Appropriate Patient Selection in the Focal Treatment of Prostate Cancer: The Role of Transperineal 3-Dimensional Pathologic Mapping of the Prostate—A 4-Year Experience

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This study was undertaken to evaluate the usefulness of transperineal mapping biopsy of the prostate as a staging procedure in the appropriate selection of patients for treatment with focal cryoablation. Between October 2001 and January 2006, a total of 80 patients underwent extensive template-guided transperineal pathologic mapping of the prostate (3-DPM), in conjunction with repeat transrectal ultrasound (TRUS)-guided biopsies. Before 3-DPM was performed, the following clinical variables were recorded: age, prostate-specific antigen (PSA), percent free PSA, total prostate volume, transition zone volume, Gleason score, TNM stage, number of positive cores, and maximum percent of positive cores. Results of 3-DPM were compared with those of TRUS-guided biopsies to determine patient suitability for focal cryoablation; this served as the study end point. Of 80 study patients, 43 (54%) were deemed unsuitable for focal cryoablation. When compared with 3-DPM in assessing patient suitability for focal cryoablation repeat TRUS-guided biopsies yielded a false-negative rate of 47%, a sensitivity of 54%, and a negative predictive value of 49%. None of the pre–3-DPM variables correlated significantly with patient suitability for focal ablation. Treatment selected by the 80 study patients included total gland cryoablation (30%), expectant management (23%), radical prostatectomy (18%), focal cryoablation (11%), external irradiation (10%), brachytherapy (6%), and combined external irradiation and brachytherapy (1%); 1% were undecided about treatment selection. In this study, we demonstrated that 3-DPM (1) effectively excluded patients with clinically significant unsuspected cancer outside the area destined to be ablated, (2) appeared to do so more effectively than repeat TRUS-guided biopsies, and (3) was able to precisely locate the site of the cancer to be selectively ablated. UROLOGY 70 (Suppl 6A): 27–35, 2007. © 2007 Elsevier Inc.

Prostate cancer is known to be heterogeneous, with a variable and sometimes unpredictable natural history. This realization has sustained the controversy over the optimal management of early-stage cancer. Treatment options vary from a minimalist approach of expectant management to radical surgery. Because most treatments are associated with potential morbidity, and because in some instances, the potential for overdiagnosis and overtreatment is present,[1–3] the concept of expectant management initially discussed by Barnes[4] and Whitmore *et al.*[5] has recently gained wider consideration.[6–9] In an attempt to reach an intermediate position between watchful waiting and treatment that encompasses the whole gland, recent interest has been generated by Onik *et al.*[10,11] and others[12,13] in cryotherapy as a modality for partial or focal treatment, wherein selective ablation is applied only to the side of the prostate that contains the cancer. This procedure has been referred to as "focal," "conformal," "lumpectomy," or "hemi-treatment" cryoablation. In theory, this approach could minimize treatment morbidity without sacrificing treatment efficacy. Unfortunately, patients with seemingly low-volume, low-stage cancer detected by standard office transrectal ultrasound (TRUS)–guided biopsies frequently are shown to have more advanced cancer on radical prostatectomy specimens, in terms of both stage and grade.[14–20] As a result, it is important that the selection process for patients undergoing "focal" therapy must not include patients with clinically significant unsuspected cancer outside the area destined to be ablated. In an effort to analyze the potential likelihood of this event, we reviewed the records of 80 patients who would have been deemed suitable for consideration of focal cryoablation. Before definitive therapy was provided, these patients underwent a staging procedure that we have previously described as consisting of extensive transperineal template-guided 3-dimensional pathologic mapping of the

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Dr. Barzell is a consultant for CIVCO Medical Solutions. Dr. Melamed has no financial arrangement or affiliation with a corporate organization or a manufacturer of a product discussed in this supplement.

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0090-4295/07/$32.00
doi:10.1016/j.urology.2007.06.1126

Table 1. Presenting group categories

Group I (n = 28)	Patients presenting for focal cryoablation
Groups II and III (n = 52), EM	Patients considering EM (older age group) or treatment less aggressive than RP (younger age group)
Group II (n = 23), cancer volume <0.1 cm^3	Single microfocus of Gleason score ≤ 6[22]
Group III (n = 29), cancer volume <0.5 cm^3	No more than 3 cores + 50% or less involvement per core, Gleason score ≤ 6, PSAD ≤ 0.15, all + cores on 1 side[9,23]

PSAD = prostate-specific antigen density, RP = radical prostatectomy.

prostate (3-DPM), as well as repeat transrectal prostate biopsies. Results attained through transperineal mapping were compared with those acquired via repeat transrectal biopsies, and data were used to evaluate patient suitability for focal cryoablation.

