducted investigations of prostate cancer treatment due to their consistent inclusion and exclusion criteria. In addition, measurement of successful clinical outcome in some studies is subject to bias, but in prostate cancer, PSA is generally accepted as a surrogate for long-term treatment success as a valid endpoint. Consistency of findings (in trends and magnitude of effects) replicated by more than one investigator and persistence over time add to the weight of findings from multiple investigations and enhance the validity of conclusions in the absence of more desirable prospective, randomized multicenter studies.

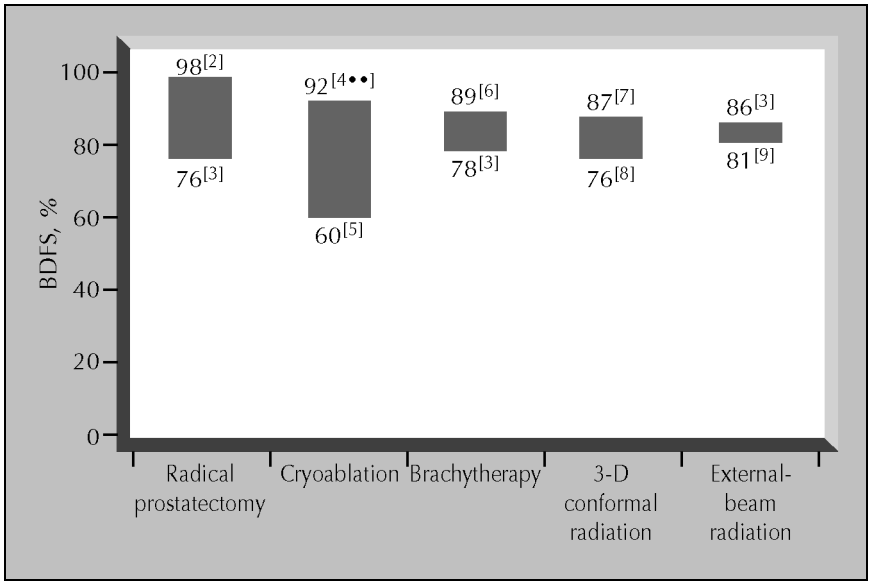

Figure 1. The range of biochemical disease-free survival (BDFS) rates reported in the past 10 years for low-risk disease.

The Established Role of Cryoablation

Efficacy

The comparative analysis that follows is based on all studies of primary prostate cancer therapies reporting rates of 5-year biochemical disease-free survival (BDFS). All of the studies used in this analysis have been published as full manuscripts in the peer-reviewed literature in the past 10 years (1992–2002), and this analysis stratifies the study results by risk group. Low risk is defined as tumor (T) stage T1 to T2a, Gleason score less than or equal to 6, and PSA less than 10. Moderate risk is defined as one of the following: stage higher than T2a, Gleason score greater than 6, or PSA greater than 10. High risk is defined as two or more of the following: stage higher than T2a, Gleason score greater than 6, and/or PSA greater than 10. Although BDFS definitions across the studies are not consistent, this analysis is intended to look for trends and is not designed for conclusive comparison of the different therapies.

Figures 1, 2, and 3 show the published range of BDFS for each type of treatment observed 5 years after the treatment has taken place. It should be noted that high-intensity focused ultrasound does not appear in this comparison because there are no 5-year reports of its efficacy. For low-risk disease, all of the currently available treatment modalities (*ie*, radical prostatectomy, cryoablation, brachytherapy, three-dimensional conformational radiotherapy, and external-beam radiotherapy) achieve excellent local and systemic control (Fig. 1). Given the relative equivalence in efficacy, treatment decisions for patients with low-risk disease are based more on morbidity and QOL factors rather than on the ability of a given treatment to cure the cancer. Notably, the durable long-term results (>15-year follow-up) for radical prostatectomy reinforce its role as the gold-standard therapy for localized prostate cancer.

More uncertainty arises in determining the optimal approach for patients with moderate- and high-risk disease, as shown in Figures 2 and 3. Comparing these findings with those shown in Figure 1, a drop in efficacy can be observed for all therapies with increasing disease risk. However, the drop is not as substantial for cryoablation as it is for both surgical and radiotherapy series. Based on this comparison, the efficacy of cryosurgery appears to be at least equivalent, if not superior to, efficacy for all forms of radiotherapy and surgery in moderate- and high-risk patients.

