Focal Treatment or Observation of Prostate Cancer: Pretreatment Accuracy of Transrectal Ultrasound Biopsy and T2-weighted MRI

Lucas Nogueira, Liang Wang, Samson W. Fine, Rodrigo Pinochet, Jordan M. Kurta, Darren Katz, Caroline J. Savage, Angel M. Cronin, Hedvig Hricak, Peter T. Scardino, Oguz Akin, and Jonathan A. Coleman

OBJECTIVES To test the hypothesis that men with prostate cancer (PCA) and preoperative disease features considered favorable for focal treatment would be accurately characterized with transrectal biopsy and prostate magnetic resonance imaging (MRI) by performing a retrospective analysis of a selected cohort of such patients treated with radical prostatectomy (RP).

METHODS A total of 202 patients with PCA who had preoperative MRI and low-risk biopsy criteria (no Gleason grade 4/5, 1 involved core, <2 mm, PSA density ≤0.10, clinical stage ≤T2a) were included in the study. Indolent RP pathology was defined as no Gleason 4/5, organ confined, tumor volume <0.5 mL, and negative surgical margins. MRI ability to locate and determine the tumor extent was assessed.

RESULTS After RP, 101 men (50%) had nonindolent cancer. Multifocal and bilateral tumors were present in 81% and 68% of patients, respectively. MRI indicated extensive disease in 16 (8%). MRI sensitivity to locate PCA ranged from 2% to 20%, and specificity from 91% to 95%. On univariate analysis, MRI evidence of extracapsular extension ($P = .027$) and extensive disease ($P = .001$) were associated with nonindolent cancer. On multivariate analysis, only the latter remained as significant predictor ($P = .0018$).

CONCLUSIONS Transrectal biopsy identified men with indolent tumors favorable for focal treatment in 50% of cases. MRI findings of extracapsular extension and extensive tumor involving more than half of the gland are associated with unfavorable features, and may be useful in excluding patients from focal treatment. According to these data, endorectal MRI is not sufficient to localize small tumors for focal treatment. UROLOGY 75: 472–477, 2010. © 2010 Elsevier Inc.

Prostate cancer (PCA) is the most common cancer in men and a leading health care issue in the United States.[1] PCA screening based on prostate-specific antigen (PSA) measurement is widely used and has led to a substantial increase in the detection of PCA throughout the last decade.[2,3] Early detection has led to a well-recognized shift toward low-stage disease and the identification of a considerable number of men diagnosed with small tumors discovered at an earlier age, effectively adjusting the chronology of the disease.[4]

Current curative treatment options for localized PCA include surgery and radiation, both of which carry associated risks of treatment-related morbidity, including urinary, sexual, and bowel dysfunction.[5] For small, indolent prostate tumors, these approaches may be more aggressive than necessary. Efforts have been made to develop new modalities of curative treatment for PCA that can minimize morbidity. Recently, interest has turned to the use of active surveillance and focal therapy strategies as effective alternative options for management. Active surveillance entails closely monitoring tumor development, without therapy, with the option to initiate treatment at a later time.[6] Focal therapy modalities encompass organ-sparing treatments, using new technologies ideally intended to ablate subtotal portions of the prostate that contain tumor while minimizing related side effects. In the development of trials to study these treatments, patient selection plays a crucial role to ensure that these organ-sparing approaches are not tumor sparing.

Selection criteria for active surveillance or focal therapy are strongly based on biopsy techniques designed to diagnose PCA, but are not optimized to quantify the extent or grade of the disease. The design of most focal or

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From the Departments of Surgery, Radiology, Pathology, and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY

Reprint requests: Jonathan A. Coleman, M.D., Urology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10065. E-mail: colemaj1@mskcc.org

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hemiablation trials involves transrectal prostate biopsy, with or without prostate magnetic resonance imaging (MRI) criteria, for assessing patients and determining eligibility. The value of MRI in evaluating men with low-stage disease has been shown to add incrementally to prognostic models; yet, its role in localizing small tumors is less well defined.[7]

We carried out a retrospective analysis to test the hypothesis that candidates for organ-sparing management of PCA would be accurately evaluated, using diagnostic transrectal ultrasound (TRUS) biopsy techniques and prostate imaging with T_2-weighted MRI. To this end, we analyzed a highly selected cohort of low-risk, surgically treated patients, with presurgical disease features favorable for active surveillance or focal therapy. We explored the utility of clinical features, including prostate biopsy and T_2-weighted endorectal-coil MRI, to characterize this group of patients with regard to potential for organ-sparing management.

