"Male Lumpectomy": Focal Therapy for Prostate Cancer Using Cryoablation

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The introduction of breast-sparing surgery (ie, "lumpectomy") revolutionized the management of breast cancer. The use of lumpectomy showed that quality of life could be optimized without compromising treatment efficacy. Complications of prostate cancer treatment, including impotence and incontinence, adversely alter the male self-image similarly to the way the loss of a breast does for a woman. Traditional thinking holds that prostate cancer is multifocal and therefore is not amenable to focal treatment. However, histopathologic findings from published data have indicated that up to 25% of prostate cancers are solitary and unilateral. Furthermore, the significance of minute secondary cancers might be minimal. These observations raise the question of whether certain patients can be identified and treated with a limited "lumpectomy." In this study, focal cryoablation has been used to ablate the area of known cancer as determined by staging biopsies. The serum prostate-specific antigen (PSA) concentration was obtained every 3 months for 2 years and every 6 months thereafter. American Society for Therapeutic Radiology Oncology (ASTRO) criteria for PSA recurrence were used. A total of 55 patients with ≥1 year of follow-up had undergone focal cryoablation. Follow-up ranged from 1 to 10 years (mean, 3.6 years). At the original transrectal ultrasound biopsy, the mean and median numbers of cores taken were 9.9 and 10 (SD, ± 3.5), respectively. Mean and median numbers of positive cores were 1.8 and 1 (SD, ± 1.3), respectively. Of the 55 study patients, 52 (95%) had stable PSA levels with no evidence of cancer despite a medium to high risk for recurrence in 29 patients. All biopsy findings were negative among the 26 patients with a stable PSA level who had undergone routine biopsy at 1 year. No local recurrence was noted in treated areas. Potency was maintained in 44 (86%) of 51 patients. Of the 54 patients without previous prostate surgery or radiotherapy, all were continent. These preliminary results indicate that "male lumpectomy"—in which the prostate tumor region itself is destroyed—preserves potency in most patients and limits other complications (particularly incontinence) without compromising cancer control. Additional studies and long-term follow-up are needed to confirm that this treatment approach could have a profound effect on prostate cancer management. UROLOGY 70 (Suppl 6A): 16–21, 2007.

The introduction of breast-sparing surgery (ie, "lumpectomy") to treat breast cancer revolutionized the management of breast cancer. The use of lumpectomy showed that the quality of life of individual select patients can be successfully integrated into treatment without major loss of cancer treatment efficacy.[1] Prostate cancer in men raises many of the same issues that breast cancer does in women. Treatment complications such as impotence and incontinence affect the male self-image and psyche similarly to the way the loss of a breast affects a woman. A number of recent studies have questioned the efficacy of aggressive treatment of prostate cancer.

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Dr. Onik holds stock in Endocare, Inc. Dr. Vaughan has no financial arrangement or affiliation with a corporate organization or a manufacturer of a product discussed in this supplement. Dr. Lotenfoe has no financial arrangement or affiliation with a corporate organization or a manufacturer of a product discussed in this supplement. Dr. Dineen has no financial arrangement or affiliation with a corporate organization or a manufacturer of a product discussed in this supplement. Dr. Brady has no financial arrangement or affiliation with a corporate organization or a manufacturer of a product discussed in this supplement.

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Current management covers both ends of the treatment spectrum. Patients can elect no treatment (ie, "watchful waiting"[2]) or aggressive whole-gland treatment, such as radical prostatectomy (RP). Focal therapy, in which just the known area of cancer is destroyed, appears to be a logical extension of the watchful-waiting concept. Focal therapy minimizes the risk associated with expectant management in that the clinically threatening index cancer is treated while the risk for lifestyle-altering complications associated with morbid whole-gland treatment is reduced.

Cryoablation under imaging guidance, in contrast to traditional treatment such as RP and radiotherapy, is technically well suited to the "lumpectomy" approach. In this report, we discuss the rationale for the "male lumpectomy" management strategy for prostate cancer and present the results of focal cryoablation in 55 patients, all of whom underwent follow-up for ≥1 year.