Among the recent cryoablation studies, biopsy results were reported by Bahn *et al*. [4••] and Donnelly *et al*. [16••]. Bahn *et al*. [4••], with a mean follow-up of 5.72 years, found an overall positive biopsy rate of 13%, whereas Donnelly *et al*. [16••] reported that 72 of the 73 patients in their study were negative for local malignancy. The biopsy outcomes for brachytherapy, conformal-beam radiotherapy, and external-beam radiotherapy are less compelling. The proportions of positive biopsy findings in brachytherapy studies ranged from 5% to 26%, with mean follow-up of 18 months to 10 years [6,17,18]. However, the study that produced the 5% rate of positive biopsy findings was highly selective, being comprised solely of patients with low pretreatment PSA levels and with disease characterized by slow-growing, mildly aggressive tumor in the early clinical stages [6]. The proportion of positive biopsy findings in conformal-beam radiotherapy was 48% at a mean follow-up of greater than 30 months [21], and the proportion of positive biopsy results in external-beam radiotherapy ranged from 20% to 71%, with mean follow-up of 2 to 6.8 years [20–24]. These results are summarized in Table 1.

Morbidity

The ability of cryoablation to eradicate tissue effectively has never been questioned. Analogous to radiotherapy, the question has been whether a sufficient dose of cold could be delivered to treat the cancer effectively without causing

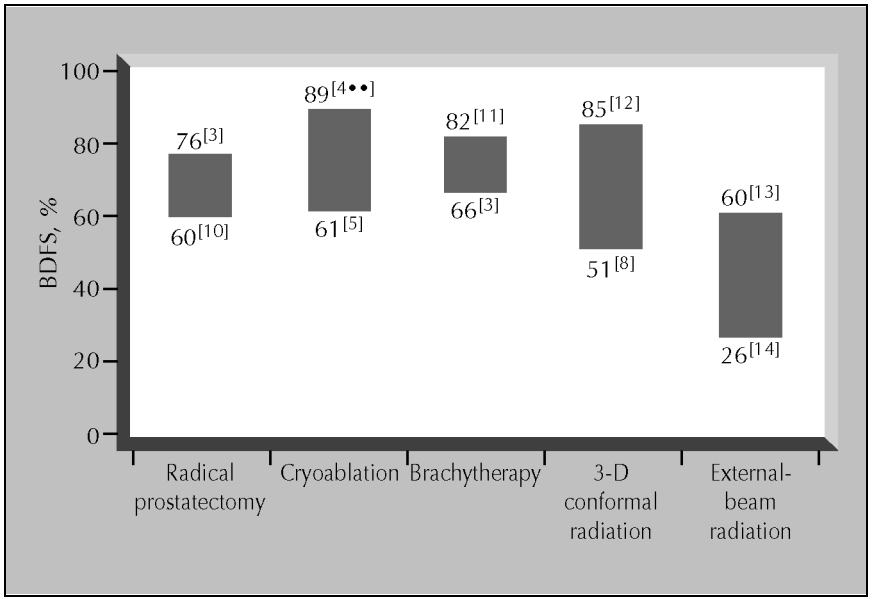

Figure 2. The range of biochemical disease-free survival (BDFS) rates reported in the past 10 years for moderate-risk disease.