MATERIAL AND METHODS

Patient Methods

After institutional review board approval was obtained, data were collected from a prospectively updated PCA database. Search criteria included surgically treated men with low-risk biopsy criteria, who had been studied with presurgical prostate MRI and had whole-mount prostate pathology tissue maps available after radical prostatectomy (RP) prepared in 4-mm sections as previously described.[8] This search identified 202 of 2985 men who underwent RP at our institution between April 2000 and March 2007. Biopsy selection criteria followed that described by Goto.[9] One positive core with <2 mm of cancer, no Gleason grade 4/5, PSA density ≤0.10, and clinical stage T2a or less. Patients treated preoperatively with androgen deprivation or radiation therapy were excluded. Patients were divided into indolent (group 1) or nonindolent (group 2) cancer based on the whole-mount RP specimen pathology.[10] Group 1 was defined as follows: no Gleason grade 4 or 5, organ confined, tumor volume <0.5 mL, and negative surgical margins.

To determine the sampling accuracy of transrectal ultrasound biopsy by sextant, whole-mount maps were assessed for tumor involvement by sextant location, for example, right/left, base/mid/apex. To determine possible sampling errors in the anterior portion of the gland, the base and mid sectors were further subdivided into anterior and posterior, yielding 10 sectors altogether. Additional data recorded from each RP specimen were Gleason score, surgical margins, extracapsular extension (ECE), positive surgical margin, seminal vesicle invasion, and lymph node involvement. Location of tumor on prostate biopsy was compared with prostate maps.

Preoperative T_2-weighted, endorectal-coil MRI studies were obtained not before than 6 weeks after prostate biopsy as per institutional practice. Radiographic interpretation was provided by experienced radiologists with a report that indicated localization and level of suspicion for tumor in the prostate, as described earlier. ECE, seminal vesicles, and lymph nodes involved were also assessed. MRI was performed with a 1.5-T whole-body magnetic resonance imager (GE Medical Systems, Milwaukee, WI). Patients were examined in the supine position; the body coil was used for excitation, and the pelvic phased-array coil (GE Medical Systems) was used in combination with an expandable endorectal coil (Medrad, Pittsburgh, PA) for signal reception. Thin-section, high-spatial resolution transverse, coronal, and sagittal T_2-weighted fast spin-echo images of the prostate and seminal vesicles were obtained, and 4 signals acquired. T_2-weighted images were postprocessed to correct for the reception profile of the endorectal coil.

Statistical Methods

To allow for anatomic variation in the diagnostic properties of MRI, the prostate was categorized by quadrant: right/left and anterior/posterior. MRI interpretation for cancer suspicion by quadrant was scored as definitely no cancer (I), probably no cancer (II), indeterminate (III), probably cancer (IV), or definitely cancer (V). For sensitivity and specificity analyses, MRI scores were classified as 1/2/3 vs 4/5. The same 5-grade score was applied for the presence of extracapsular extension. Sensitivity and specificity of MRI at detecting cancer in each of the 4 quadrants of the prostate were assessed using whole-mount maps as the gold standard.