MATERIALS AND METHODS

Between October 2001 and January 2006, 80 patients with previously diagnosed prostate cancer detected by office TRUS-guided biopsies underwent staging 3-DPM of the prostate cancer before definitive therapy was provided. The first 14 patients did not have repeat transrectal biopsies, but the last 66 patients underwent concomitant repeat TRUS-guided biopsies at the time 3-DPM was performed.

Indications for 3-DPM, Presenting Group Category, and Preoperative Clinical Variables

Indications for a re-staging 3-DPM varied among the 80 patients. As is shown in Table 1, the 80 patients were divided into 3 presenting group categories according to the reasons why they presented for 3-DPM. Group I consisted of 28 patients who presented specifically for focal cryoablation; groups II and III (52 patients) presented for consideration of expectant management (older patients) or to request less aggressive treatment than radical prostatectomy (younger patients). Group II (23 patients) had a single microfocus of Gleason score ≤ 6 cancer and fulfilled Epstein's criteria for "clinically insignificant" cancer (<0.1 cm^3 cancer) in 44% of radical prostatectomy specimens[21]; group III (29 patients) had no more than 3 positive cores, exhibited $\leq 50\%$ involvement per core, presented with a Gleason score ≤ 6, and had a prostate-specific antigen density (PSAD) ≤ 0.15, thus fulfilling Epstein's criteria for ≤ 0.5 cm^3 cancer in 79% of radical prostatectomy specimens.[9,22] An additional requirement for this study was that all positive biopsy specimens were taken from 1 side only.

Watchful waiting was considered in most patients, so it was believed that repeat TRUS-guided biopsies at the time of 3-DPM would be prudent in the event that the latter approach was more apt to pick up peripheral zone cancer. Before 3-DPM biopsies were performed, the following pre–3-DPM clinical variables were recorded: age, prostate-specific antigen (PSA) concentration, percent free PSA, total gland volume, PSA density, transition zone (TZ) volume, PSAD TZ, Gleason score, TNM stage, number of positive cores, and maximum percent of positive cores.

Biopsy Technique and Specimen Organization

Of the 80 study patients, all of the last 66 underwent repeated TRUS-guided biopsies at the time of 3-DPM; these included targeted biopsies performed at the known site of cancer (as detected on previous office TRUS biopsy) and systematic biopsies throughout the rest of the gland. The 3-DPM biopsy technique has been previously described[23] and has not been materially modified (Figure 1). However, the specimen organization has been changed, and the new organization is depicted in Figure 2. Midline biopsies are now segregated, and each octant is divided into 3 zones, yielding 26 separate specimen jars. Although individual labeling of XYZ coordinates and processing of each core would have yielded a more detailed map, the added costs involved in pathologic processing were considered prohibitive. In most patients, biopsies were performed as outpatient procedures under light general anesthesia or intravenous sedation with local infiltration. However, 5 patients underwent 3-DPM in our office under a periprostatic block and perineal local anesthesia—a procedure that was readily accomplished with minimal discomfort and without complications.

Pathologic and Clinical Classification

Between August 2005 and January 2006, the pathologic slides were then retrospectively reviewed at a separate institution by one of the authors (MRM) who was "blinded" as to pre–3-DPM clinical variables, treatment undertaken, and clinical course. Histopathologic criteria were established, more or less empirically, to define histologically favorable and less favorable carcinomas; these criteria served as the basis for classifying patients into low-, moderate-, and high-risk categories. It was recognized that these criteria may need continued refinement as experience grows: (1) All Gleason score 7 to 10 carcinomas were classified as potentially high risk; and (2) Gleason score ≤ 6 carcinomas were further classified according to extent of disease as follows: low risk (no carcinoma detected at 3-DPM, or carcinoma in no more than 2 biopsy cores measuring no more than 2.5 mm in any single core); moderate risk (carcinoma in no more than 4 cores, measuring no more than 5.0 mm in any single core and not more than 10 mm in total); high risk

