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Original Article

Long-Term Results of Optimized Focal Therapy for Prostate Cancer: Average 10-Year Follow-Up in 70 Patients

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Abstract

Background: Following the lead of lumpectomy for breast cancer, focal therapy for prostate cancer was introduced in order to limit morbidity while providing good cancer control. Focal therapy is now an established trend in prostate cancer management, but long-term data have not been available. This report presents results on 70 patients treated with focal cryoablation, followed for an average of 10 years.
Methods: Between May 7, 1996, and December 28, 2005, seventy patients were treated with focal cryoablation. All patients were pre-staged using an additional prostate biopsy—either transrectal ultrasound (TRUS) biopsy or transperineal three-dimensional prostate mapping biopsy (3D-PMB). All patients were treated with focal cryoablation of the known tumor(s). Biochemical disease-free status was determined by the Phoenix criteria.
Results: Disease-specific survival was 64/64 (100%). Overall biochemical disease free survival (BDFS) was 62/70 (89%). BDFS results stratified according to the D'Amico criteria were: 8/9 (89%) high risk; 28/32 (88%) medium risk; and 26/29 (90%) low risk. There was no statistically significant difference between the risk levels. Of those patients staged by TRUS biopsy, 8 of 24 patients had a documented local recurrence (33%). Those staged by (3D-PMB), 2 of 46 (4%) patients had a local recurrence. Nine out of ten retreated local recurrences (90%) remain BDF. Continence after the first treatment was 100% (no pads). Potency after the first treatment was 94%, including retreatments was 74%.
Conclusions: The long-term cancer control results of focal cryoablation appears superior in medium- and high-risk patients to radical whole gland treatments. Focal therapy is associated with extremely low morbidity. If confirmed and applied widely, focal cryoablation could result in a substantial decrease in prostate cancer related mortality while offering a better post treatment quality of life.

Key words: prostate cancer; focal therapy; cryoablation; cryosurgery; male lumpectomy; 3D mapping biopsy

Introduction

The introduction of breast-sparing surgery (i.e., ''lumpectomy'') revolutionized the management of breast cancer. The use of lumpectomy showed that quality of life could be optimized without compromising treatment efficacy. In 2002, Onik et al. introduced the concept of focal therapy for prostate cancer (i.e., a male lumpectomy).[1] Following the lead of breast cancer management, the intention was to limit prostate cancer treatment morbidity while maintaining good cancer results. A number of short-term studies regarding focal therapy using a variety of ablation methods have been reported, confirming that incontinence can be virtually eliminated as a complication of prostate cancer treatment and that potency can be maintained in up to 85% of patients.[2–5] These results have now established focal therapy as a major trend in

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prostate cancer management, resulting in the publication of scientific articles and topical textbooks, and the convening of international scientific forums and consensus conferences of experts to define the approach.[6–8]

No long-term data on patients who have undergone focal therapy, however, have yet been available. The two seminal questions associated with the strategy have always been (1) what is the cancer control efficacy of focal therapy compared with radical treatments, and (2) which patients might benefit from this conservative approach. In this study we will present the first long-term data on 70 patients at a single center who underwent focal therapy for prostate cancer using cryoablation and who have been followed for an average of 10 years. This is the longest such series reporting results on focal therapy for prostate cancer. Also unique is that this is the first series in which the concept has been applied to patients with locally extensive cancer and high Gleason scores—patients previously reserved for radical treatments. We also present our unique method for focal therapy, which has been optimized in our ongoing experience to provide the theoretically best cancer control results possible.

Methods

Patients were considered for cancer-targeted cryoablation if they had biopsy-demonstrated prostate cancer and if the maintenance of potency and/or continence was a major concern of the patient. Usual cryosurgical informed consent was given, which included discussion of incontinence, tumor recurrence, and rectal fistula. All patients were informed of the additional risk of tumor being left untreated in any tissue not frozen. In addition, patients after February 1, 2000 signed an additional Florida Hospital Institutional Review Board–approved consent for this study.

All patients were staged for focal cryosurgery using an additional prostate biopsy. A repeat biopsy on the side opposite the demonstrable cancer was carried out to exclude bilateral disease, initially with transrectal ultrasound (TRUS) biopsy and then later (after March 19, 2002) with three-dimensional prostate mapping biopsy (3D-PMB). 3D-PMB was carried out according to methods previously reported by Onik et al.[9] To summarize, under general anesthesia, biopsy needles were inserted transperineally into the prostate gland using a brachytherapy grid, guided by TRUS imaging. The biopsies were taken under sterile conditions. The samples were obtained at 5-mm intervals throughout the volume of the prostate. Each sample was labeled as to its exact coordinates, and the specimens were inked so that the proximal and distal location and orientation of each specimen was known. This allowed the pathology results to be correlated with the ultrasound (US) image to reconstruct a 3D picture of the extent and exact location of the patient's cancer. Specimens were processed according to the optimization principles elucidated by Bostwick et al.[10] All specimens were read by a specialist in uropathology and confirmed by a secondary read carried out by Bostwick Laboratories. Patients with Gleason 8 or above were placed on neoadjuvant androgen deprivation therapy (ADT) for 6 months prior to the procedure. All patients were removed from ADT after the procedure.