Whether information obtained from an MRI could improve on a standard prediction model to determine who has clinically significant cancer, we created a multivariable standard logistic regression model to predict group (nonindolent or indolent), using PSA and the extent of the biopsy (≤8 cores vs >8 cores) as predictors. PSA was modeled with splines to account for the nonlinear relationship between PSA and outcome. Clinical stage and biopsy Gleason score were not included because of homogeneity of the cohort with regard to stage and grade. Predictive accuracy was assessed by area under the curve (AUC), with bootstrap correction for overfit, to determine whether the addition of MRI information, including tumor extent and ECE involvement, could improve on the predictive accuracy of the standard model. Tumor extent was defined as follows: MRI examinations that received a score of I or II in all 4 quadrants were defined as minimal involvement, a score of IV or V in 2 or more quadrants was defined as extensive involvement, and all other studies were classified as moderate involvement. Statistical analyses were performed using Stata 10.0 (StataCorp LP, College Station, TX), with $P < .05$ considered statistically significant.

RESULTS

Preoperative and RP pathology data are shown in Table 1. Of the 202 patients included in our analyses, 101 (50%) met postoperative criteria for indolent disease on final RP pathology. There were no important differences between groups with regard to age, PSA serum levels, and clinical stage. Median prostate volume from MRI in group 2 patients was smaller than in group 1 patients (33 vs 41 mL, respectively; $P = .02$). The median number of prostate biopsy cores per patient was 11 (range 6-22); 136 men (67%) and 92 men (47%) had >8 and ≥12 or more prostate biopsy cores, respectively. Thirty-five men (17%) had undergone a previous biopsy procedure, with 7 (3.5%) having undergone ≥2. Gleason score in RP specimen was upgraded in 32% (n = 64) of patients. Prostate cancers of pathologic stage pT3 or pT4 were found in 10% (n = 21) of all patients. Preoperative biopsy correctly identified the location of the index tu-

Table 1. Preoperative patient characteristics and pathology data following radical prostatectomy

Characteristic	All Patients N = 202	Group 1 (Indolent) n = 101	Group 2 (Nonindolent) n = 101
Median age, (y)	59 (54-63)	57 (53-63)	59 (55-64)
Median PSA, (ng/mL)	5.2 (3.8-6.7)	5.1 (3.8-7.0)	5.3 (3.9-6.7)
Median prostate volume from MRI (mL)	38.3 (26-52)	41 (29-59)	33 (25-47)
Median 5-y preoperative nomogram recurrence probability, (%)	8.6 (8.1-10.6)	8.5 (8.0-10.5)	8.7 (8.1-10.6)
Median no. cores	11 (8-13)	12 (8-13)	10 (7-13)
Extended biopsy (>8 cores), n. (%)	136 (67%)	70 (69%)	66 (66%)
Clinical stage, n. (%)			
T1c	174 (86)	88 (87)	86 (85)
T2a	28 (14)	13 (13)	15 (15)
Tumor extent from MRI, n. (%)			
Minimal involvement	19 (9)	16 (16)	3 (3)
Moderate involvement	167 (83)	84 (83)	83 (82)
Extensive involvement	16 (8)	1 (1)	15 (15)
ECE involvement from MRI, n. (%)	27 (13)	8 (8)	19 (19)
Final Gleason score			
≤6	138 (68)	101 (100)	37 (37)
7	63 (31)	0 (0)	63 (62)
≥8	1 (0.5)	0 (0)	1 (1)
Positive surgical margins	15 (7)	0 (0)	15 (15)
Extraprostatic extension	19 (9)	0 (0)	19 (19)
Seminal vesicle invasion	3 (1)	0 (0)	3 (3)
Pathologic stage			
pT0	13 (6)	13 (13)	0
pT2a	45 (22)	36 (36)	9 (9)
pT2b	104 (51)	43 (43)	61 (60)
pT2c	19 (9)	9 (9)	10 (10)
≥pT3a	21 (10)	0 (0)	21 (21)
Median tumor volume, (mL) (IQR)	0.26 (0.04-0.82)	0 (0.01-0.22)	0.82 (0.42-1.38)

ECE = extracapsular extension; MRI = magnetic resonance imaging; PSA = prostate-specific antigen.
Values in parentheses are ranges, unless specified otherwise.