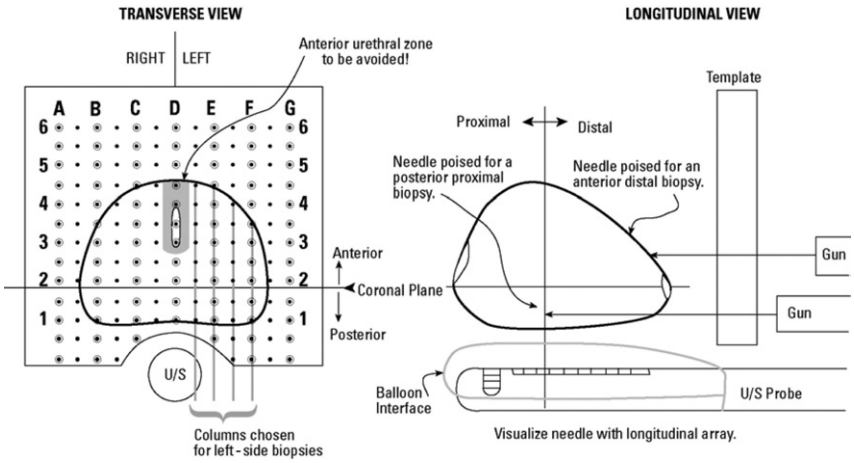

Figure 1. Prostate as seen by transrectal ultrasound during saturation biopsy. Please note that once a column is selected for biopsy, the needle should be manipulated so that its course can be visualized with the longitudinal array as illustrated. During this maneuver, it is crucial to maintain a fixed sagittal orientation of the ultrasound (U/S) probe. This technique prevents the needle from tracking and sampling outside the area intended for biopsy. While one is performing these biopsies, it is crucial to avoid injury to the prostatic urethra. This is accomplished by keeping a catheter in place to readily identify the urethra, and then by steering the biopsy needle away from this area. It is also important that midline biopsies are taken posterior to the urethra only because anterior midline biopsies will injure the urethra. Reprinted with permission from Urology Times.[23]

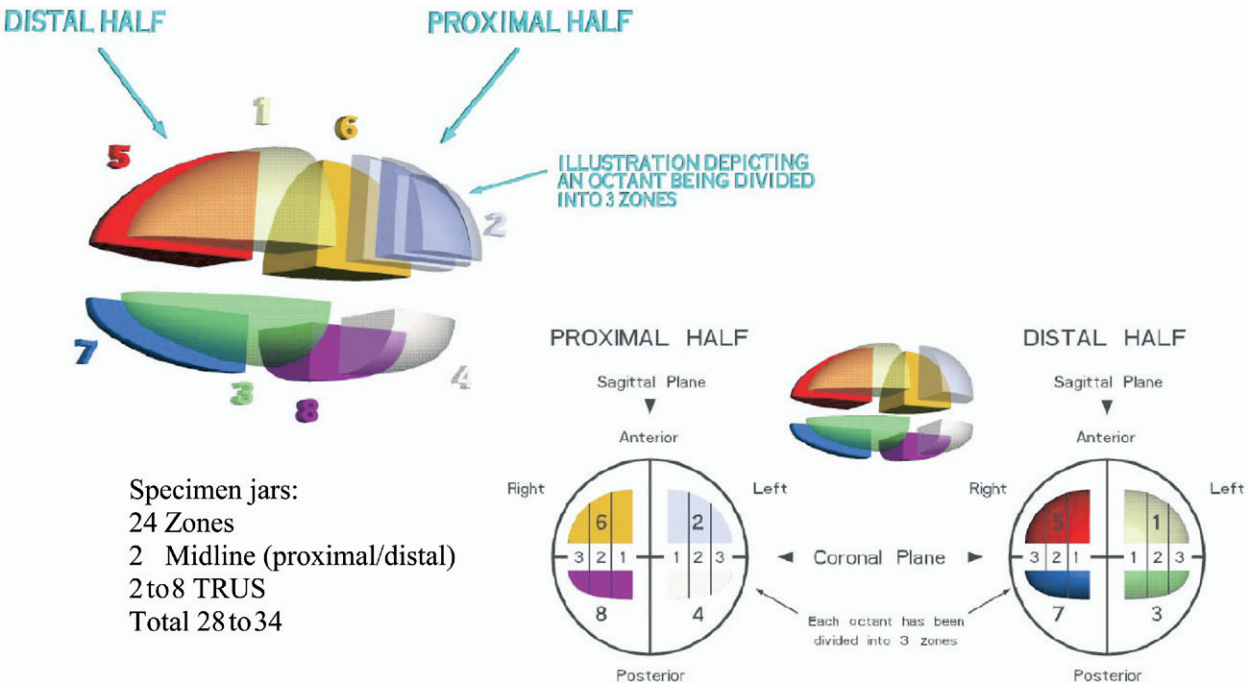

Figure 2. Each octant is divided into 3 zones, and midline biopsies are segregated. Number of specimen jars = 24 zones + 2 midline (proximal/distal) + 2 to 8 TRUS (total = 28 to 34).

