JOURNAL OF ENDOUROLOGY
Volume 20, Number 9, September 2006

Focal Prostate Cryoablation: Initial Results Show Cancer Control and Potency Preservation

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ABSTRACT

***Background*: Focal prostate cryoablation is the less-than-complete ablation of the gland with ice. Known tumor is ablated aggressively, whereas contralateral prostate tissue and surrounding structures are spared. This method offers targeted local cancer control aiming at sexual potency and urinary continence preservation in patients whose prostate cancer is believed to be unilateral.**

***Patients and Methods*: Patients who had a strong desire for preservation of sexual function and continence were informed of focal prostate cryoablation as an investigational treatment option for clinically organ-confined, unilateral tumor identified by color Doppler ultrasonography and confirmed by targeted and systematic biopsy. Only stage, not preoperative serum prostate specific antigen concentration (PSA) or tumor differentiation, was considered a potential contraindication. Thirty-one men with a mean age of 63 years underwent the procedure. Follow-up consisted of PSA measurement every 3 months for 1 year and every 6 months thereafter, with biopsies at 6 months and 1, 2, and 5 years and following any three consecutive PSA rises. Potency was determined with a patient questionnaire filled in without the physician present.**

***Results*: At a mean follow-up of 70 months, biochemical disease-free status, according to the ASTRO definition, was maintained by 92.8% of patients (26/28) and a 96.0% negative-biopsy rate (24/25) was observed. The one biopsy-positive patient was subsequently treated with full-gland cryoablation and remains disease free. Potency was maintained by 48.1% of patients (13/27) and another 40.7% (11/27) were potent with oral pharmaceutical assistance, yielding a total potency-preservation rate of 88.9%. No complications were observed.**

***Conclusion*: Focal cryoablation can provide biochemical and local control of prostate cancer while preserving potency and continence. Further investigation is needed.**

INTRODUCTION

BEFORE THE WIDESPREAD USE of prostate specific antigen (PSA) screening, most cases of prostate cancer were diagnosed at a locally advanced or metastatic stage, beyond the point where cure was possible. The advent of widespread PSA screening in the late 1980s has resulted in a downward stage migration, with most cases of prostate cancer now being diagnosed while they are organ confined.[1] Surprisingly, there continues to be a gap between prostate cancer incidence and mortality in the United States. Many researchers believe this discrepancy may be secondary to the more common diagnosis of nonlethal prostate tumors that exhibit a slow, indolent course, otherwise termed "insignificant disease."[1]

In 2003, Epstein and colleagues[2] published a set of validated criteria that differentiated insignificant from biologically significant (i.e., malignancy destined to metastasize or kill the host) disease: PSA density <0.15 ng/mL, Gleason sum ≤ 6, presence of malignancy in fewer than three of six biopsy cores, and no more than 50% malignant involvement in each positive core. The primary objective in developing these criteria was to identify tumors that may not require immediate, or any, intervention, for which surveillance (watchful waiting) would be the

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management strategy. Further, the authors recommended discretion in that, although they had validated the criteria, their institution was cautious when considering watchful waiting for the younger patient "given the unknown long-term behavior of untreated cancer in a younger individual."[2]

Regardless, there are disadvantages to watchful waiting. Many patients find the idea of forgoing treatment for a cancerous tumor unacceptable, and patient anxiety can be problematic. There also is the potential to miss the opportunity for cure if the tumor progresses. The treatment options for prostate cancer are limited to either no intervention or total prostate eradication (definitive local therapy) with radical surgery, radiotherapy, or cryoablation. The absence of an intermediate-level intervention has prompted the development and refinement of treatments aimed at treating the known tumor while sparing healthy prostate tissue, such as targeted, focal cryoablation.[3,4]

The development of focal cryoablation for prostate cancer follows the path that resulted in a paradigm shift in the management of breast cancer. Breast-conserving surgery (lumpectomy) revolutionized the way that localized breast cancer was treated. It spares the maximum volume of breast tissue to minimize cosmetic impact while maintaining the efficacy of radical mastectomy for properly selected patients. Focal cryoablation was developed to offer an intermediate-level treatment between watchful waiting and total glandular destruction or removal. It is substantiated by the recognition that as many as 35% of all prostate cancers are solitary[3,4]; that for multifocal tumors, the median ancillary (nonindex) lesion has been shown to be as small as 0.3 cc[5]; and that whole-gland cryoablation is effective in long-term cancer control.[6–8]