Table 2. Sensitivity and specificity of MRI by prostate location

Prostate Location	MRI Score	Cancer Present on Whole Mount Maps		Sensitivity/ Specificity (%)
		Yes	No	I/II/III vs IV/V
Left anterior	Unlikely cancer (I/II)	42	69	16%/91%
	Indeterminate (III)	45	20	
	Likely cancer (IV/V)	17	9	
Right anterior	Unlikely cancer (I/II)	35	78	2%/95%
	Indeterminate (III)	55	27	
	Likely cancer (IV/V)	2	5	
Left posterior	Unlikely cancer (I/II)	47	36	7%/95%
	Indeterminate (III)	87	19	
	Likely cancer (IV/V)	10	3	
Right posterior	Unlikely cancer (I/II)	55	38	20%/93%
	Indeterminate (III)	60	17	
	Likely cancer (IV/V)	28	4	

mor in 98 patients (49%). Overall, multifocal and bilateral tumors were present in 81% and 68% of patients, respectively. The posterior mid-gland was the most common tumor location (n = 126). The prostate apex was involved in 33% (n = 33) and 59% (n = 60) of the group 1 and group 2 patients, respectively, and was the only site of tumor in 8% (3 of 37) of patients, with tumor at only 1 location.

Table 2 shows the sensitivity and specificity of MRI for each of the 4 prostate locations: right/left and anterior/posterior. When MRI level of suspicion scores was assessed into grade I/II/III vs grades IV/V, the sensitivity was 2%-20%, and specificity was 91%-95%. The sensitivity and specificity of ECE were 58% and 100%, respectively. Negative predictive value of MRI for overall extent of tumor was 58%.

Regarding the MRI-detected extent of tumor, 19 patients (9%) were classified as having minimal involvement, 167 (83%) moderate involvement, and 16 (8%) extensive disease. Although most patients in both groups

Table 3. Multivariable logistic regression analysis for prediction of nonindolent cancer

Predictor	Odds Ratio	95% CI	*P*
PSA	*	*	.3
Extent of biopsy			.7
Limited	Ref	Ref	
Extended	0.87	0.46-1.66	
ECE from MRI			.4
No	Ref	Ref	
Yes	1.51	0.57-4.01	
Tumor extent from MRI			.0018
Minimal	Ref	Ref	
Moderate	5.39	1.49-19.5	
Extensive	70.5	6.20-802	

CI = confidence interval; ECE = extracapsular extension; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; Ref = reference.
* Odds ratio for PSA not presented because PSA was modeled with splines to account for the nonlinear relationship between PSA and outcome.

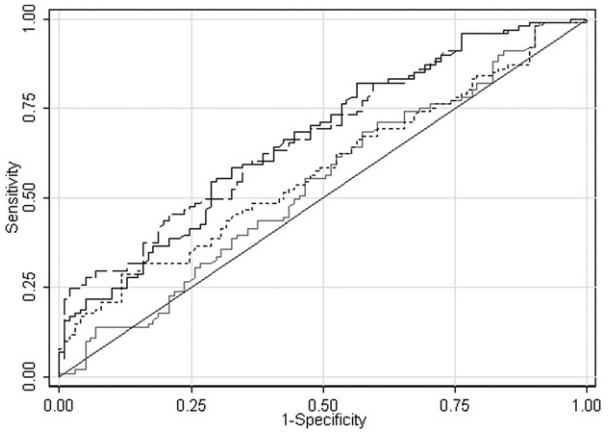

Figure 1. Area under the curve of 4 models. Base model (solid grey line) includes PSA (with cubic splines), number of cores taken from biopsy. Other models include MRI-detected ECE, (dashed line), tumor extent from MRI (solid black line), or both (green line).

were found to have moderate tumor according to the MRI tumor extent, more patients were classified as tumor-free in group 1 (16%, n = 16) than in group 2 (3%, n = 3). Similarly, more patients in group 2 as compared to group 1 were classified as having extensive tumor on MRI (15%, n = 15 and 1%, n = 1, respectively). Overall, 27 (13%) patients were classified as having extracapsular extension; 8 (8%) in group 1 and 19 (19%) in group 2.