Procedure

The ultrasound-guided percutaneous prostate cryoablation procedure was the same as that described originally by Onik et al.[11] All patients were treated in a collaborative approach with an interventional radiologist who was fellowship-trained in US guided interventions and a urologist. The following changes were made to the procedure to accommodate the concept of tumor targeting and to increase the safety and efficacy of the procedure:

1. The extent of freezing was tailored to the particular patient and was determined by the patient's clinical parameters, which included Gleason grade, stage, prostate-specific antigen (PSA) level, and extent and location of cancer on preoperative biopsies. A margin of at least 5 mm was obtained around the coordinates of the known tumor based on the mapping biopsies. Ablation was carried out in all known areas of cancer, regardless of whether they met the criteria for a significant tumor or not. At no time was any cancer knowingly left untreated, even if it meant treating focal areas bilaterally.
2. In all patients, an effort was made to spare one neurovascular bundle (NVB) on the side opposite the tumor. The NVB was destroyed on the side of the patient's tumor if the biopsy showed cancer within a centimeter of the NVB.
3. Cryoprobes were placed approximately 1 cm apart in the regions 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 with the intent to prophylactically prevent seminal vesicle recurrence in those patients who demonstrated positive midline biopsies posterior to the urethra. Cryoprobes were placed in a free-hand method, which allowed orientation of the probes to optimally conform to the area treated. This is significantly different than the template approach used by most practitioners of cryosurgery.
4. Tissue temperature monitoring was carried out in critical locations such as the apex of the gland and the neurovascular bundle on the side of the tumor to ensure adequate tumor destructive freezing temperatures of minimum -35°C for at least two freeze–thaw cycles. When a tumor was of a Gleason grade 7 or greater or adjacent to the urethra, three freeze–thaw cycles were carried out to a temperature of at least -20°C. We eventually reverted to the three freeze technique in all cases, since it results in less tissue volume destroyed to obtain cancer destruction. Thermocouples were also placed at the outer margin of the known coordinates of the tumor to ensure adequate destructive temperatures at the tumor margin itself. The temperature of the NVB opposite the tumor and the area of the external sphincter were also monitored to prevent complications associated with these structures.
5. In order to eliminate the chance for a urethrorectal fistula and to ensure the ability to gain adequate tumor temperatures at the capsule when tumors were adjacent to Denonvillier's fascia, a 22-gauge spinal needle was placed into Denonvillier's fascia via a transperineal route just prior to the start of freezing. Once noted to be in an adequate position, normal saline was injected into the space separating the rectum from the prostate. The space was maintained by continued down-

ward pressure of the transrectal ultrasound transducer consistent with the technique previously reported by Onik et al.[12]

6. An argon gas based system was used to carry out the freezing (Healthtronics), replacing the original liquid nitrogen freezing equipment.
7. A Foley catheter was left in place for a variable amount of time after the procedure depending on the extent of freezing, replacing the previous suprapubic tube.

Patient follow-up

All patients previously on ADT were removed from therapy after the procedure. A PSA was obtained every 3 months for the first 2 years and then every 6 months thereafter. Patients were considered to be biochemically disease free (BDF) if they had a stabilized PSA using the Phoenix criteria (Nadir +2 ng/mL). All patients were advised to have routine biopsies of both treated and untreated gland sides at 1 year, regardless of their PSA stability. Biopsy was carried out on any patient who had evidence of disease progression on PSA, using a 3D-PMB once that option became available. Any patient with demonstrated localized recurrent disease was offered repeat cryoablation or an alternative therapy such as radical prostatectomy or radiation.

During our early experience patients were kept overnight in the hospital; we subsequently determined that the procedure could be routinely carried out on an outpatient basis. All patients were placed on an aggressive potency rehabilitation program consisting of oral agents, a vacuum erectile device used daily, and for patients who had neoadjuvant hormone therapy, penile injection therapy.

Patients were followed up by written questionnaire and phone call. For this article, each patient was called personally to obtain the latest PSA results and assess for complications. Patients were considered potent if they had erections sufficient for vaginal penetration and they were satisfied with their sexual functioning, whether or not they were on oral agents. Patients using any other potency aids were considered impotent. Patients were considered incontinent if they used any pads at any time.

Statistical methods

All statistical methods were performed using JMP Pro 10 (SAS Inc.). No samples were excluded from the analyses. Samples were grouped as low, medium, and high risk according to the D'Amico classification. To test for differences in prostate cancer recurrence among groups, a chi-square analysis was used and the Pearson chi-square value reported. The survival function in JMP Pro 10 was used to generate the Kaplan-Meier plots for biological disease free survival.

Patient demographics

Seventy-six consecutive patients who had focal cryoablation were evaluated for this study. Six of these patients (6/76, 7.8%) were lost to follow-up despite major efforts to contact them over a 2-month period, which included attempting to contact patients according to last known phone and address in patient records, contact of known relatives included in patient records, search of online social networking sites, search of online ''people find'' databases, search of online obituary databases, and cancer registries. They constituted five patients in the low risk category and one patient in the high risk category. All were biochemically stable at their last follow-up approximately 4 years prior to this publication, in 2009.

The 70 patients whom we were able to locate and interview constitute the patient population for this study. All have at least 8 years follow-up (ranging from 8 to 18 years with a mean follow-up of 10.1 years). The ages at time of treatment ranged from 45 to 77 years, with an average of 62.3 years. Stage was T1c in 56 patients, T2a in 6 patients, T2b in 3 patients, T2c in 4 patients and T4 in one patient. Forty-one patients were Gleason 6 or less, 24 were Gleason 7 (6 patients 4 + 3, 18 patients 3 + 4), and 5 patients were Gleason 8 or greater. Fifty-five patients had a PSA <10 at diagnosis, 13 patients between 10 and 20, and 2 patients greater than 20. We stratified the 70 patients using the D'Amico classification. By these criteria, 29 (41.4%) were low risk, 32 (45.7%) were medium risk, and 9 (12.8%) were high risk (Table 1).

Results

Overall actuarial survival was 66 of 70 (94%). Disease-specific survival was 66 of 66 (100%). Overall biochemical disease free survival (BDFS) was 62 of 70 (89%); BDFS for high risk patients was 8 of 9 (89%), BDFS for medium risk patients was 28 of 32 (88%), and BDFS for low risk patients was 26 of 29 (90%) (Fig. 1). Return of prostate cancer did not statistically differ among the three groups (chi-squared = 0.071, degrees of freedom [DF] = 2, $p = 0.965$).