MATERIALS AND METHODS

Patient Selection

Patients were considered for cancer-targeted cryoablation if, as determined through transrectal ultrasound–guided biopsy, cancer was confined to 1 side and maintenance of

0090-4295/07/$32.00
doi:10.1016/j.urology.2007.06.001

potency and/or continence was a major concern of the patient. All patients provided routine cryosurgical informed consent. All patients were informed of the additional risk that untreated cancer may remain in unfrozen tissue. Patients enrolled after February 1, 2000 signed an additional consent form for the use of these data. Patients underwent repeat biopsy on the side opposite the known cancer. After March 1, 2001, all patients underwent 3-dimensional (3-D) mapping transperineal biopsy under heavy sedation or general anesthesia. A brachytherapy grid was used, and biopsy cores were obtained every 5 mm throughout the prostate volume. Each sample was separately labeled and was processed by location. The proximal segment of each core was inked to indicate its orientation in relation to the base or apex.

Patients who were taking combined hormonal therapy before cryoablation stopped this therapy immediately after treatment ended.

Procedure

Ultrasound-guided percutaneous prostate cryoablation was performed as previously described by Onik *et al.*[3] The following changes were made to the procedure to accommodate the concept of cancer targeting and to enhance safety and efficacy:

1. The extent of freezing was tailored to the individual patient and was determined by clinical parameters such as Gleason grade, stage, prostate-specific antigen (PSA) concentration, and extent and location of cancer as seen on preoperative biopsy cores.
2. In all patients, an attempt was made to spare a single neurovascular bundle (NVB) on the side opposite the cancer. The NVB was destroyed on the side of the patient's tumor if the biopsy showed cancer within 1 cm of the NVB.
3. Cryoprobes were placed approximately 1 cm apart in the region to be destroyed and within 5 mm of the capsule on the side of the tumor. A cryoprobe was placed into the region of the ejaculatory ducts directly posterior to the urethra to prophylactically prevent seminal vesicle recurrence in patients who had had positive midline biopsy cores posterior to the urethra.
4. Tissue temperature monitoring was performed in critical locations such as the apex and the NVB on the side of the tumor to ensure adequate tumor destructive freezing temperatures of $\geq -35°$ C. The temperature of the NVB opposite the tumor also was monitored to prevent NVB destruction.
5. To decrease the risk for urethrorectal fistula, just before the start of freezing a 22-gauge spinal needle was placed into Denonvilliers fascia through the transperineal route. After adequate placement had been confirmed, normal saline was injected into the space separating the rectum from the prostate. This space was maintained by continued downward pressure of the transrectal ultrasound transducer.
6. An argon gas–based system was used to perform the freezing (Endocare, Inc., Irvine, CA); this replaced the original liquid nitrogen freezing equipment.
7. The Foley catheter remained in place for a variable time after the procedure, depending on the extent of freezing, thereby replacing the previous suprapubic tube.