On univariate analysis, patients with MRI-detected ECE (odds ratio 2.7, 95% confidence interval [CI] 1.2-6.5, $P = .027$) and MRI-detected tumor extent (moderate: odds ratio 5.3, 95% CI 1.5-18.8; extensive: odds ratio 80.0, 95% CI 7.5-856, $P = .001$) were more likely to have pathologic evidence of nonindolent cancer. On multivariable analysis (Table 3), only tumor extent from MRI remained a strong significant predictor (moderate: odds ratio 5.39, 95% CI 1.49-19.5; extensive: odds ratio 70.5, 95% CI 6.20-802, global $P = .0018$).

When additional information obtained from the MRI was included in the multivariable logistic regression model, a small improvement in predictive accuracy was observed. The multivariable base model that included PSA and extent of biopsy had an AUC of 0.489, which increased to 0.616 when including MRI-detected ECE, and to 0.525 when including MRI-detected tumor extent. Adding both MRI-detected ECE and tumor extent increased the AUC to 0.624 (Fig. 1). We conducted a sensitivity analysis to investigate whether small, but high-grade tumors were affecting our results, as these tumors are difficult for MRI to detect. For 82 patients with clinically significant cancer, 19 additional patients were classified as having indolent disease when clinically significant tumors were restricted to those with tumor volume >0.5 cm, extracapsular extension, seminal vesicle invasion, lymph node involvement, or positive surgical margins. We repeated our analysis considering these patients as having indolent cancer, and there was no important difference in results. The predictive accuracy of the model using this definition of clinically significant cancer was 0.581, increasing to 0.664 and 0.619 with the addition of MRI-detected tumor extent and MRI-detected ECE, respectively, and to 0.675 with both additional predictors.

COMMENT

Widespread early detection of PCA by the use of PSA and digital rectal examination has helped detect PCA at an earlier stage. A proportion of these tumors are of limited biological risk to patients, prompting the development of active surveillance protocols as an option for management. However, several patients on active surveillance will demonstrate progression of disease, arguably missing the opportunity for curative treatment.[11,12] Underestimation of tumor characteristics with biopsy and clinical features is not uncommon.[13,14] Although oncologically efficient, current treatment options can affect sexual, urinary, and bowel function, which may be avoidable in a subset of patients. The issue remains how to appropriately characterize and stratify patients with PCA at the time of initial diagnosis and provide effective treatment options for those who would benefit. Increasingly, options for treatment have become less invasive.

Focal therapy modalities for PCA encompass prostate-sparing techniques, using new technologies such as cryotherapy, immunotherapy, high-intensity focused ultrasound, photodynamic therapy, interstitial laser therapy, and radiofrequency ablation. Purported benefits of these techniques allow for ablation of the tumor area only, and not the entire prostate, potentially minimizing treatment-related side effects. To be effective, accurate tumor targeting and patient selection are needed in the development of clinical trials.

Focal therapy is treatment to a sub volume of the prostate; therefore, ideal patients would include those with limited unilateral disease. However, multifocal PCA is common, present in 67%-87% of all pathologic spec-

imens after RP, even among men with small cancer volume (<0.5 mL).[15] Although related to a more aggressive disease, multifocal PCA does not necessarily represent a contraindication for focal therapy. An index tumor (defined as the largest) is frequently identified and represents the most important determinant of prognosis. Even when the cancer is multifocal, most nonindex tumors appear to be biologically indolent on the basis of their small size and low grade. Ohori et al[16] found that among patients with multifocal disease, 80% of the total tumor volume was present in the index tumor. In 92% of patients, ECE arose from the largest cancer.[16] It is generally accepted that the tumor progression is mediated by index tumors of larger volume (>0.5 mL) and higher grade (Gleason score ≥7). To prove effective, accurate localization and characterization of the index tumor for candidate focal therapy patients are needed.