(carcinoma involving ≥5 cores and extending >5.0 mm in any single core, or >10.0 mm in total).

Definitions

For the purposes of this study, the following definitions were applied: focal cryoablation was defined as cryoablation on 1 side only; conformal cryoablation was defined as bilateral cryoablation with sparing of at least the neurovascular bundle on the unaffected side; and bilateral cryoablation was defined as whole-gland cryoablation.

Patients were deemed suitable for focal cryoablation if cancer was present on only 1 side after completion of repeat TRUS-guided and 3-DPM biopsies (ie, absence of

Table 2. Clinical and histologic characteristics of 80 patients*

	Range		Average	Median
Age (yr)	46	80	68.2	69
% Free PSA	5.00	43.00	16.47	15.2
Total gland volume	12.6	137.0	43.0	42.15
Transition zone volume	3.1	76.1	20.0	16.40
PSAD	0.017	0.660	0.160	0.14
PSAD transition zone	0.042	4.323	0.51	0.31
No. of cores taken at initial TRUS	4	16	11.0	12
Months from initial TRUS to 3-DPM	1	35	4.3	2.5
Gleason score at initial TRUS biopsy	4	8	6.0	6.0
No. of cores positive at initial TRUS biopsy	1	7	1.8	1.0
Maximum % core involvement at initial TRUS	0.1	100	25.4	20.0%
Total number of biopsies at 3-DPM†	20	138	66.3	69
Number of biopsies per side at 3-DPM†	20	80	38.56	38.75
Number of biopsies per cm^3 of prostate at 3-DPM	0.57	4.10	2.02	1.88
Total number of repeat TRUS biopsies at 3-DPM	3	15	7.1	7
Number of repeat TRUS biopsies per side at 3-DPM	2	10	4.3	4

3-DPM = transperineal template-guided 3-dimensional pathologic mapping of the prostate; PSA = prostate-specific antigen; PSAD = PSA density; TRUS = transrectal ultrasound.
* Groups I, II, and III combined.
† Although all patients in groups II and III (expectant management) underwent bilateral 3-DPM, patients in group I (focal) who had high-grade or high-volume cancer underwent unilateral 3-DPM only, on the side opposite the index cancer, to prove the absence of cancer on what might be the untreated side.

Table 3. T stage and Gleason score distribution

Presenting Group Category	Clinical T Stage			Gleason Score
	T1c	T2a	T3	
Group I (n = 28), focal	19	8	1	6–8
Group II (n = 23), expectant management cancer volume <0.1 cm^3	23	0	0	≤6
Group III (n = 29), expectant management cancer volume <0.5 cm^3	29	0	0	≤6

Table 4. Gleason score reassignment after transperineal template-guided 3-dimensional pathologic mapping of the prostate

	Same Ratio (%)	Downgraded Ratio (%)	Upgraded Ratio (%)
All patients (N = 80)	64/80 (80)	3/80 (4)	13/80 (16)

cancer on the side contralateral to the initial presenting lesion). Suitability for focal cryoablation, as defined above, was the end point of this study.

RESULTS

Clinical and pathologic characteristics of the 80 study patients are detailed in Table 2. It should be noted that not all patients underwent bilateral 3-DPM. Although all patients in groups II and III (expectant management) underwent bilateral 3-DPM, some patients in group I (focal) who had high-grade or high-volume cancer underwent only unilateral 3-DPM. This was performed contralateral to the side of the index cancer to prove the absence of cancer on what might become the untreated side. Because these patients had a proven significant tumor burden on 1 side on initial TRUS-guided biopsy, no "clinical" reason could be given to re-biopsy that side. For this reason, to avoid confusion, the values used for analysis in this report were the number of biopsies per side and the number of biopsies per cubic centimeter of prostate. As is shown in Table 2, a median of 38.75 biopsies were performed per side at 3-DPM, and 1.88 biopsies were completed per cubic centimeter of prostate. TNM stage and Gleason score distribution for the 3 presenting clinical categories are outlined in Table 3. By definition, groups II and III were classified as T1c and Gleason 6, and group I had the more typical distribution of stage and grade seen in community practice.