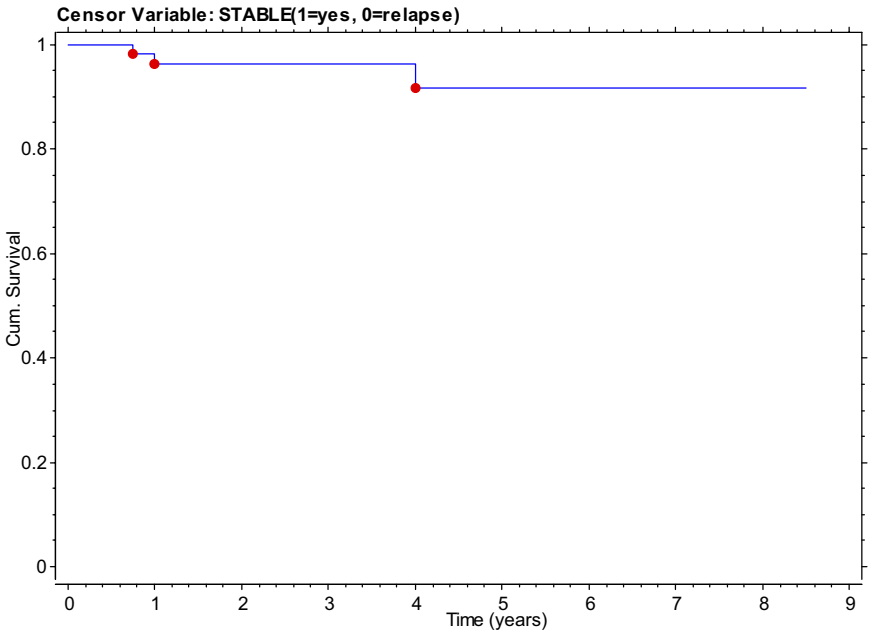
Patient Follow-up

All patients stopped combined hormonal therapy after the procedure had been performed. The serum PSA level was measured every 3 months for the first 2 years and every 6 months thereafter. Patients were considered to have a stable PSA level if they met the American Society for Therapeutic Radiology Oncology (ASTRO) criterion of being biochemically disease free. All patients were advised to undergo routine biopsy at 1 year, regardless of their PSA stability, to include both treated and untreated sides. Written questionnaires and telephone interviews were used for follow-up. Patients were considered potent if erections were sufficient for vaginal penetration and they were satisfied with their sexual function, whether or not they were taking oral agents. Patients were considered incontinent if they used pads at any time during the day.

RESULTS

From June 1995 to December 2005, 93 patients underwent cancer-targeted cryoablation. Of these, 55 had not had radiotherapy failure and had undergone $\geq$1 year of follow-up (mean follow-up, 3.6 years). Mean and median numbers of cores taken at transrectal ultrasound–guided biopsy were 9.9 and 10 (SD, $\pm$ 3.5), respectively. The mean and median numbers of positive cores were 1.8 and 1 (SD, $\pm$ 1.3), respectively. Using accepted criteria to stratify patients according to risk for recurrence (PSA level >10 ng/mL, Gleason score >6, and stage greater than T2a), in which patients with 1 risk factor are considered at medium risk and those with $\geq$2 risk factors are considered at high risk, 20 patients were categorized as medium risk and 9 as high risk; the remainder were considered to be at low risk. Preoperative androgen deprivation was provided for 6 months to 25 of the 29 medium- or high-risk patients.

Of the 55 patients, 52 (95%) had a stable PSA level at the most recent follow-up examination, with the postoperative PSA level stabilizing at some fraction of the preoperative PSA level, depending on the extent of the gland freeze (Figure 1). The mean preoperative PSA level was 8.3 ng/mL, and the mean postoperative PSA level was 2.4 ng/mL. An unstable PSA level was noted in 4 (7%) of the 55 patients within the first year postoperatively. In these 4 patients, biopsy revealed persistent cancer in a previously unfrozen portion of the gland. All 4 patients were treated with additional cryotherapy, essentially converting the procedure to a whole-gland freeze. Afterward, all 4 patients had a stable PSA level,



Survival Summary Table for Monitor Time(Years)
Censor Variable: STABLE (1=yes, 0=relapse)

# Obs.	55
# Events	3
# Censored	52
% Censored	94.545
# Missing	0
# Invalid	0

Figure 1. Kaplan-Meier cumulative survival plot for follow-up (monitor) time. Obs. = observed.

which measured <0.2 ng/mL. Of the 26 patients with a stable PSA who underwent routine biopsy at 1 year, all had negative biopsy findings on the treated and untreated sides. No patient, including the 3 patients with persistently unstable PSA levels, had positive biopsy findings in a treated portion of the gland. The overall and disease-specific survival rate was 100%.

Preoperatively, 51 patients were potent. Potency was maintained in 44 (85%) of the 51 patients who had undergone a single cryosurgical treatment; the 4 patients who were re-treated and whose procedure was converted to whole-gland cryotherapy became impotent as would be expected.

Of the 93 total patients who had undergone focal cryotherapy, 1 patient, who had a history of preoperative transurethral resection of the prostate, reported incontinence that required 2 pads daily. All patients without a history of transurethral resection of the prostate remained continent and did not require the use of pads.