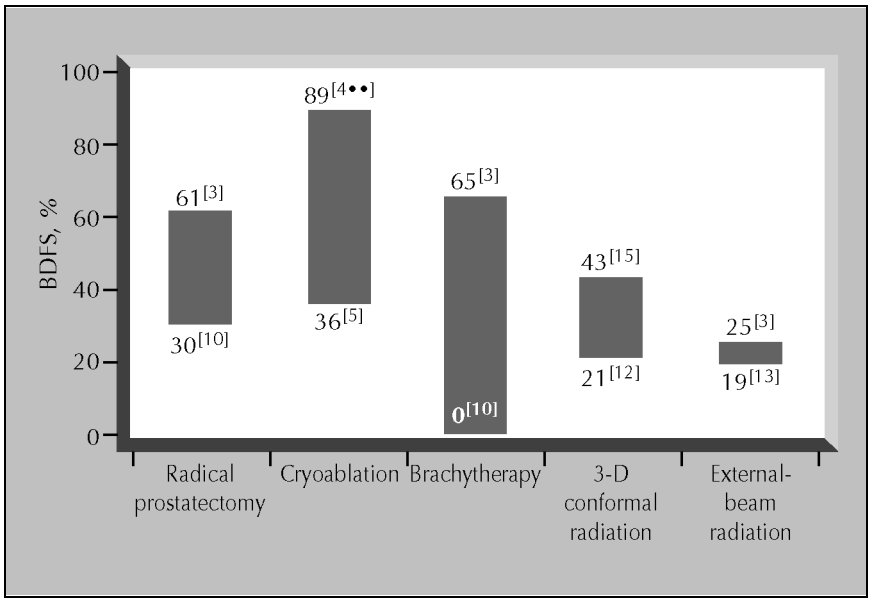

Figure 3. The range of biochemical disease-free survival (BDFS) rates reported in the past 10 years for high-risk disease.

unacceptable morbidity. The morbidity associated with prostate cryoablation has steadily declined with advances in technology, refinements in clinical protocols, and greater understanding of cryobiology [25]. The latest studies illustrate the very low rates of morbidity associated with the current practice of cryoablation in comparison with other prostate cancer therapies.

It is well known that the adverse changes in bowel, bladder, and sexual function have the greatest impact on the lives of prostate cancer patients who have received treatment for localized cancer. Of the three latest cryoablation studies [4••,16••,26], only one found rectal complications (Bahn *et al*. [4••], with fistula in <0.1%), whereas rates of incontinence in the three studies ranged from 1.3% to 5.4%, and rates of postoperative impotence ranged from 82.4% to 100%. In contrast to the low morbidity exhibited in the latest cryoablation studies are the bowel, bladder, and potency data taken from several studies involving radical surgery and beam radiotherapy.

Among radical surgery studies, rates of bowel urgency ranged from 6% to 16% [27,28], rectal bleeding ranged from 1% to 3% [28,29], and diarrhea ranged from 6% to 19% [27,29]. Among recipients of beam radiotherapy, bowel urgency ranged from 19% to 43% [27,28], rectal bleeding from 13% to 17% [28,29], and diarrhea from 12% to 42% [27,29]. Urinary morbidity among radical surgery patients included incontinence in 7% to 52% [28,30], whereas urinary morbidity among beam radiotherapy patients included incontinence in 0% to 15% [28,29]. Incontinence in all studies was defined as the use of at least one pad per day.

Impotence occurred at a rate of 51% to 96% in radical surgery studies [29,31], and 50% to 61% in beam radiotherapy studies [28,32]. The reporting of morbidity data in

Table 1. Positive biopsy results observed following radiotherapy and cryoablation

Study	Treatment	Patients, *n*	Pretreatment PSA, *ng/mL*	Gleason score	Clinical T stage	Median follow-up	Positive biopsy, %
Stock *et al.* [18]	Brachy	97	75% <20	82% <7	T1–T2	18 mo	26
Ragde *et al.* [6]	Brachy	126	78.7% <10; median, 5.0	2–6	T1–T2	7 y	5†
Ragde *et al.* [17]	Brachy	152	Median, 11.0	91% <8	98% <T3	10 y	15
Zelefsky *et al.* [19]	3D-CRT	743	Median, 15.0	81% <8	T1–T3	>30 mo	48
Dinges *et al.* [20]	XRT	82	Median, 14.0	NR	T2–T3	24 mo	27
Crook and Bunting [21]	XRT	102	NR	NR	T1–T3	40 mo	20*
Babaiain *et al.* [22]	XRT	31	70% >10	NR	T1–T3	51 mo	71
Laverdiere *et al.* [23]	XRT	120	Median, 11.2	24.3% >6	T1-T3	24 mo	62
Ljung *et al.* [24]	XRT	55	NR	35% >6	T1-T3	6.8 y	67
Bahn *et al.* [4••]	Cryo	590	24.5% >10	58.4% >6	T1-T4	5.72 y	13
Donnelly *et al.* [16••]	Cryo	76	38% >10	56% >6	T1-T3	5.1 y	15