Gleason score concordance between the initial TRUS biopsy and subsequent 3-DPM is depicted in Table 4. The Gleason score was upgraded in 13 of 80 patients (16%). It should be emphasized that the end point for this study was the suitability of patients for focal cryoablation, as defined in the Materials and Methods section. Table 5 examines suitability for focal cryoablation as a function of the presenting group category; as can be seen, no appreciable difference was noted among the 3 groups with respect to this end

Table 5. Suitability for focal cryoablation vs presenting group category

Suitability for Focal Cryoablation	Presenting Group Category			
	Focal Ratio (%)	EM <0.1 cm^3 Ratio (%)	EM <0.5 cm^3 Ratio (%)	Combined Ratio (%)
Yes	13/28 (46)	10/23 (44)	14/29 (48)	37/80 (46)
No	15/28 (54)	13/23 (56)	15/29 (52)	43/80 (54)

EM = expectant management.

Table 6. Suitability for focal cryoablation vs risk for cancer

Suitability for Focal Cryoablation	Risk for Cancer		
	Low Ratio (%)	Moderate Ratio (%)	High Ratio (%)
Yes (n = 37)	18/37 (49)	7/37 (19)	12/37 (32)
No (n = 43)	9/43 (21)	12/43 (28)	22/43 (51)

Table 7. Accuracy of transperineal template-guided 3-dimensional pathologic mapping of the prostate vs repeat transrectal ultrasound (TRUS) biopsies in predicting suitability for focal cryoablation

Unsuitable for Focal Cryoablation (n = 36)			
Transperineal Positive	Transperineal-Only Positive	TRUS-Only Positive	Both Transperineal and TRUS Positive
36/36 (100%)	31/36 (86%)	0	5/36 (14%)

Table 8. False-negative rate of repeat transrectal ultrasound (TRUS) biopsies*†

TRUS Negative (suitable by TRUS)	True Negative (suitable by 3-DPM)	TRUS False Negative (unsuitable not detected by TRUS)
61/66 (92%)	30/66 (45%)	31/66 (47%)

3-DPM = transperineal template-guided 3-dimensional pathologic mapping of the prostate.
* Of 80 patients, 66 had a complete set of repeat TRUS biopsies at 3-DPM.
† If suitability for focal cryoablation is posed with the expectation of a Yes or a No answer, the following results:
TRUS: 61 Yes, 5 No
3-DPM: 30 Yes, 36 No

point. Although these results were unexpected, they allowed us to combine the 3 presenting group categories into a single combined group for the purposes of analysis. As can be seen, 43 of 80 patients (54%) were unsuitable for focal cryoablation.

Table 6 examines suitability for focal cryoablation as a function of risk for cancer as defined previously. A total of 49% of patients suitable for focal cryoablation were in the low-risk category, and 51% of those deemed unsuitable were in the high-risk category.

Table 7 compares the accuracy of 3-DPM and repeat TRUS in detecting patients who were unsuitable for focal cryoablation. Transperineal biopsies detected 36 of 36 (100%) unsuitable candidates; repeat TRUS biopsies picked up only 5 of 36 (14%).

Table 8 presents the false-negative rate of repeat TRUS biopsies. If suitability for focal cryoablation is posed with the expectation of a yes or no answer, and the question is posed only in those instances in which repeat TRUS-guided biopsies were done at the time of 3-DPM (n = 66), then 61 of 66 (92%) were considered suitable for focal cryoablation by repeat TRUS findings; however, only 30 of 66 (45%) were deemed suitable by 3-DPM findings. Thus, repeat TRUS-guided biopsies had a false-negative rate of 47% (31 of 66) in excluding patients from focal cryoablation.

Table 9 examines the "relative" sensitivity and negative predictive values for repeat TRUS versus 3-DPM. Because only 18% of patients in this study underwent radical prostatectomy, the true sensitivity of 3-DPM could not be evaluated. Therefore, for purposes of analysis and discussion, the assumption was made that 3-DPM had 100% sensitivity. Thus, the values in this table for repeat TRUS-guided biopsies are "relative" to 3-DPM. As can be seen, 3-DPM by definition had 100% sensitivity and a 100% negative predictive value, but TRUS-guided biopsies had 54% sensitivity and a 49% negative predictive value.