DISCUSSION

The main theoretical objection to focal therapy is that prostate cancer is often multifocal. As with breast cancer, however, prostate cancer consists of a spectrum of diseases, some of which might be amenable to focal therapy. Prostate cancer pathology data have shown that a significant number of patients have a single focus of cancer, and that many others have additional foci that might not be clinically significant.[4–7] Until now, however, little attention has been paid in trying to differentiate those patients with unifocal and multifocal cancer because all treatments have been aimed at total gland removal or destruction.

In a study conducted to examine RP specimens, Djavan *et al.*[4] showed that patients with unifocal cancer constituted one third of cases. Villers *et al.*[5] showed that 80% of multifocal tumors were <0.5 cm^3, indicating that they might not be of clinical significance. These results were confirmed by Rukstalis *et al.*[6] and Noguchi *et al.*,[7] who reported that pathologic examination revealed the presence of unifocal tumors in 20% and 25% of patients, respectively, and that when the size criterion of ≤0.5 cm^3 was used to indicate an insignificant tumor, an additional 60% and 39%, respectively, of patients were considered potential candidates for focal treatment.

The question then is whether patients with unifocal cancer can be identified preoperatively. Optimization of biopsy results by a second set of biopsy cores and improved gland sampling will diminish the risk of missing a significant multifocal tumor.[8] In addition, the demonstra-

tion of negative biopsy findings on the nerve-sparing side predicted negative margins at nerve-sparing RP.[9] Newer biopsy techniques (not performed in our original series) are now in use by which the gland is biopsied transperineally every 5 mm with the use of a brachytherapy-type grid; this could result in the exclusion of patients with significant multifocal disease. A recent report by Crawford *et al.*,[10] who used computer simulations of RP and autopsy specimens, demonstrated that transperineal prostate biopsy cores spaced at 5-mm intervals through the volume of a prostate had a sensitivity of 95% in finding clinically significant tumor. Our results from 110 patients who underwent 3-D global mapping biopsies for additional staging showed that cancer could be detected in 50% of patients who had previously had negative biopsy findings in the supposedly uninvolved prostate lobe.[11]

Because the anatomy of the prostate gland does not make it amenable to partial removal or lumpectomy, tumor destruction by another modality is needed to realize "lumpectomy" in a man. Cryoablation is the obvious choice because it has a long history of effective tumor treatment in various parts of the body. The early rocky start that prostate cryoablation experienced has been largely mitigated by major technical advances in the procedure such as improved urethral warmer design, and this procedure has been shown to be an effective and safe alternative in the treatment of patients with prostate cancer involving the whole gland. Approximately 6 years ago, prostate cryoablation was approved by Medicare as a treatment for primary prostate cancer (removing it from the investigational category). Long-term 5- and 7-year data have been published by Donnelly *et al.*[12] and Bahn *et al.*[13] that confirm cryoablation as a treatment that is competitive with both surgery and radiotherapy in the treatment of prostate cancer.

A published report by Katz and Rewcastle[14] reviewed the 5-year biochemical disease–free survival of patients treated with brachytherapy, computed tomography, conformal radiotherapy, RP, and cryoablation for every report published in the past 10 years. Results were stratified according to whether patients had a low, medium, or high risk for biochemical failure. According to this analysis, the range of results for cryoablation was equivalent to that for all other treatments for low- and medium-risk patients and appeared to be superior for high-risk patients. Overall complication rates were similar for all modalities. The only report that directly compared cryoablation with RP, published by Gould,[15] showed that cryoablation was equivalent to RP in low-risk patients. However, as the preoperative PSA level increased, cryoablation results became superior to those of RP. The basis for this apparent superiority in high-risk patients might be the ability of cryoablation to treat extracapsular cancer extension and to be repeated if needed. On the basis of these results, one can conclude that cryoablation is safe and effective for the treatment of patients with prostate cancer, and that its inherent ability to be tailored to the extent of a patient's disease makes it a platform on which a treatment such as lumpectomy can be based.