Twenty patients (20/70, 28.5%) patients had bilateral multifocal disease that required bilateral focal freezing at their first procedure; of those, 19 of 20 (95%) were BDF. In total, 10 out of 70 (14%) patients had a local recurrence that needed treatment, and 9 of 10 (90%) remain BDF. Seven patients (7/70, 10%) were retreated with cryoablation to the opposite side of the original procedure, and all (7/7, 100%) are BDF. Two patients with local recurrence underwent

Table 1. Patient Demographics

Patients	70	
Follow-up	8–18 years	Mean 10.1 years
D'Amico risk level		
Low	29 (41.4%)	
Medium	32 (45.7%)	
High	9 (12.8%)	
Gleason score		
≤6	41 (58.5%)	
7	24 (34.2%)	
≥8	5 (7.1%)	
Stage		
T1c	56	
T2a	6	
T2b	3	
T2c	4	
T4	1	
PSA level at diagnosis		
<10	55	
10–20	13	
>20	2	

PSA, prostate-specific antigen.

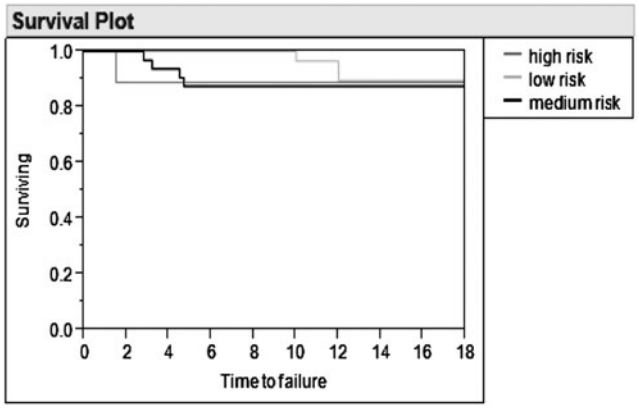

FIG. 1. Kaplan Meyer plot with biochemical disease free survival (BDFS) according to the D'Amico criteria for risk level (time to failure in years).

radiation and both are BDF. One patient underwent a radical prostatectomy and radiation and is now on ADT. All patients that were biochemical failures ultimately had negative biopsies and either demonstrated gross evidence of metastatic disease or are presumed to have micrometastatic disease.

In the 24 patients pre-staged with TRUS biopsy, 8 had local recurrence (33%). The distribution of freezing extent in the group was as follows, focal $n=1$, 1/2 gland $n=13$, 3/4 gland $n=4$, full gland with just one nerve spared $n=6$, and in the 46 patients pre-staged with 3D-PMB, 2 had local recurrence (4%) The distribution of freezing extent in this group was focal $n=35$, 1/2 $n=9$, 3/4 $n=2$, full gland with just nerve spared $n=0$. The rate of local recurrence between the two groups was clinically and statistically significant (chi-squared = 10.821, DF = 1, p-value = 0.0010).

Of the 70 patients, 65 had one nerve spared, 4 had both NVBs spared, and one had neither NVB spared. Twenty-four patients had routine follow-up biopsies, of which all were negative. In the 10 treated for local recurrence all were positive on the opposite side of the treatment. There were no positive biopsies in the area that was treated (Table 2).

Morbidity

All patients were continent with no pads immediately after the first procedure (100%). One patient who converted on a second procedure to a whole gland freeze had mild stress incontinence requiring pads while playing golf.

TABLE 2. PATIENT RESULTS

Overall actuarial survival $n=70$	66/70 (94%)
Disease-specific survival $n=66$	66/66 (100%)
Biochemical disease-free survival	62/70 (89%)
BDFS high risk (D'Amico)	8/9 (89%)
BDFS medium risk (D'Amico)	28/32 (88%)
BDFS low risk (D'Amico)	26/29 (90%)
Bilateral multifocal	19/20 (95%)
Local recurrence $n=10$	9/10 (90%)
Continent after primary procedure	70/70 (100%)
Retained potency (includes retreatment)	43/58 (74%)

BDFS, biochemical disease-free survival.

As to potency, focal therapy did extremely well. Of the 70 patients, 58 (83%) were potent preoperatively (pretreatment baseline function). Of these 58, 54 (94%) were potent postoperatively with or without the use of oral agents, to their satisfaction, within 6 months. However, 11 of 58 patients (20%) were ultimately rendered impotent by additional treatment (7 by additional cryoablation, 4 by a combination of ADT, radiation, and/or radical prostatectomy). Thus, 43 of 58 potent patients (74%) ultimately retained potency. Of the 43 potent patients, 29 (67%) were using phosphodiesterase type-5 inhibitors. Of the 43 potent patients, 3 had both NVB spared (3 of 4 total with bilateral sparing). The remaining 40 patients had only one NVB spared. These results are consistent with other focal therapy series.

Discussion

Four basic cancer management principles have been developed over decades and accepted by the oncologic community:

1. Screen for the disease with as sensitive a test as possible,
2. Definitively diagnose with the highest diagnostic yield,
3. Stage the cancer accurately, and
4. Treat aggressively, tailoring the treatment to the stage of disease.

The high complication rates associated with standard radical prostate cancer treatments and the evidence that many prostate cancer are not clinically significant, and will ultimately not cause patient mortality, have led to screening, diagnostic, staging and management strategies for prostate cancer that are markedly at odds with these principles.

Finding prostate cancer early offers patients the greatest number of therapeutic choices. However, early detection has become difficult due to new guidelines against routine PSA screening by U.S. Preventive Services Task Force, a volunteer panel of medical professionals that ruled against wide use of a simple and effective screening tool.[13]

The method used for diagnosis and staging, TRUS biopsy, is still standard practice despite evidence that it misses up to 46% of significant cancers and has been shown in level one data to be inferior in diagnostic and staging capabilities to the alternative of 3D-PMB.[9] In addition, the fear of the complications of radical treatments has led to wider use of active surveillance (i.e., waiting until cancer shows progression to finally act). This strategy is unprecedented in cancer management.[14]

It is our thesis that if the treatment for prostate cancer could be accomplished with markedly reduced morbidity while maintaining good cancer control, the major dilemma in the treatment of prostate cancer would be solved and a return to established cancer management principles might then be accomplished.