Treatment selected according to presenting group is depicted in Table 10. Of those patients who presented for focal cryoablation, only 8 of 28 (29%) underwent the procedure, 9 of 28 (32%) required whole gland or conformal cryoablation, 5 of 28 (18%) had a radical retropubic prostatectomy, and the remainder underwent intensity-modulated radiation therapy (IMRT) with or without brachytherapy. Of patients who presented for consideration of expectant management, 39% in group II (cancer volume <0.1 cm^3) and 31% in group III (cancer

Table 9. "Relative"* sensitivity and negative predictive value for repeat transrectal ultrasound (TRUS) vs transperineal template-guided 3-dimensional pathologic mapping of the prostate (3-DPM)

	Repeat TRUS	3-DPM
Sensitivity	$\frac{55}{55 + 47} = 54\%$	$\frac{55}{55 + 0} = 100\%$
Negative predictive value	$\frac{45}{45 + 47} = 49\%$	$\frac{45}{45 + 0} = 100\%$

* Please note that because only 18% of patients in this study underwent a radical prostatectomy, the true sensitivity of 3-DPM could not be evaluated. Therefore, for purposes of discussion, the assumption was made that 3-DPM had 100% sensitivity. Thus, the values in this table for repeat TRUS are "relative" to 3-DPM.

Table 10. Treatment selected for various presenting group categories

	Presenting Group Category			3 Groups Combined
Treatment	Focal Cryoablation Group I (n = 28)	Expectant Management <0.1 cm^3 Group II (n = 23)	Expectant Management <0.5 cm^3 Group III (n = 29)	Group I + Group II + Group III, (N = 80)
Cryoablation				
Whole gland	6	2	8	16/80 (20%)
Conformal	3	0	5	8/80 (10%)
Focal	8	1	0	9/80 (11%)
Total	17	3	13	33/80 (41%)
Expectant management*	0	9*	9*	18/80 (23%)
Radial retropubic prostatectomy	5	5	4	14/80 (18%)
IMRT	4	3	1	8/80 (10%)
Brachytherapy	1	2	2	5/80 (6%)
IMRT + brachytherapy	1	0	0	1/80 (1%)
Undecided	0	1	0	1/80 (1%)

IMRT = intensity-modulated radiation therapy.
* It should be noted that of the 52 patients who presented for consideration of expectant management, 9 of 23 (39%) in group I, and 9 of 29 (31%) in group II ended up selecting this approach on the basis of negative or extremely favorable findings at transperineal template-guided 3-dimensional pathologic mapping of the prostate.

volume <0.5 cm^3) opted for expectant management on the basis of negative 3-DPM biopsies or minimal potentially insignificant cancer on 3-DPM. A detailed analysis of the latter 2 groups is the subject of a separate publication.[24]

For all patients who were undergoing cryoablation, a 3-D pathologic map of the location of the cancer at the time of the procedure was invaluable. In cases in which focal or conformal cryoablation was carried out, the map was crucial. It permitted selective targeted ablation of the areas of cancer, while sparing uninvolved portions of the prostate. For those who were undergoing brachytherapy, the 3-D map was very helpful in dosimetry planning. Although a 3-D map provided some value for patients who were undergoing radical prostatectomy, any advantages were negated by the fibrosis encountered at surgery. Of 14 patients who underwent radical retropubic prostatectomy, extensive fibrosis was encountered in 8 (57%), mild fibrosis in 2 (14%), and no fibrosis in 3 (21%); findings were unstated for 1 patient (7%). Although in some cases surgery was very difficult and was not to be attempted by the "occasional" radical prostatectomist, extensive fibrosis did not negatively influence blood loss, length of hospitalization, or other morbidities. All 14 patients were fully continent. However, preservation of the neurovascular bundle was not possible in most of the patients in whom extensive fibrosis was encountered.

As is shown in Table 11, Pearson correlation analysis was used to study 11 pre–3-DPM variables and 2 post–3-DPM variables versus suitability for focal cryoablation. Of all these variables, only the number of biopsies per side at 3-DPM correlates significantly with suitability for focal cryoablation ($r = 0.23$, $P = 0.04$ [<0.05]).