Our early results on the use of focal cryoablation to treat patients with prostate cancer, as reported in *Urology*,[16] indicated that patients with unifocal prostate cancer can be successfully identified. Findings from additional patients and longer follow-up reported in the present study have confirmed our earlier results. Within the context of our mean follow-up of approximately 3.6 years, this approach has been successful in achieving local cancer control and has yielded equivalent results to those cited for whole-gland cryotherapy, as evidenced by stable PSA levels in 95% of patients. These results are particularly impressive in that 53% of our patients were at medium or high risk for cancer recurrence. This is very different from the other minimally invasive procedure for prostate cancer—brachytherapy—in that medium- and high-risk patients are no longer treated with brachytherapy alone owing to high local recurrence rates. It is also of great significance that, in contrast to breast cancer, in which adjuvant radiotherapy is considered a requirement for lumpectomy patients, thus adding to the complications and cost of treatment, the results reported here were obtained without additional radiotherapy.

One of the difficulties of focal therapy involves defining a successful result from the cancer recurrence point of view. In this procedure, it is known that variable amounts of prostatic tissue are left untreated. Depending on the degree of untreated tissue, one would expect to see a postoperative PSA reading $\geq$0.2 ng/mL. Just as in patients without prostate cancer, however, we would expect PSA stability (ie, no rise in PSA level over time in patients adequately treated). This criterion of PSA stability, coupled with 100% negative biopsy results (in the 26 patients who had stable PSA levels and who had undergone the 1-year routine biopsy), is consistent with commonsense clinical practice. With the use of these criteria, focal cryoablation resulted in a biochemical disease–free survival rate of 95% and a disease-specific survival rate of 100%. In addition, the efficacy of treatment of the index tumor in our patient population was evidenced by that fact that no patient experienced local recurrence in a treated area.

Results also indicated that our ability to properly choose those patients with unifocal disease is excellent. Only 4 patients (7%) had evidence of persistent cancer in areas of the gland that were untreated. We believe that critical to this success is the use of the transperineal 3D mapping biopsy of the full gland volume every 5 mm in the X, Y, and Z planes. Of 110 patients who had undergone staging based on this biopsy method, approximately 50% were found to have bilateral disease—as demonstrated on the 3-D mapping biopsy—that had been missed on the original transrectal ultrasound biopsy. Our 7% rate of clinically significant cancers missed is consis-

tent with the finding of 5% predicted through computer simulation of this biopsy method by Crawford *et al.*[10]

Our cancer control results were actually equivalent to, or even superior to, what one would expect for whole-gland cryosurgery or for other treatment modalities such as RP and the various forms of radiotherapy. This is particularly true when one considers that 53% of treated patients had a medium to high risk for recurrence. Although longer follow-up is certainly needed to fully assess whether these results will continue, the data, as illustrated by the Kaplan-Meier curve (Figure 1), have not yet indicated that the rate of failure will increase over time.

We believe that the initial excellent cancer control results attained can be attributed to several technical strengths of the procedure. Although the procedure is focal, it should be appreciated that it is still very aggressive in the areas that it does treat. If the index tumor is adjacent to known areas of potential extracapsular extension, such as the NVBs, these can be prophylactically treated by extending the freezing to encompass the periprostatic tissue in these locations, thereby minimizing the risk of local failure. This locally extensive freezing makes focal cryoablation an aggressive, yet conservative, treatment. Another factor that accounts for the success rate is the fact that treatment can be repeated when necessary. In our series, the 4 patients with evidence of persistent residual cancer all were treated successfully, and they were returned to a biochemically disease-free status. This potential for re-treatment is unique among prostate cancer treatments and represents 1 of the major safety nets that makes this cancer management strategy less risky than others.