Several features have been proposed as important determinants for success with focal treatment.[4] Unilateral tumors allow for limited treatment to be applied with risk to 1 neurovascular bundle. Using the SEARCH database, Scales et al[17] showed that only 35% of the unilateral tumors on prostate biopsy had unilateral disease in the RP pathology. In the present study, focal and unilateral cancers were seen in 39 patients (18.7%) and 67 patients (32%), respectively. Tumor volume represents another important feature. High-volume tumor in needle biopsy correlates with the extent of tumor on the RP specimen; however, the converse is not always true.[18] In the current series, 35% of tumors had a volume >0.5 mL, which excluded them from the indolent PCA group. Tumor grade performs well as a predictor of biochemical failure, systemic recurrence, and overall survival in prostate cancer. Upgrading of tumors from biopsy to final pathology is well documented; in our study, 68 patients (33%) had an upgrade in RP Gleason score similar to that seen in other series of similar, though less selected, patients.[19,20] Inaccuracy of standard diagnostic TRUS biopsy for identifying higher risk features of prostate tumors supports the need for development of improved evaluative techniques, when considering surveillance or focal therapy.

Transperineal stereotactic mapping biopsies using a brachytherapy template guide have been used to provide more detailed spatial and histologic information, but are more invasive. Obtaining accurate data with this strategy requires 5-mm spacing of samples under general anesthesia, and carries a greater risk of urinary retention and voiding dysfunction.[21-23]

Image-based localization and treatment techniques represent an optimal approach to management. Among the current imaging modalities, MRI is the most extensively studied and perhaps the most promising one. MRI sensitivity for disease detection ranges from 40% to 90%, and reports for detection of tumors >1 cm are as high as 85%.[24-26] The accuracy of MRI for smaller tumors is less established. MRI information assessed using 4 prostate quadrant localization demonstrated moderate sensitivity, that is, 2%-20% but strong specificity, that is, 91%-95%, yielding an overall negative predictive value of 58%. MRI improved the prediction for minimal disease that included clinical and pathologic preoperative data. This is particularly of interest in this group of patients with homogenous clinical parameters that lack discriminatory features other than serum PSA. Our data do not support the use of T2-weighted endorectal MRI to localize small tumors for focal therapy, but suggest that MRI is useful for excluding patients from focal therapy trials on the basis of radiographic evidence of more extensive disease.

Limitations in this analysis include those of retrospective studies. Only surgical patients with preoperative MRI were included, indicating clinical selection of patients by the treating surgeon. As part of a surgical series, these patients may not accurately reflect the biology found among patients managed with active surveillance. TRUS biopsy procedures were nonstandardized, including samples obtained from referring physicians. Sampling adequacy was assessed using number of cores, and univariate analysis—which stratified patients by the extent of their biopsy—did not identify biopsy number as significant. MRI was limited to T_2-weighted imaging, which may differ from results that are possible with higher magnetic field strengths or multiparametric imaging capabilities that include diffusion-weighted, dynamic contrast, or spectroscopy capabilities.[27] Localization data were analyzed using a quadrant system instead of sextant because of the difficulties in colocalizing segments of the base, mid, and apex between MRI and pathology specimens, whereas planes of laterality and anterior-posterior dimensions are clearly defined and readily translatable. For many studies involving correlation of imaging studies with prostate pathology, the issue of accurate colocalization is difficult because processing of pathologic specimens may involve anatomic sectioning in planes dissimilar to the imaging planes of MRI.

CONCLUSIONS

Current clinical criteria for identifying men with PCA eligible for organ-sparing management strategies correctly indicate indolent cancer in 50% of cases when using initial diagnostic TRUS biopsy criteria. T_2-weighted MRI is helpful in further evaluating these patients to indicate those with greater likelihood of having more extensive disease than suspected, yet is not sufficient to localize these small tumors for focal therapy trials.

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