The impotence and incontinence that many patients experience after definitive prostate-cancer treatment negatively impact male self-esteem and psyche in a way comparable to the psychological impact of mastectomy on female breast-cancer patients. Similar to lumpectomy, the goal of focal cryoablation is to treat only the region of the tumor while preserving a major portion of the prostate gland to maintain the quality of life. Onik and colleagues[3] demonstrated the efficacy of focal cryoablation in carefully selected patients by preserving the potency of seven of nine patients. In this retrospective analysis, we present the cancer-control and potency-preservation data from a series of consecutive patients treated with focal prostate cryoablation. To our knowledge, this is the largest series with the longest follow-up reported to date.

PATIENTS AND METHODS

Between July 1995 and May 2004, men who had clinically organ-confined prostate cancer were informed of focal cryoablation as a potential treatment option if their tumor was believed to be confined to one lobe of the prostate and if maintenance of preoperative sexual function and urinary continence were their primary concerns. All patients underwent an initial six- to eight-core diagnostic biopsy by their urologists. If the man expressed interest in focal cryoablation, a thorough color Doppler ultrasound study was performed, including targeted biopsy of all the suspect lesions with nearby neurovascular-bundle and seminal-vesicle biopsies if extracapsular extension of the tumor was suspected. If both these biopsies yielded no evidence of prostate cancer on one side of the gland, unilateral treatment was discussed further with the patient, who had to be willing to adhere to a vigilant follow-up regimen. Note that patients were included only if their cancer was believed to be unilateral, but none was excluded on the basis of preoperative PSA or Gleason score.

Table 1. Demographics of 31 Patients

Mean age (range)	63 (51–75)
Mean preoperative PSA (ng/mL)	4.95
<4	11 (35.5%)
4–10	17 (54.8%)
>10	3 (9.8%)
Biopsy Gleason score	
5	3 (9.8%)
6	20 (64.5%)
7	8 (25.8%)
Mean gland volume (cm^3) (range)	37.96 (13–88)

All 31 patients entering the trial gave informed consent prior to treatment. Their average age was 63 years. The mean gland volume was 37 cm^3, with a range of 13 cm^3 to 88 cm^3. The mean baseline PSA was 4.95 ng/mL, with values of <4 ng/mL in 35.5% (N = 11), 4 to 10 ng/mL in 54.8% (N = 17), and >10 ng/mL in 9.7% (N = 3). Three subjects (9.8%) had preoperative Gleason scores of 5, 20 subjects (64.5%) of 6, and 8 subjects (25.8%) of 7. A summary of the baseline characteristics is provided in Table 1.

The cryoablation procedure was similar to that originally described by Onik and associates[9] utilizing two freeze cycles, a Food and Drug Administration-approved urethral warming device, multiple cryoprobes, and an argon-based cryomachine. However, by reducing the number of probes and adjusting their placement, it is possible to perform focal ablation that destroys only the targeted portion of the prostate and periprostatic tissue adjacent to the treatment zone.[3,4] This combination of aggressive freezing at targeted locations within the prostate while maintaining the integrity of the urethra, external sphincter, and contralateral lobe, including the neurovascular bundle, is the premise of focal cryoablation.

Patients underwent a vigilant follow-up regimen because the untreated prostate lobe may have harbored occult disease that could subsequently develop as a clinically significant malignant neoplasm. Follow-up consisted of PSA measurements every 3 months and biopsy at 6 months and 1, 2, and 5 years after cryoablation, as well as any time there were three consecutive rises in the serum PSA concentration.

A patient was considered to be biochemically disease free if, after treatment, his serum PSA did not rise on three subsequent occasions, the American Society for Therapeutic Radiation and Oncology (ASTRO) definition of biochemical failure.[10] Potency was evaluated with a questionnaire that was a modified version of the Brief Male Sexual Function Index.[11] A patient was considered to be fully potent if he answered "yes" to the question "Are you able to obtain a full erection when you are stimulated?" Incontinence was defined as any leakage of urine later than 3 months after the focal cryoablation procedure.