*15% Indeterminate.
†13% Indeterminate.
Brachy—brachytherapy; Cryo—cryoablation; 3D-CRT—three-dimensional conformal radiotherapy; mo—months; NR—not reported; PSA—prostate-specific antigen; XRT—external-beam radiotherapy; y—years.

treatment studies of primary prostate cancer varies widely. All studies reviewed herein used patient-derived data, which are believed to be more accurate with respect to treatment morbidity than physician-derived data. An example of this discrepancy is the study by McCammon *et al.* [33], who reviewed complications resulting from "nerve-sparing" radical surgery, an approach that is intended to retain presurgical potency. These investigators found that the physician-reported studies arrived at 1-year potency rates of 54% to 71%, whereas the patient-reported studies arrived at 1-year potency rates of 2% to 32%.

Quality of life

The impact on quality of life is now recognized as a vitally important dimension in evaluating a treatment for prostate cancer. A new long-term study on the impact of cryoablation on QOL provides strong evidence that QOL following cryoablation is comparable, if not superior, to QOL after other treatments [34••]. These authors administered two scales, the Functional Assessment of Cancer Treatment–Prostate (FACT-P) and the Sexuality Follow-up Questionnaire (SFQ). After 1 year, the results of these assessments indicated a return to presurgical functioning in all areas, with the exception of sexual functioning. At 3 years, close to 50% of impotent men who were potent prior to the procedure regained the ability to have erections that were sufficient for sexual intercourse. All other areas of functioning remained high, and no delayed-onset morbidity was associated with cryoablation.

In sharp contrast to the gradual regeneration of sexual functioning in a large proportion of patients and the absence of late-onset morbidity associated with cryoablation, several studies have documented a decline in sexual function, protracted morbidity, and emergence of late-onset morbidity among brachytherapy patients. Lee *et al.* [35] found a significant decline that persisted at 3 months in urinary symptoms, physical side effects, and overall QOL associated with brachytherapy; Van den Hoeven *et al.* [36] found that 48% of their sample developed erectile dysfunction at 3 months that persisted at 12 months; Ben-Josef *et al.* [37] reported that 71% of the patients in their sample were able to have intercourse at 36 months, declining to 50% at 60 months; Zelefsky *et al.* [38] observed that 79% of the patients in their sample were able to engage in intercourse at 24 months, declining to 47% at 60 months; and Hollenbeck *et al.* [39] found at 24-month follow-up that 33% of patients aged under 69 years and 26% of patients aged over 69 years were able to achieve intercourse, compared with 78% and 61%, respectively, of age-matched controls.

Late-onset morbidity associated with brachytherapy has been documented by Zelefsky *et al.* [38], who found that protracted grade 2 urinary toxicity, which manifested after the implant and persisted more than 1 year, occurred in 31% of study patients, with a median duration of 23 months. The 5-year actuarial likelihood of developing a urethral stricture (grade 3 toxicity) was 12%, with a 59% likelihood of resolution or improvement 36 months from onset. The 5-year likelihood of grade 2 rectal toxicity was 11%. In a study by Merrick *et al.* [40], 19.2% of patients receiving brachytherapy reported worsening bowel function following implantation.

Collectively, these results indicate that brachytherapy can lead to persistent morbidity after the treatment, delayed onset, and progressive morbidity that persists over time, including gradual long-term erosion in sexual functioning. In sharp contrast, cryoablation results in substantially less bowel and bladder morbidity, no delayed-onset morbidity, and the reversal of erectile dysfunction in many patients over time.

With more global measures of QOL, the results from Robinson *et al.* [34••] compare favorably with those from Litwin *et al.* [41], who measured the 5-year QOL outcomes of radical surgery, radiotherapy, and observation; and with those of Krupski *et al.* [42], who performed a 9-month QOL follow-up study in brachytherapy patients (Table 2). All authors used the FACT-P questionnaire, which has a maximum score of 30 for each domain, with the higher score indicating higher QOL. The QOL following cryoablation was comparable, if not superior, with that of conventional prostate cancer therapies. As summarized in Table 2, compared with patients undergoing cryoablation, brachytherapy patients manifested significantly worse scores on the "Social/family well-being" scale; cryoablation patients had higher scores on the "Functional well-being" scale than did patients who underwent radical surgery and radiotherapy; and cryoablation patients produced somewhat higher scores on the "Relationship with doctor" scale than did patients receiving all other treatments (scores on this scale unavailable for brachytherapy patients). Thus, QOL among cryoablation patients is comparable with that of patients receiving surgery, radiotherapy, brachytherapy, or observation and superior along some QOL outcome dimensions.