The main conceptual objection to focal treatment is that prostate cancer is often a multifocal disease. Prostate cancer, however, is a spectrum of diseases, some of which may be amenable to focal therapy. The prostate cancer pathology literature shows that a significant number of patients have a single focus prostate cancer and that many others have additional cancer foci that may not be clinically significant.[15–18] Until the

concept of focal therapy was proposed, however, little attention was paid to differentiating those patients with unifocal disease from those with multifocal disease, since all treatments aimed at total gland removal or destruction.

In a study examining radical prostatectomy specimens, Djavan et al. showed that patients with unifocal disease constituted nearly one third of the cases.[15] In addition, Villiers et al. showed that 80% of multifocal tumors were less than 0.5 cc.[16] In Stamey's Stanford group and Noguchi et al., pathologic examination showed that unifocal tumors were present in 20% and 25% of patients, respectively; using the size criteria of 0.5 cc or less as an insignificant tumor, an additional 60% and 39% of patients, respectively, might be candidates for a focal treatment approach.[17] Based on this pathological evidence, an opportunity exists to investigate a focal treatment approach for prostate cancer.[18] A recent study looking at the findings of 3D-PMB on the selection of patients for focal therapy showed that 94% of patients might be a candidate for some variation of a focal therapy approach.[19]

Many prostate cancers do not affect patient longevity, and there is a high prevalence of prostate tumors in autopsy series of patients who have died of other causes.[20] As already mentioned, 0.5 cc tumor volume has been suggested as a cutoff for tumor significance. There is controversy about this definition and what the criteria should be. As we learn more about tumor phenotyping, hopefully further light will be shed on how to fully define and thus identify the cancer that has minimal chance for progressing.[21]

Our approach to focal therapy was based on the conservative principle that we will use the most sensitive method in fully staging the patient prior to performing focal therapy, in order to find as many tumors as possible, and characterize them as accurately as possible according to Gleason grade and stage. We considered all cancer identified as significant regardless of its size on biopsy, and therefore any known cancer was treated. We feel that at this point in the evolution of focal therapy, no compromise on this principle should be considered.

At this time the most accurate method for staging patients for focal therapy is the 3D-PMB. Crawford et al.,[22] using computer simulation on radical prostatectomy (RP) and autopsy specimens, demonstrated that transperineal prostate biopsies, spaced at 5-mm intervals throughout the volume of a patient's prostate, had a sensitivity of 95% in finding clinically significant tumors 0.5 cc or greater. A follow-up study recently published in which the results of actual 3D-PMB biopsies were compared to whole mount radical prostatectomy specimens confirmed these results, with 96% of clinically significant tumors (Gleason 7 or greater, volume >0.5 cc) identified by 3D-PMB.[23]

Onik et al. showed the impact of 3D-PMB on the staging of prostate cancer vs. standard TRUS biopsy in 180 patients that all had unilateral tumors on TRUS biopsy.[9] All patients had a repeat 3D-PMB for staging purposes. In this series, 61% of patients after 3D-PMB were determined to have additional cancer on the previously negative side as determined by earlier TRUS biopsy. In addition, 23% of patients were upgraded to a Gleason 7 or greater. In this series, complications related to 3D-PMB were self-limited, with 7.7% requiring short-term Foley drainage and two patients with hematuria, only one of which required bladder irrigation.

Barqawi et al. confirmed the importance of 3D-PMB in staging prostate cancer. In his experience with 180 patients, all of whom were categorized as low risk by TRUS biopsy using the Epstein criteria, 27% percent were upgraded to Gleason 7 or above and 45% were upstaged.[24] Morbidity was again low and self-limited, with 3% requiring transient Foley catheter drainage. Taira et al. also demonstrated the value of 3D-PMB in staging; in their study, all patients met the Epstein criteria for low risk disease and 3D-PMB showed that 71.9% had clinically significant cancer; of patients with cancer, 66.1% had bilobar involvement and 44.6% harbored a Gleason score of 7 or above.[25] Bittner et al. studied 485 patients all of whom had at least one negative TRUS biopsy (45% had two or greater).[26] Cancer was ultimately detected in 226 patients (46.6%) using 3D-PMB method, including 196 (86.7%) with clinically significant disease according to the Epstein criteria. Lastly, Tsivian et al. looked at the morbidity of 3D-PMB, finding results consistent with the other studies but adding the knowledge that 3D-PMB had no effect on the erectile function of patients.[27]

3D-PMB provides better cancer detection and staging than TRUS biopsy but it is the ability of 3D-PMB to provide superior localization of the tumor site over TRUS biopsies that we found essential in carrying out focal therapy. Our protocol was to process each sample separately with its exact coordinates recorded and able to be later correlated with a grid displayed over the US. Each core was inked on its proximal end and labeled as to base and apex (some locations needed two biopsies from the same coordinates to cover the length of the gland). Other centers using 3D-PMB to stage for focal therapy, in an effort to limit pathology costs, grouped their pathology into zones.[28] We found this method to be inadequate for truly targeted tumor destruction rather than destruction of half a gland (hemi-gland treatment). This information allowed us to guide the focally destructive agent to optimize destruction of the tumor while limiting the area that needed to be treated, thus minimizing the chance for side effects and optimizing cancer results.

These theoretical reasons for using 3D-PMB for the staging of focal therapy are supported by the data presented on the impact of 3D-PMB on the local recurrence rates we reported. In 24 patients staged with just a TRUS biopsy, recurrent disease was later discovered in 33% (Fig. 2). Only 4% staged with the 3D-PMB however demonstrated recurrent cancer. This is consistent with a recent focal therapy series by Bahn and colleagues,[4] who using only TRUS biopsy for staging later discovered residual disease in 25% of his focally treated patients. In addition, since the greatest impact on potency (94% decreasing to 74%) is caused by the need for re-treatment, the impact of 3D-PMB on potency preservation by focal therapy may be substantial.