RESULTS

The mean follow-up was 70 months (range 2–107 months). Shortly after treatment, one patient died causes unrelated to his prostate cancer. Two patients treated recently have not yet returned for follow-up, two refused post-treatment biopsy, and one patient was lost to follow-up. Postoperative PSA measurements were available for 28 patients. Biochemical survival according to the ASTRO definition was observed in 92.9% of patients (26/28). At least one post-treatment biopsy result was available for 25 patients. On average, however, each of these patients underwent 2.36 post-treatment biopsies consisting of six cores plus cores from any regions appearing suspect on color Doppler ultrasonography. No evidence of disease was found in 24 of these 25 patients (96.0%). Cancer was detected in one patient in the apex of the untreated lobe 12 months after the procedure. He subsequently underwent whole-gland cryoablation and is currently biochemically and clinically disease free.

A total of 13 men (48.1%) regained full potency after the procedure, and another 11 men (40.7%) were able to achieve erections sufficient for intercourse with the use of oral pharmaceutical assistance. This yields a total potency-preservation rate of 88.9% (24/27): patients able to achieve erections sufficient for complete intercourse with or without oral pharmaceutical assistance. There were no reports of incontinence, and no other complications were observed.

DISCUSSION

Some observers believe screening for PSA results in overdiagnosis and overtreatment of prostate cancer. This argument is supported by the fact that approximately one third of men over the age of 50 years will display incidental prostate cancer at autopsy,[12] yet only 10% to 16% will develop invasive cancer during their lifetimes, and only 2.5% will die from it.[13,14] The justification for screening and treatment lies in the simple fact that prostate cancer still kills more than 30,000 men a year in the United States. That being said, focal cryoablation may be able to provide men who have limited tumor volumes with aggressive focal control of known disease without adversely impacting their quality of life.

Treatment selection for focal cryoablation is based on the location of the cancer within the prostate. Unfortunately, scant attention has been paid until recently to differentiating patients with unifocal from those with multifocal disease because curative therapy was identical for both tumor manifestations. However, as many as 35% of localized prostate cancers are unifocal,[3] and unifocal tumor can be differentiated reliably from multifocal disease with a sensitivity of 90% by using the PSA density of the transition zone and the percent of free to total PSA.[14] The PSA density is computed by dividing the absolute PSA value by the weight of the prostate gland,[15] and patients with multifocal disease were observed to have a transition-zone PSA density of >1.5 ng/mL/cc and free/total PSA of $<9\%$.[15] Additional findings by Rukstalis et al[5] indicate that as many as 80% of prostate cancer patients might be candidates for focal treatment when a tumor size of ≤ 0.5 cc is used as the criterion for disease significance. Unfortunately, this information is relatively new and was not utilized in the selection of the patients described herein. Given these recent observations, the criterion we used—two sets of biopsies both showing no evidence of bilateral disease—is, at best, minimally sufficient. That being said, it remains impossible to confirm unilateral disease with absolute certainty. We can hope a radiographic marker will eventually be developed that can depict the spatial distribution of cancer within the prostate reliably.

Many patients who exhibit small tumors are advised to forgo aggressive treatment in favor of observation. This watchful waiting approach is justified by the fact that prostate cancer grows very slowly in many cases. Age is a primary factor in the decision to follow a prostate cancer thought to be clinically insignificant.[12] A primary drawback of expectant therapy is that tumors may become incurable before they become palpable, especially in younger patients with potentially long lifespans, in contrast to older men with a limited life expectancy and substantial comorbidity.[1,15] Such patients need to be followed regularly for signs of progression, and many will need additional procedures such as rebiopsy and possibly curative treatment. In the U.S., most men with Gleason ≥ 6 prostate cancer choose some form of definitive therapy rather than watchful waiting.[1]