The newly published long-term results of prostate cryoablation demonstrate durable efficacy equivalent to that of other therapies for low-risk disease and possibly but not conclusively superior efficacy for moderate- and high-risk prostate cancer. Is there a scientific basis for this clinical observation? Two fundamental shortcomings of the standard therapies can limit their ability to treat all prostate cancer effectively: positive margins observed after radical prostatectomy and preferential ablation of patients with lower Gleason score cancer by radiotherapy. The ability of radical prostatectomy to remove all the cancer is limited if the cancer extends beyond the surgical margin. Positive margins occur in up to 40% of patients undergoing radical prostatectomy [43]. During cryosurgery, one can and usually does freeze beyond the margins of the gland, which will minimize the changes of yielding positive margins. In patients who are at high risk for extracapsular extension, the operator can freeze aggressively beyond the capsule of the gland.

Radiotherapy damages the nucleus of individual cells, and the more aggressive the cancer is, the harder the cells are to kill. Although any cell will be irreversibly damaged if it is exposed to enough radiation, the sensitivity of the anatomic neighborhood of the prostate limits the lifetime dose of radiation that can be delivered to the gland. Clinical results indicate that efficacy of radiotherapy declines significantly if a patient's Gleason score is greater than 7. In fact, if cancer recurs after a trial of radiotherapy, it is often a more aggressive form, indicating a preferential killing of less aggressive cells only to leave those that are more radioresistant [44].

Also, the technical, procedural, and scientific evolution of targeted cryoablation of the prostate in the past decade has led to significant reduction in the morbidity associated with the procedure. Morbidity after cryoablation is mild in comparison with morbidity after other therapies, with the exception of sexual function impairment. However, sexual function returns in time in a large proportion of patients, and no late-onset morbidities are observed. These findings contrast with those for radiotherapy—specifically brachytherapy—for which several recent studies document a decline in sexual function, protracted morbidity, and emergence of late-onset morbidity.

The Potential Future Role of Cryoablation

Current prostate cancer treatment options are limited to whole-gland ablation because of the multifocal nature of prostate cancer, a phenomenon established prior to the PSA era. Coincidentally, whole-gland treatment is necessitated by both radical prostatectomy and radiotherapy. One cannot surgically remove only a portion of the prostate because of the urethra, and there is a lifetime dose of radiation that can be delivered to the prostate without a drastic increase in morbidity. These factors lead to a therapeutic approach using a one-time maximum dose of radiation. The stage shift resulting from widespread PSA screening has led some researchers to question the clinical significance of ancillary multifocal tumors and to ask whether it is possible to predict unifocal cancer, unilateral cancer, or clinically insignificant multifocal prostate cancer preoperatively.

Approximately 65% to 80% of prostate cancer is multifocal. Villers *et al.* [45], however, showed that 80% of incidental tumors are less than 0.5 cm^3, indicating that a significant proportion of multifocal tumors, other than the dominant tumor preoperatively identified, may not be clinically significant. Rukstalis *et al.* [46] found that the ancillary lesion size was only 0.3 cm^3 and that 79% of men were likely to have significant cancer eradicated if the index cancer was targeted. Djavan *et al.* [47] showed that patients with multifocal disease could be reliably differentiated from patients with unifocal disease with a sensitivity of 90% using transition-zone PSA density and ratio of free to total PSA. In addition, Epstein *et al.* [48] found that tumors are more likely to be multifocal when biopsies are diagonally positive (*ie*, left apex, right mid) or horizontally positive (*ie*, left apex, right apex) than when they are vertically positive (*ie*, left apex, left mid). Also, optimization of biopsy protocols can greatly diminish the chances of missing a significant multifocal tumor. Levine *et al.* [49] showed that obtaining a second set of biopsies increased the number of cancers detected by 30%.