Even when carrying out a 3D-PMB, certain technical issues must be addressed to gain optimal results. In an effort to minimize costs, some authors have grouped biopsy cores into zones within the prostate rather than place each specimen in a separate vial with its exact location indicated.[28] Exact targeting of the tumor is therefore not possible which leads to having to destroy the whole prostate lobe (hemiablation). We believe that although at first appearing as the more conservative approach, hemiablation will not yield the same cancer control results due to compromise in placing probes to destroy normal tissue rather than targeting the cancer for optimal tumor destruction (Fig. 3). As can be seen by our data the use of 3D-PMB shifted our extent of freezing from hemiablation in the

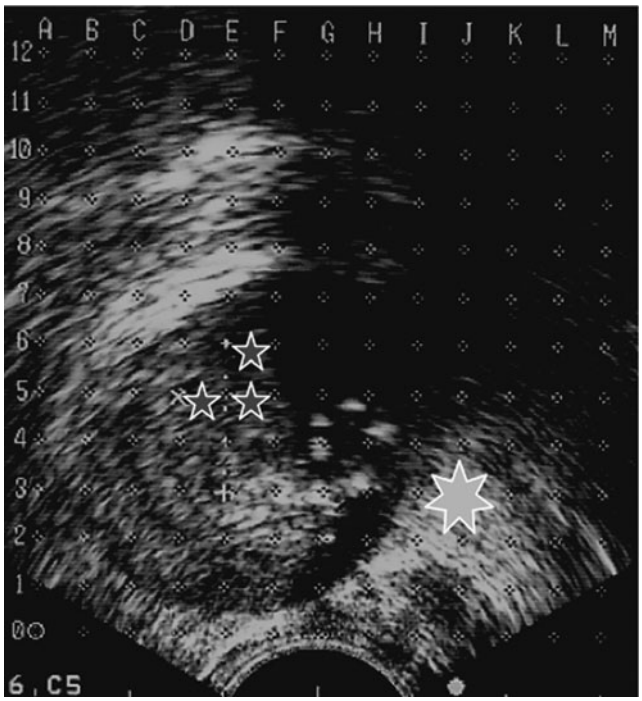

FIG. 2. Patient originally treated with a Gleason 6 on the left side (right side of this ultrasound [US] scan) demonstrated by transrectal ultrasound biopsy; 6 years post treatment had a rise in prostate-specific antigen (PSA) level. A mapping biopsy revealed a recurrent tumor in the anterior right gland (in three cores, three small stars). The large star shows the area of previous treatment. The left side of the gland has completely resorbed. The anterior right gland was retreated and the patient remains disease free 5 years later.

majority of cases prior to 3D-PMB to a focal approach (just ablation of the cancer focus) after 3D-PMB.

Some groups are suggesting multiparametric (mpMRI) for staging and guiding focal therapy of prostate cancer. A study by Delongchamps et al. comparing mpMRI to the gold standard of whole mount radical prostatectomy specimens show that its sensitivity for picking up clinically significant tumors in the peripheral zone of the prostate was 85% and just 62% in the transition zone.[29] These results were confirmed in a study by Bratan et al. comparing mpMRI in 175 patients with radical prostatectomy specimens. Detection rates for tumors of <0.5 cc was 45 per 155 (29%); for tumors 0.5–2 cc, the rate was 19 per 35 (54%); and for tumors >2 cc the rate was 9 per 12 (75%).[30] A study by Abd-Alazeez et al. comparing mpMRI to 3D-PMB showed that the specificity for finding any cancer was just 28% and for Gleason 7 or greater just 20%.[31] Based on these data, mpMRI clearly does not meet the standard for solely guiding or staging for focal therapy.

Partial removal or lumpectomy of the prostate by surgical means is not technically feasible. Therefore, tumor destruction by another modality is needed to carry out a ''lumpectomy'' in a male. Cryoablation is the obvious choice since it has a long history of effective tumor treatment in various parts of the body. The early difficult start that prostate cryoablation experienced has been largely mitigated by major technical advances in the procedure, such as improved urethral warmer design and argon based cryosurgical systems with greater freezing control. Cryoablation has now been shown to be an effective and safe alternative in treating prostate cancer involving the whole gland. In July 1999, prostate cryoablation was approved by Medicare as a treatment for primary prostate cancer (removing it from the investigational category). Level-one evidence is now available on the efficacy of cryoablation. Donnelly et al. reported in 2010 a randomized study of 244 patients to either cryoablation or external beam radiation therapy.[32] The median follow-up was 100 months. Of interest is that 92% of patients were in the medium and high risk categories. Disease progression at 36 months was observed in 23.9% (PSA nadir + 2 ng/mL) of men in the cryoablation arm and in 23.7% (PSA nadir + 2 ng/mL) of men in the radiotherapy arm. No differences in overall or disease-specific survival were observed. At 60 months, the observed failure rates in the two groups were equal, but at 84 months, the observed difference was in favor of cryoablation. At 36 months, more patients in the radiotherapy arm had a cancer-positive biopsy (28.9%) compared with patients in the cryoablation arm (7.7%) It should also be noted that in the cryoablation arm 6 patients remained disease free 7 to 9 years later after a retreatment with cryoablation (one of the major advantages of this type of therapy) but were counted as failures based on the criteria

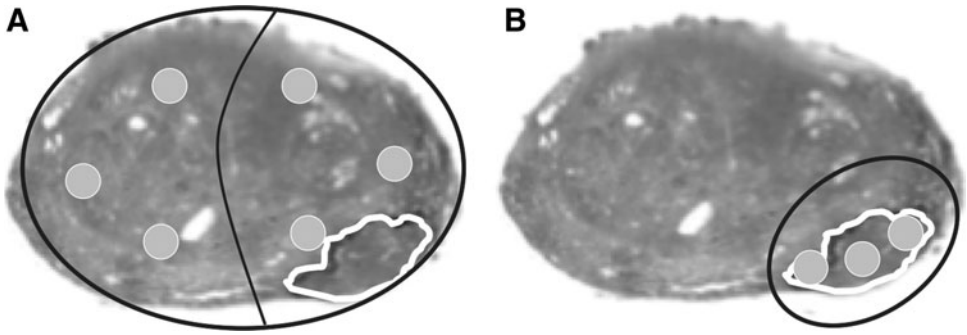

FIG. 3. Whole-mount radical prostatectomy specimen. The white outlined area at the left posterolateral margin of the prostate is a focal prostate cancer. **(A)** Placement of six cryoprobes (gray dots) for total gland ablation. By schematically bisecting the gland (dark line down the center), the three gray dots in the side containing tumor represent a hemicryoablation that would destroy that side of the gland and the tumor with it. The cryoprobes are not arranged optimally to destroy the tumor. **(B)** The exact position of the tumor is known by 3D-PMB. The three cryoprobes are arranged to optimally destroy the tumor while encompassing far less tissue.

accepted at the start of the study. The authors concluded that the long-term trend in the data favored cryoablation.