Current treatment options for prostate cancer are limited to whole-gland destruction through removal (radical surgery), irradiation (external-beam radiotherapy, brachytherapy), and ablation (cryoablation) or watchful waiting, with no middle-ground alternative available for men with malignancy believed to be confined to a single prostate lobe. Cryoablation has proven medium-term efficacy, with 5- and 7-year follow-up studies demonstrating biochemical disease-free survival rates comparable to those of radical surgery and radiotherapy in low-risk patients and possibly superior in medium- and high-risk patients, with very low rates of serious morbidity.[6–8] However, when cryoablation is performed adequately, the combined neurovascular insult of penile arterial blood-flow impairment[16] and cavernosal-nerve damage[17] results in rates of impotence between 40% and 100%, depending on such factors as operative technique, preoperative function, and method of potency assessment.[7] Because in cryoablation the neurovascular bundles are frozen and not severed, as in radical surgery, axonal regeneration is possible. Several studies have documented the return to preoperative potency after cryoablation in men who were rendered impotent by the procedure. Robinson and associates[18] reported that 3 years after cryoablation, 5 (13%) of 38 subjects potent at the time of intervention had returned to intercourse and another 13 (34%) had with the help of erectile aids (pharmaceutical or mechanical). Bahn and colleagues[7] found that 95% of subjects who were potent before cryotherapy became impotent, but that 5% regained their potency at a mean of 16 months. Despite evidence that some men experience a return to precryoablation potency, neurovascular regeneration can take several years, and the return to potency is far from certain, making whole-gland cryoablation an unattractive option for men who strongly desire the preservation of sexual functioning.

Onik et al[3] were the first to publish the results of potency-sparing focal cryoablation. Their series of nine patients had a mean age of 62.77, a mean and median baseline PSA of 8.02 ng/mL and 7.01 ng/mL, respectively, and clinical stage T_{1c} to T_{2b} disease, with a Gleason range of 3 to 8. At a mean follow-

up of 36 months (range 6–72 months), seven patients were potent, all had achieved stable PSA (mean and median post-cryoablation values 1.472 ng/mL and 0.725 ng/mL, respectively), and the six patients who underwent post-treatment biopsy all showed no evidence of disease.

In the current series, we substantiate the observations of Onik et al with a larger sample and a longer follow-up. The cancer-control rate in our series is encouraging, with 93% of the patients achieving stable PSA and a negative biopsy rate of 96.0%. Our observation that 88.9% of patients were able to achieve intercourse, either unassisted or with oral pharmaceutical assistance, is remarkable because only the nerves associated with contralateral lobe were spared, the others being ablated along with cancerous tissue to minimize the chance of local recurrence or metastatic spread. In contrast, the potency-preservation figures for patients undergoing a bilateral nerve-sparing radical prostatectomy, where both neurovascular bundles are left intact, range from 31% to 86%.[19,20] The figures for unilateral nerve-sparing prostatectomy are lower, ranging from 13% to 64%.[19,21]

Focal cryoablation is perhaps most comparable to unilateral nerve-sparing radical surgery, in that both procedures destroy one neurovascular bundle while leaving the contralateral one intact. Focal cryoablation appears to provide a higher rate of potency preservation than the bilateral nerve-sparing procedure, yet minimizes the risk of spread/recurrence by aggressive ablation of the neurovascular bundle on the side of the known malignancy. This success is thought to be attributable in part to the minimal vascular disruption and the absence of physical nerve manipulation and trauma.[3,4]

Focal cryoablation has the advantage over brachytherapy as a monotherapy in that whereas brachytherapy is limited to patients with low-volume, low Gleason-grade disease, the most important parameter for focal cryoablation is disease location. Because an elevated PSA or Gleason score (tumor differentiation) are not grounds for exclusion, many focal cryoablation candidates would not be eligible for brachytherapy. Cryoablation uniformly ablates tissue as a whole by destroying the microvasculature, in contrast to radiation therapy, which destroys individual cells.[22] Although patients were not selected on the basis of favorable tumor characteristics, 96% of the men produced negative biopsies and 93% achieved stable PSA measurements at follow-up. All returns of sexual function occurred within 1 year of focal cryoablation, unlike brachytherapy, where many patients experience late-onset morbidity that can include loss of sexual function.[23–25]

CONCLUSION

The results of this study substantiate other early reports of focal prostate cryoablation and demonstrate that focal cryoablation may be more effective than bilateral nerve-sparing prostatectomy in preserving potency in appropriately selected patients. By offering a high rate of sexual-function and urinary-continence preservation and effective cancer control, focal cryoablation may fill a void in the therapeutic options available to patients with unifocal or unilateral prostate cancer who desire to maintain their quality of life. Further investigation is warranted.

ACKNOWLEDGMENT

The authors gratefully acknowledge the assistance of Mark Rose, M.A., for his valuable help during the preparation of the primary manuscript.

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ABBREVIATIONS USED

ASTRO = American Society for Therapeutic Radiation and Oncology; PSA = prostate specific antigen.