Onik *et al.* [50••] recently reported a pilot study of patients with cancer believed to be confined to one lobe of the prostate in which cryosurgery was applied focally. The focal prostate cryosurgery procedure they described was an attempt to exploit the advantages of cryosurgery, particularly with respect to excellent treatment of potential extracapsular extension, while minimizing the sexual

Table 2. Quality of life (QOL) of men treated with cryosurgery, radical prostatectomy, radiotherapy, brachytherapy, and observation, with higher scores indicating better QOL outcomes

Variables	Cryosurgery [41]† (*n*=65)	Surgery [41]* (*n*=98)	Radiotherapy [41]* (*n*=60)	Brachytherapy [42]‡ (*n*=41)	Observation [41]* (*n*=60)
FACT-P scales	Mean	Mean	Mean	Mean	Mean
Physical well-being	26.1	25.4	24.9	25.4	25.2
Social/family well-being	21.9	21.6	21.6	14.9	21.1
Emotional well-being	18.1	16.6	17.3	21.3	16.6
Functional well-being	24.6	20.9	21.2	23.6	20.7
Relationship with doctor	7.5	6.5	6.5	NA	6.3

*Average follow-up of 5 years.
†At 3 years.
‡Follow-up of 9 months.
FACT-P—Functional Assessment of Cancer Treatment—Prostate; NA—not available.

function morbidity following whole-gland cryosurgery. Consistent with this goal, the procedure performed was a unique combination of a "minimal" procedure on the opposite side from the cancer but an aggressive cryosurgical treatment on the side where the cancer was located. As part of the aggressive focal treatment, the neurovascular bundle (NVB) on the side of the tumor was aggressively destroyed in all patients. The decision to treat focally was based on the extent of the patient's disease and was done with the primary goal of providing sufficient and effective cancer control and, secondarily, minimizing morbidities, specifically impotence.

Follow-up ranged from 6 to 72 months, with a mean of 36 months. All of the patients were reported to have a stable PSA, with the postoperative PSA stabilizing at some fraction of the preoperative PSA depending on the extent of the gland freeze. All patients who were biopsied routinely showed no clinical evidence of disease. No patients had significant incontinence after the procedure, and potency, defined as erection sufficient to complete intercourse to the satisfaction of the patient, was maintained in seven of nine patients (77%).

These results are encouraging. The preservation of sexual functioning associated with focal nerve-sparing cryosurgery is better than expected, given that only one NVB was spared. In contrast, the literature on nerve-sparing radical prostatectomy shows a significant decrease in potency rates when one NVB is spared rather than two. Impotence rates for unilateral nerve sparing vary from 13% [51] to 41% [52]. Clearly, the impotence associated with radical prostatectomy is not solely attributed to nerve damage during the procedure but is also effected by changes in vascular competency [53]. Focal cryoablation involves minimal vascular disruption if an NVB is spared. Some of this difference could also be related to the lack of nerve manipulation and associated nerve trauma when a nerve is spared by cryosurgery.

Another difference between focal cryoablation and nerve-sparing radical cryosurgery may be the comparative rate of return of sexual function between the two procedures. Potency following nerve-sparing radical prostatectomy is often reported to return about 18 months after the procedure. In the Onik *et al.* [50••] study, the return to function was very rapid; following nerve-sparing cryosurgery, if potency returned it did so within 1 year.

Although the results from Onik *et al.* [50••] are encouraging, it would be premature to consider focal cryoablation as a mainstream therapy given the current inability to determine the aggressiveness, extent, and spatial distribution of cancer accurately within the prostate. However, with ever-advancing diagnostic technologies and tests it may soon be possible to stage prostate cancer well enough to justify a focal approach. Cryoablation has a demonstrated ability to eradicate even the most aggressive forms of prostate cancer such as radioresistant disease [54], and it can be focused to ablate extremely aggressively in targeted locations within the prostate. The marriage of aggressive focal cryotherapy with accurate spatial diagnostic staging could have a drastic impact on treatment philosophies for managing prostate cancer.

Conclusions

The use of prostate cryoablation is expanding rapidly because of its demonstrated safety and efficacy in the treatment of both radio-recurrent and primary prostate cancer. Prostate cryoablation should be offered as a treatment option for all patients presenting with localized disease. Furthermore, the potential of cryoablation to be applied focally may become significant if and when diagnostic tests become advanced enough to predict and localize foci of cancer accurately within the prostate.

Acknowledgments

Dr. Rewcastle is a faculty member in the Department of Radiology at the University of Calgary, Alberta, Canada, and is employed by Endocare, Inc.

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