Adverse events are listed in Table 12. Although the complication rate of 12.5% was high, all events were minor and transient and did not require additional measures other than temporary catheterization when retention developed, or a change of antibiotics with 1 episode of fever. The incidence of complications appears to have increased with the advent of increased numbers of transperineal biopsies per patient as practiced over the past 3 years.

DISCUSSION

The purpose of this report was neither to explore the soundness, nor to debate the pros and cons, of partial prostate ablation. Only further study, ideally conducted

Table 11. Pearson correlation coefficients for 11 pre–transperineal template-guided 3-dimensional pathologic mapping of the prostate (3-DPM) variables, and 2 post–3-DPM variables vs suitability for focal cryoablation

	R	P
Pre–3-DPM Variables		
Age (yr)	−0.05	0.66
PSA at initial TRUS	0.05	0.65
% Free PSA at initial TRUS	−0.11	0.43
Total gland volume	−0.05	0.63
Transition zone volume	−0.14	0.24
PSA density (total gland)	0.05	0.64
PSA density (transition volume)	0.09	0.45
Gleason score at initial TRUS	−0.03	0.81
No. of cores positive on initial TRUS	0.18	0.11
T stage at initial TRUS-guided biopsies	−0.06	0.60
Maximum % involvement of positive cores	0.07	0.54
Post 3-DPM variables		
Total no. of biopsies per side at 3-DPM*	0.23*	0.037*
No. of biopsies per cm^3 of gland volume at 3-DPM	0.21	0.06

PSA = prostate-specific antigen; TRUS = transrectal ultrasound.
* Only statistically significant correlation.

Table 12. Complications

Retention	5
Perineal ecchymosis	2
Scrotal hematoma	1
Fever	1
Gross hematuria*	1*
Total	10/80 (12.5%)

* Not requiring catheterization or admission.

in a prospective fashion, and time will tell whether focal therapy establishes itself as an acceptable alternative to current treatment modalities.

The impetus for this study came from 2 sources. First was the recognition that validated criteria for identifying patients who can safely be managed expectantly or with partial prostate ablation do not exist. Second was our need to make sure that patients who were embarking on unproven paths, whether focal cryoablation[10–13] or expectant management,[6–9] did not unknowingly harbor more extensive cancer than was predicted by TRUS-guided prostate biopsies.[14–20] Therefore, we believed it was crucial to accurately re-stage these patients before embarking on these "unproven" paths.

The transperineal approach for saturation biopsies[23,25–28] was chosen rather than the transrectal approach, as practiced by many,[29–35] for a number of reasons. First was our favorable previous experience with 3-DPM when used as a diagnostic tool.[23] Second was the limitation of the standard transrectal approach in accessing the anterior and apical areas of the prostate. Third was the inherent inaccuracy in sampling and mapping that occurs when manual positioning of the needle guide is used and visual 3-D recall is relied on when a large number of TRUS-guided biopsies are performed. Fourth was the difficulty inherent in translating findings on TRUS-guided biopsy to a transperineal grid system through which most of the currently less invasive treatment modalities are delivered. Conversely, the template-guided transperineal approach allows for a more systematic approach to sampling and provides a set of fixed reproducible coordinates that can be used for accurate mapping of cancer within the prostate (3-DPM) and subsequent treatment planning when the latter is desirable. Arguably, this method of staging is laborious and invasive and may ultimately be replaced by imaging studies that can accurately define the extent and location of cancer—a requirement not met by current imaging modalities, including color Doppler[36] and magnetic resonance imaging with spectroscopy.[37] Although future nomograms[38,39] based on information gathered at TRUS biopsy on pathologic, biomarker, and biochemical variables might ultimately accurately predict volume and aggressiveness of disease, current nomograms are unlikely to do, as can be seen in findings that none of the pre–3-DPM variables correlated with suitability for focal cryoablation (this study), nor with risk of cancer.[24]

Using the study definition of "suitability for focal cryoablation" as the end point, we found that even though most patients had low-volume, low-grade cancer at presentation, 54% were found to be unsuitable for 1-sided cryoablation. This study is unique in that most of the patients who underwent transperineal biopsies concurrently underwent transrectal biopsies. This allowed direct comparison between transperineal 3-DPM and TRUS-guided biopsy findings. Although the number of repeat TRUS-guided biopsies was limited to an average of 4.3 per side—and arguably, a TRUS-guided "saturation" biopsy scheme[29–35] would have provided a fairer comparison between these 2 biopsy methods—it should be emphasized that the purpose of the repeat TRUS-guided biopsies was not to prove the superiority of one biopsy scheme over another, but to ensure that the transperineal approach did not miss cancer that was more readily detected by the TRUS-guided biopsy route. As it turns out, there were no TRUS-positive biopsies that were not also picked up by the transperineal approach; conversely 31 of 36 (86%) positive biopsies were picked up only by the transperineal approach (Table 7).