The only article directly comparing full gland cryoablation with radical prostatectomy, published by Gould, showed cryoablation to be equivalent to RP in low risk patients, but as a patient's preoperative PSA increased, cryoablation results were superior to RP.[33] The basis for this apparent superiority in high risk patients may be the ability of cryoablation to treat extra-capsular extension of cancer and the ability to be repeated if needed.

Based on these results, one can conclude that cryoablation is a safe and effective treatment for treating prostate cancer; that its utilization in treating high risk cases is a reasonable alternative, with some evidence showing it may be a preferred method; and lastly, that its inherent ability to be tailored to the extent of a patient's disease makes it a platform upon which a treatment such as focal therapy (i.e. lumpectomy) can be based.

We feel our study population reflects a fair cross section of what would be expected from a usual prostate cancer practice. Our selection of patients covered all D'Amico risk levels with 58% of our patients falling into medium to high risk categories (which is very similar to the patient risk distribution seen in the long-term study on intensity modulated radiation therapy [IMRT] by Alicikus et al.)[34] Our patient population was very different than the current recommendations made by most authors, defining the ideal patient population for focal therapy as low risk patients, basically looking upon focal therapy as an extension of the active surveillance approach. Based on the superior results in high risk whole gland data already alluded to,[35] we felt justified in exploring the utilization of focal therapy on all risk levels of prostate cancer patients.

In this regard, our results appear to be unique. We showed no statistically significant difference in BDFS rates between the D'Amico risk classes with the low risk group at 90%, medium and high risk groups having 88% and 89% BDFS, respectively. This is the first time to our knowledge that equivalence of cancer control in all risk levels has been reported in long-term follow-up with a treatment for localized prostate cancer.

When compared to other series in length of follow-up and success criteria to our study, focal cryoablation has a decidedly better BDFS than either IMRT alone or robotic radical prostatectomy in all risk groups, but particularly medium and high risk patients.[34,36,37]

In a 10-year follow-up study on high dose IMRT, conducted at the Memorial Sloan Kettering Cancer Center, BDFS was 81% for the low risk group, 78% for the medium risk group and for the high risk group 62%. Both our study and the MSKCC study used the same Phoenix criteria for success.[34]

Similar long-term results are seen for robotic radical prostatectomy. One large study, recently publish by Ginzburg et al. on the positive margin rates of robotic radical prostatectomy showed positive margin rates of 23% in low risk patients and 28.6% and 41.7% respectively in medium and high risk patients.[37] At just 5 years the overall BDFS rate was 72%. These are under appreciated immediate failure rates for what is considered the gold standard for prostate cancer treatment, and significantly lower compared to our long-term disease free survival results.

While not every positive margin results in biochemical failure, data now confirm that margin status does affect survival. This has prompted the American Society for Radiation Oncology/American Urological Association to issue guidelines that adjuvant radiation therapy should be offered to those with positive margin status.[38] Considering the large number of positive margin status patients, this is another major source of additional morbidity to patients and cost to the delivery of prostate cancer care.

Why all risk levels of patients having focal cryoablation would manifest the same cancer control results might have a number of possible explanations that include:

1) Cryoablation works with equal effectiveness in destroying both low and high Gleason score disease. This is very different than radiation in that higher Gleason score, more aggressive tumors are relatively more radio-resistant than less aggressive tumors. With cryoablation there is no dose threshold. If a more aggressive cancer is encountered increased effectiveness of the treatment can be carried out by adding an additional freezing cycle. In this study there was no instance in which we could demonstrated a local failure in an area treated.
2) Cryoablation can be repeated if a local failure does occur or recurrent cancer is demonstrated in a region left untreated. In our study 9 out of 10 patients that demonstrated locally recurrent disease were BDFS after re-treatment. This is unique to prostate cancer treatments and its possible effect on disease free survival should not be underestimated. Focal cryoablation has an ability to treat extra-capsular disease. Patients at high risk for positive margins at prostatectomy have a better chance of local control with ablative therapy. This was very well illustrated by one of our patients who had a T4 lesion already invading the bladder base, a PSA of 200, and a Gleason score of 10. He is now 8 years out from his focal cryoablation with no evidence for recurrence (Fig. 4). In our technique we always prophylactically treated the extracapsular region in areas of potential spread. This included freezing the NVB on the side of the lesion if the cancer was within 1 cm of the NVB and freezing the central seminal vesicles if tumor was noted in the midline and had access to the midline ejaculatory ducts. We also have used a localized removal of urethral tissue in some patients who had tumor next to the urethra, when there was concern that the urethral warmer might prevent a completely destructive freeze at that site.
3) A cryoimmunological response must also be considered for these results in medium and high risk patients. Based on the human and animal data, it is likely that in some patients there is exposure of tumor antigens at the time of the procedure that acts as an in vivo cancer vaccine, preventing later metastasis from occurring.[39] Ablin et al. first reported the spontaneous remission of metastatic prostate cancer after freezing of the primary tumor for palliation.[40] Recent studies using cryoablation with immune enhancing therapies such as ipilimumab (Yervoy®) and dendritic cell therapy have shown that the combination of cryoablation with either, to be synergistic in its effect to prevent distant metastasis, more so than either cryoablation or the other therapies alone.[41,42] This raises the possibility of interesting future adjuvant strategies in high risk patients.