The 2 major adverse effects of treatment that patients with prostate cancer fear the most are impotence and incontinence. Any minimally invasive prostate cancer treatment must minimize the incidence of these complications if it is to claim an advantage over available whole-gland treatments. The procedure we have described appears to fulfill the goal of a lumpectomy type of procedure in that extremely low morbidity results. Even in total-gland cryosurgical ablation, incontinence is seen in $<2\%$ of patients.[17] Incontinence, with our more minimal cryosurgical approach, would be expected to be negligible, because only a portion of each sphincter has the potential to be damaged. All but 1 of our patients was continent immediately, and that patient had previously undergone transurethral resection of the prostate—a situation that is known to increase the risk for incontinence associated with cryosurgical ablation. We believe this is a positive secondary effect of our attempt to improve potency; nerve-sparing RP can still result in incontinence rates as great as 6%, with many other patients gaining urinary control only after an extended period.[18]

The preservation of potency associated with focal cryoablation was better than we had expected. Of the 51 patients who could be evaluated for potency, 44 remained potent (85%) and satisfied with their sexual functioning. Nonetheless, because this was a retrospective study, in which standard sexual functioning questionnaires were not used, investigator bias and patient inclination to please the treating physician should be considered factors that may have affected reported results. To avoid local recurrence, only 1 NVB was spared in all our patients, making these results particularly interesting. Published data on nerve-sparing RP have shown a significant decrease in potency rates when 1 NVB versus 2 is spared,[19] with the usual potency rate for 1 NVB left at about 30%. Achieving high potency rates with our unilateral nerve-sparing procedure, without the risk of a positive margin on the tumor side, is an advantage of this procedure compared with bilateral nerve-sparing RP. These superior results for cryoablation and unilateral nerve sparing can be explained by the minimal vascular disruption associated with cryoablation and the lack of nerve manipulation and trauma associated with RP.

Focal cryoablation also seems to provide advantages over brachytherapy and external-beam radiotherapy. Different from brachytherapy, which is limited by whether patients have low-volume, low Gleason grade disease, our procedure is limited by whether disease is confined to 1 side of the gland, and not by other clinical parameters. On the basis of Gleason grade, PSA level, and disease extent, nearly 50% of the patients we treated would not have been candidates for brachytherapy alone.

Radiotherapy has not appeared to maintain its initial potency advantage over the long term. Potency rates after 2 years have been essentially equivalent to those reported after nerve-sparing RP.[20] Urinary tract complications of brachytherapy can have a significant effect on patient lifestyle.[21] Rectal complications, a major concern with radiotherapy, have been virtually eliminated in our procedure by separating the rectum and the prostate through saline injection into Denonvilliers fascia before freezing. In addition, available curative options for brachytherapy patients with local failure are limited. Finally, a major drawback of radiotherapy is that patients in whom radiotherapy fails have demonstrated a significant increase in Gleason grade and tumor aggressiveness in their recurrent cancer, and this has adversely affected patient survival.[22] This is not a favorable characteristic in a procedure that may be applied to a younger patient population.

At present, we are using cryoablation to provide cancer-targeted treatment because it has demonstrated long-term efficacy in the treatment of patients with prostate cancer. Other modalities, such as high-intensity focused ultrasound, will be investigated to determine whether they can produce equivalent results to those of focal cryoablation. Which ablation modality is used ultimately is less important than that a population of patients with prostate cancer can be identified and successfully treated through a "lumpectomy" approach. Undoubtedly, focal radiotherapy will be attempted as well. We believe that,

ultimately, radiotherapy will not be competitive with direct cancer ablation performed by other methods because of its lack of real-time feedback to guide treatment, the limitations of dose threshold (ie, the ability to repeat treatment after failure), and the inherent nature of radiation scatter, which makes damage to surrounding structures less predictable.

CONCLUSION

Study results reported here demonstrate that a procedure that targets the cancerous portion of the prostate (ie, a "male lumpectomy") can provide good cancer control while limiting patient morbidity. Additional prospective studies, with larger numbers of patients and longer follow-up periods, are needed to evaluate the full implications of such a treatment approach. During this time, when patients must choose between "watchful waiting" and high-morbidity whole-gland treatments, a lumpectomy approach, which has so markedly changed the management of breast cancer for women, would be a welcome option for the male cancer population.

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