It was surprising and unexpected to find that no correlation was observed between the volume and the grade of cancer on the initial TRUS biopsy and patient suitability for focal cryoablation (Table 5). Group I (focal) patients had a higher stage and grade of cancer at presentation, whereas group II (cancer volume <0.1 cm^3) had a single microfocus of Gleason score ≤ 6; however, 54% of the former and 56% of the latter were deemed unsuitable for focal cryoablation. Of patients suitable for focal cryoablation (Table 6), 49% were classified as low

risk and arguably could have been managed by watchful waiting. Conversely, of those patients who were unsuitable for focal cryoablation, 51% were classified as high risk. It thus appears that 3-DPM was able to separate low-risk patients who might be suitable for focal ablation (or watchful waiting) from high-risk patients who were likely to fail focal ablation therapy.

It is noteworthy that of all the pre– and post–3-DPM variables (Table 11), only the number of specimens per side correlated significantly with suitability for focal cryoablation: in other words, the more biopsies we took, the more cancer we found. This should come as no surprise to many practitioners of the art who have intuitively known this fact for the many decades.

In this study, relying on TRUS-guided biopsies alone for selecting patients for focal cryoablation resulted in a failure rate of 47%. However, the study was "biased" toward transperineal biopsies inasmuch as many more transperineal than TRUS-guided biopsies were performed per patient. Although we prefer the transperineal approach, there is no reason why a TRUS-guided saturation biopsy scheme that has the capacity of providing reproducible XYZ coordinates and a scheme for 3-D mapping would not be equally suitable. Until the time that such a scheme becomes available, or better imaging modalities or more predictive nomograms are developed, 3-DPM appears to be the logical way to appropriately select patients for focal ablation.

On the basis of our findings, focal ablation should not be attempted without a confirmatory re-staging procedure to include 3-DPM or extensive TRUS-guided saturation biopsies. Although the frequency of complications (12.5%) was high, all were minor. Given the number of biopsies taken, significant hematuria was conspicuously absent—a fact that is attributable to meticulous avoidance of injury to the prostatic urethra (Figure 1). Despite numerous articles on transrectal saturation biopsies, only a few[32,35] have reported associated complication rates.

Given the fact that the number of biopsies at 3-DPM correlated with suitability for cryoablation and the observation that the complication rate seemed to increase proportionately with the number of biopsies at 3-DPM, we asked whether there was an "optimal" number of biopsies that would maximize one's chances of detecting significant cancer while minimizing the morbidity of biopsies. A number that seemed to give a good "visual" cutoff but did not reach statistical significance was somewhere between 1.6 and 1.8 biopsies per cubic centimeter of prostate tissue.

Although the value and place of focal cryoablation as primary treatment have not yet been determined, the advantage of focal cryoablation for radiation salvage[40–45] procedures seems intuitively clear. Salvage total gland cryoablation is associated with a significant risk for incontinence and other morbidities that can potentially be eliminated or reduced by focal treatment that allows for partial sparing of the urethra and/or the neurovascular bundle. In appropriately selected radiation salvage cases, there appears to be no reason to ablate the whole gland in situations where highly selective targeted ablation is feasible. In this setting, 3-DPM has a distinct theoretical advantage inasmuch as this route avoids transrectal saturation biopsies through an area potentially compromised by radiation proctitis.

CONCLUSION

A vital key to the success of selective focal ablation of the prostate is proper patient selection. The latter is dependent on a staging procedure that can exclude patients whose cancer is outside the area destined to be treated while precisely locating the targeted area to be selectively ablated. A re-staging procedure that uses 3-DPM as described in this article appears to fulfill these criteria.

Acknowledgment: We are greatly indebted to Saul Lowitt, PhD, for the statistical analyses and for invaluable help in data organization and management. We wish to thank Carol Grant, RN, and Julia Parrish, CCRC, for their meticulous help with chart review and data collection, and Michelle Walsh for her tireless efforts in preparing this manuscript for publication.

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