“Male Lumpectomy”: Focal Therapy for Prostate Cancer Using Cryoablation

Gary Onik, David Vaughan, Richard Lotenfoe, Martin Dineen, and Jeff Brady

The introduction of breast-sparing surgery (ie, “lumpectomy”) revolutionized the management of breast cancer. The use of lumpectomy showed that quality of life of individual select patients can be successfully integrated into treatment without major loss of cancer treatment efficacy. 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.

From the Department of Radiology and Urology, Division of Surgical Imaging, Center for Surgical Advancement, Celebration Health/Florida Hospital, Celebration, Florida, USA (GO, DV, RL, MD, JB)

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Reprint requests: Gary Onik, MD, Department of Radiology and Urology, Division of Surgical Imaging, Center for Surgical Advancement, Celebration Health/Florida Hospital, 400 Celebration Place, Celebration, Florida 34747. E-mail: onikcryo@aol.com.

Current management covers both ends of the treatment spectrum. Patients can elect no treatment (ie, “watchful waiting”) 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

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doi:10.1016/j.urology.2007.06.001
5. To decrease the risk for urethrorectal fistula, just be-
4. Tissue temperature monitoring was performed in crit-
3. Cryoprobes were placed approximately 1 cm apart in
2. In all patients, an attempt was made to spare a single
1. The extent of freezing was tailored to the individual

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 accom-
modate 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 can-
cer 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 crit-
ical locations such as the apex and the NVB on the
side of the tumor to ensure adequate tumor destructive
freezing temperatures of ≥−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 be-
fore the start of freezing a 22-gauge spinal needle was
placed into Denonvilliers fascia through the transperi-
neal route. After adequate placement had been con-
firmed, 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 consid-
ered incontinent if they used pads at any time during the
day.

RESULTS
From June 1995 to December 2005, 93 patients under-
went cancer-targeted cryoablation. Of these, 55 had not
had radiotherapy failure and had undergone ≥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, ± 3.5), respectively. The
mean and median numbers of positive cores were 1.8 and
1 (SD, ± 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 ≥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 de-
privation 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 postop-
erative 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 postopera-
tively. In these 4 patients, biopsy revealed persistent
cancer in a previously unfrozen portion of the gland. All
4 patients were treated with additional cryotherapy, es-
sentially converting the procedure to a whole-gland
freeze. Afterward, all 4 patients had a stable PSA level,

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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 cm³, 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 cm³ 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 demonstration of a single focus with a single core of tissue may allow the possibility of focal therapy as an alternative to whole-gland removal.
tion of negative biopsy findings on the nerve-sparing side predicted negative margins at nerve-sparing RP. A recent report by Crawford et al., 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.

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. and Bahn et al. 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 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, 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, 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 ≥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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{20} Urinary tract complications of brachytherapy can have a significant effect on patient lifestyle.\textsuperscript{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.\textsuperscript{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.

References