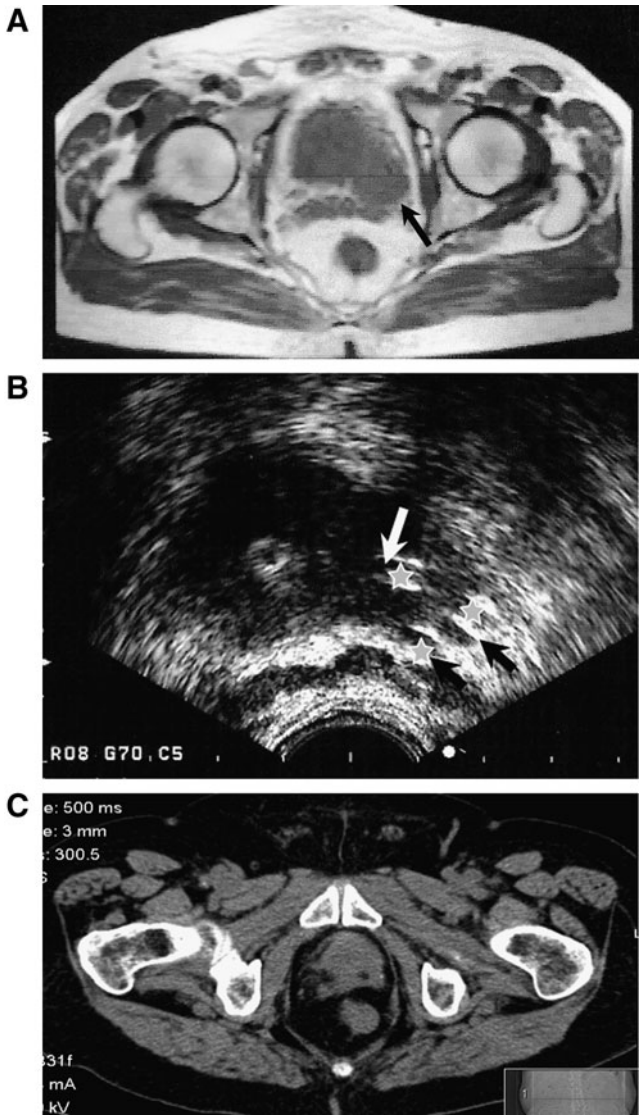

FIG. 4. **(A)** Large prostate tumor growing into the seminal vesicles and the base of the bladder (arrow). The patient had a PSA of 200 and a Gleason score of 10. He was treated with neoadjuvant androgen deprivation therapy. His PSA never dropped below 1.5 ng/mL, indicating that his tumor was hormone independent. The upper right quadrant of the gland was not involved with tumor and was not included in the treatment. **(B)** Transrectal US during the procedure on the same patient showing three cryoprobes (stars and arrows) within the extraprostatic tumor. A stent was placed into the left ureter to protect it from damage. **(C)** Computed tomography scan of the region 3 years post operatively. The mass is gone leaving residual scar tissue. At 8 years post procedure, the patient's PSA remains at 0.2.

Our results also confirm that treating multiple cancer foci bilaterally in a focal manner is possible and provides equivalent results. In our study, 19 of 20 patients treated with multiple foci on both sides of the gland were biochemically disease free. All of these patients fell into the 3D-PMB biopsy group after we began using that as our staging method.

It is should also be noted that unlike breast cancer where adjuvant radiation therapy is considered a requirement in lumpectomy patients, thus adding to the complications and the cost of treatment, our results were obtained without any additional radiation therapy.

Certainly, any minimally invasive prostate cancer treatment must minimize the incidence of impotence and incontinence, if it is to claim an advantage over the present radical whole gland treatments. The procedure we describe fulfills the goal of a lumpectomy type procedure by having extremely low morbidity. Even in total gland cryosurgical ablation, incontinence is seen in less than 3% of patients.[43] Incontinence with our more minimal cryosurgical approach would be expected to be negligible since only a portion of either the internal or external sphincter has a potential to be damaged. All of our patients were continent with no use of pads immediately after the first treatment. This is consistent with other reported series with focal therapy by cryoablation and appears to be a consistent reproducible result based on the careful monitoring of freezing temperatures in the area of the external sphincter and only partial damage.[3,44]

In contrast to these results, a recent systematic review and meta-analysis of urinary continence recovery after robotic radical prostatectomy by Ficarra et al. included 51 articles dealing with robotic radical prostatectomy.[45] The 12-month urinary incontinence rates ranged from 4% to 31% with a mean of 16% using a ''no pad definition'' similar to that used in this study. It should also be noted that the 12-month incontinence rate suggests many patients endured incontinence for some portion of the year post operatively before they become dry.

Patients who undergo IMRT have both urinary and bowel side effects to consider. In the study from MSKCC, the ten year likelihood of developing grade 2 and 3 late genitourinary complications was 11% and 5% respectively (in the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer [RTOG/EORTC] classification a grade 2 urinary complication is defined as frequency of one to two times per hour during the day and nocturia four to six times per night, moderate dysuria, or intermittent heamaturia requiring medication.[34] A grade 3 urinary complication is defined as nocturia greater than six times per night, severe dysuria, urethral strictures requiring TURP, dilatation, suprapubic or permanent catheterization.)

In the same series, late grade 2 and 3 bowel complications occurred in 2% and 1% of patients respectively. In the RTOG/EORTC classification, a grade 2 bowel complication is defined as moderate intermittent diarrhea, severe cramping, increased bowel movements five times per day, rectal discharge intermittent, frequent bleeding requiring three single laser treatments or transfusions. A grade 3 bowel complication includes watery diarrhea, bleeding requiring surgery.

The preservation of potency associated with focal cryoablation is better than we had expected, with 74% of our patients satisfied with their sexual functioning. This includes patients who were retreated. The lack of a standard sexual function questionnaire administered to our sample remains the weak point of our documentation; additionally, investigator bias as well as patient inclination to please the treating physician must be considered as possible factors affecting the results herein reported. These results, however, have been reproduced by other investigators in other focal therapy series.[3,44] In addition, we fall well within the range of potency reported for robotic radical prostatectomy. Ficarra et al. reported a meta-analysis of 15 series of robotic radical prostatectomy. In this series the

12-month potency rates ranged from 54% to 90% and the 24-month potency rates 63% to 94%.[46]

A potency comparison with radiation is more difficult since immediate impotence is not the issue. Since potency declines over years, following radiotherapy, longer longitudinal studies would reveal more accurate post-radiation data. In the 10-year follow-up IMRT article, the potency rate was 54%.[34]

Other major complications did not occur in our series. There was no blood loss, and no rectal complications nor side effects were noted. When the full range and extent of complications of the radical therapies, such as full gland radiation by various means, robotic radical prostatectomy and full gland cryoablation are considered, focal therapy as we described it has far less morbidity.

Since this is the first long-term study reported for results of focal therapy, a major question has to be how reproducible will these results be. As already stated, short-term studies have confirmed the low morbidity rates reported here but questions still have to be raised about cancer results, particularly in the results we have reported in the medium and high risk groups. In a large study with short-term follow-up reported by Ward et al., data on 1160 patients drawn from the Cryosurgery Online Database registry showed that focal cryosurgery is markedly growing in use vs. whole gland treatment.[47] In that report, the distribution of patients into risk groups was virtually identical to our series: low (47%), medium (41%) and high risk (12%). The authors reported an overall 76% BDFS at 3 years, which is 13% lower than our longer-term results. Noted is that once again they had no significant difference in results between risk groups. This degradation of results in the Ward et al. study compared to the results reported in this article's results may relate to a number of critical techniques we use to optimize results that are not widely used.

Certain technical considerations relating to the cryoablation itself are critical to consistently good results. Tumor destruction should be planned to prophylactically include areas of potential spread such as the NVB or the central seminal vesicles. This is designed to prevent local recurrences particularly in the medium and high risk patients.

Another critical technical point is the separation of the rectum from the prostate with a saline injection into Denonvillier's fascia. This technique, which many cryosurgeons do not employ, ensures that tumors in the posterior peripheral zone can be adequately frozen without stopping the freezing prematurely for fear of causing rectal damage and a urethro-rectal fistula.

The freezing process itself has a number of critical technical issues that have to be followed for optimal results. One relates to the number of freeze–thaw cycles carried out. Two freeze–thaw cycles to -40°C has been the standard recommended freezing protocol.[48] However, over time we have modified our approach and now use three freeze–thaw cycles to a less severe -20°C. This provides equivalent tumor destruction while minimizing the area that needs to be frozen. Another relates to the thawing process employed. Cryosurgical literature confirms that the parameters for optimal tissue destruction include a slow passive thaw.[49] Current cryoprobes have a warming feature to disengage them from the tissue at the end of the last freeze. Most surgeons now use this feature to actively thaw the tissue to save time during the procedure, which might possibly compromise long-term results.

Widespread use of cryosurgery for focal therapy will require training as well as development of guidance and monitoring technologies to help facilitate both mapping biopsy and the cryosurgical procedure itself.

Certainly cryoablation is not the only mode of tissue destruction that is suited to focal therapy. Since the original introduction of the concept of focal therapy using cryoablation, many different modalities to accomplish focal therapy are now being investigated, including high intensity focused ultrasound, laser, photodynamic therapy and irreversible electroporation.[50–53] Whether each will be equivalent to cryoablation in reliability of tissue destruction remains to be seen. In the higher risk patients where some cryoimmunologic effect may be a factor in the results we have presented, other modalities that do not offer this theoretical advantage should be used with some caution.

Which ablation modality ultimately becomes most prevalent may be less important than establishing the fact that a population of prostate cancer patients can be identified and successfully treated with a ''lumpectomy'' approach. Undoubtedly, focal radiation therapy will also be attempted. We believe that radiation will ultimately not be competitive with direct cancer ablation by other methods due to its lack of real time feedback to guide therapy, the limitations of dose threshold (i.e., the ability to retreat failures), the delay time to PSA nadir as a factor in patient anxiety, and the inherent nature of radiation scatter raising the possibility of damage to surrounding healthy structures. The safety and efficacy of 3D-PMB demonstrated makes incorporating this biopsy method into patient follow-up, particularly in new protocols, very reasonable and could reveal early failure of local control efforts by new technologies.

The study does have limitations. The number of patients reported is still relatively small. Additionally, the study does not attain level one criteria of a randomized control trial. The success criteria for BDFS by necessity had to be consistent with the radiation literature[34] (Phoenix criteria), since preservation of normal tissue will produce some PSA. We feel our patient follow-up has been long enough, however, that local failures (particularly in the medium and high risk groups) would have revealed themselves by now as they would in a radiation series. Our criteria for incontinence was the most stringent (i.e., no pads at any time), and we therefore feel that it can be compared very well to other treatment modalities. The weakest area of the data we present is related to potency. During the period in which these 70 patients were treated, pretreatment potency scoring with a scale such as the International Index of Erectile Function was not routine for us. In an effort to provide data that were relevant, we included patient satisfaction with the quality of their erections as part of our criteria; however, other focal series have reported similar results. The overall results, while flawed in some regards and not definitive, still challenge the long held belief that radical treatment of the whole prostate gland is obligatory for the local control of prostate cancer.

Conclusions

Within the limitations of our study, the long-term cancer control results of focal therapy using cryoablation appear competitive with radical whole gland treatments in low risk patients and superior in medium and high risk patients in achieving cancer free status. 3D-PMB is critical to restaging patients prior to focal therapy to limit the chance for local recurrence. Based on the results of this study focal therapy

achieves these cancer control results, with extremely low morbidity, virtually eliminating the risk of incontinence, and with competitive results in retention of potency. If confirmed and applied widely, focal cryoablation could result in a substantial decrease in prostate cancer related mortality while offering patients a better post treatment quality of life. Focal therapy therefore has the potential to radically change the paradigm of prostate cancer management.

Author Disclosure Statement

Dr. David Bostwick has a consulting arrangement with Bostwick Laboratories. He is Medical Director of the company and owns a noncontrolling interest in the company. For all other authors no competing financial interests exist, including honoraria, stock ownership, equity interests, arrangements regarding patents, or any other vested interests.

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