Magnetic Resonance Imaging for Predicting Prostate Biopsy Findings in Patients Considered for Active Surveillance of Clinically Low Risk Prostate Cancer

Hebert Alberto Vargas,*,† Oguz Akin, Asim Afaq, Debra Goldman, Junting Zheng, Chaya S. Moskowitz, Amita Shukla-Dave, James Eastham, Peter Scardino‡ and Hedvig Hricak‡

From the Departments of Radiology (HAV, OA, AA, DG, HH), Epidemiology and Biostatistics (JZ, CSM), Medical Physics (ASD) and Surgery (JE, PSI), Memorial Sloan-Kettering Cancer Center, New York, New York

Purpose: A barrier to the acceptance of active surveillance for men with prostate cancer is the risk of underestimating the cancer burden on initial biopsy. We assessed the value of endorectal magnetic resonance imaging in predicting upgrading on confirmatory biopsy in men with low risk prostate cancer.

Materials and Methods: A total of 388 consecutive men (mean age 60.6 years, range 33 to 89) with clinically low risk prostate cancer (initial biopsy Gleason score 6 or less, prostate specific antigen less than 10 ng/ml, clinical stage T2a or less) underwent endorectal magnetic resonance imaging before confirmatory biopsy. Three radiologists independently and retrospectively scored tumor visibility on endorectal magnetic resonance imaging using a 5-point scale (1—definitely no tumor to 5—definitely tumor). Inter-reader agreement was assessed with weighted kappa statistics. Associations between magnetic resonance imaging scores and confirmatory biopsy findings were evaluated using measures of diagnostic performance and multivariate logistic regression.

Results: On confirmatory biopsy, Gleason score was upgraded in 79 of 388 (20%) patients. Magnetic resonance imaging scores of 2 or less had a high negative predictive value (0.96–1.0) and specificity (0.95–1.0) for upgrading on confirmatory biopsy. A magnetic resonance imaging score of 5 was highly sensitive for upgrading on confirmatory biopsy (0.87–0.98). At multivariate analysis patients with higher magnetic resonance imaging scores were more likely to have disease upgraded on confirmatory biopsy (odds ratio 2.16–3.97). Inter-reader agreement and diagnostic performance were higher for the more experienced readers (kappa 0.41–0.61, AUC 0.76–0.79) than for the least experienced reader (kappa 0.15–0.39, AUC 0.61–0.69). Magnetic resonance imaging performed similarly in predicting low risk and very low risk (Gleason score 6, less than 3 positive cores, less than 50% involvement in all cores) prostate cancer.

Conclusions: Adding endorectal magnetic resonance imaging to the initial clinical evaluation of men with clinically low risk prostate cancer helps predict findings on confirmatory biopsy and assess eligibility for active surveillance.

Key Words: magnetic resonance imaging, prostatic neoplasms, watchful waiting
Early diagnosis of prostate cancer during the PSA era has resulted in a downward trend in cancer stage at presentation and improved overall survival.\textsuperscript{1,2} Nevertheless, the high rate of diagnosis of clinically low risk, localized prostate cancer, coupled with the minimal incidence of death from such disease, has raised concerns about overtreatment.\textsuperscript{3,4} In the quest to prevent overtreatment, active surveillance has emerged as a plausible option. AS has proven extremely effective, with disease specific survival rates reported at 97\% to 100\% after 3 to 10 years.\textsuperscript{5–9} However, appropriate criteria for selecting patients for AS are continuously debated. In 2010 the NCCN (National Comprehensive Cancer Network) recommended the use of active surveillance as the sole initial management strategy, not just an option, for patients with low risk prostate cancer and a life expectancy of less than 10 years, as well as for patients with very low risk prostate cancer and a life expectancy of less than 20 years.\textsuperscript{10,11}

A potential pitfall of basing AS decisions on biopsy findings is in the fact that high grade or large volume tumors may be missed by the biopsy needle, and the resulting delays in treatment may negatively affect outcomes. Even the most stringent criteria misclassify 16\% to 42\% of cases which, despite low risk features on initial biopsy, have unfavorable pathological features at radical prostatectomy.\textsuperscript{12} To improve the detection of large or high grade cancers, some centers recommend a second (confirmatory) prostate biopsy before the start of AS. Berglund et al found that up to 27\% of patients with very low risk features on initial biopsy had disease upgraded or up staged at confirmatory biopsy, and that patients who had upgraded and/or up staged disease on confirmatory biopsy were more likely to show an increase in stage and grade at radical prostatectomy than those whose did not.\textsuperscript{13}

MRI alone or combined with clinical parameters may be useful in the prediction of insignificant prostate cancer, particularly in the context of clinically nonpalpable tumors.\textsuperscript{14–16} Furthermore, on MRI, less aggressive tumor foci (ie Gleason score 6 or less) are more difficult to detect than more aggressive tumors.\textsuperscript{17,18} However, to our knowledge the capacity of T2-weighted MRI to predict confirmatory prostate biopsy findings has not been explored. Therefore, we evaluated T2-weighted MRI as a tool to predict pathological upgrading on confirmatory prostate biopsy in men with clinically low risk prostate cancer being considered for AS.

**MATERIALS AND METHODS**

The institutional review board approved our retrospective study and waived the informed consent requirement. Our study was compliant with the Health Insurance Portability and Accountability Act of 1996.

**Eligibility Criteria and Patient Characteristics**

Using computerized searches of our institutional database, we identified 573 patients satisfying the inclusion criteria of Gleason score 6 or less prostate cancer on initial transrectal prostate biopsy performed between January 1, 1999 and September 30, 2010, PSA less than 10 ng/ml, clinical stage T2a or less and confirmatory prostate biopsy performed within 6 months of the initial prostate biopsy. We excluded patients with no prostate MRI performed between the initial and confirmatory biopsies (173 patients), prostate MRI performed without an endorectal coil (11 patients) and MRI performed elsewhere (1 patient). Thus, our final study population consisted of 388 patients.

**MRI Acquisition**

All MRI studies were performed using whole-body units (GE Healthcare, Waukesha, Wisconsin). A body coil was used for excitation, and a pelvic phased array coil and an expandable endorectal coil were used for signal reception. Due to the length of the study period (10 years), the MRI parameters varied slightly as per the standard clinical protocols in place at our institution at the time of each examination. However, all MRI studies involved the sequences and acquisition parameters of transverse T1-weighted images (repetition time/echo time 400 to 750/10 to 14 ms, section thickness 5 mm, intersection gap 1 mm, field of view 28 to 36 cm, matrix 256 × 192); transverse, coronal and sagittal T2-weighted fast spin-echo images (repetition time/effective echo time 3,500 to 6,000/120 ms, section thickness 3 mm, no intersection gap, field of view 12 to 14 cm, matrix 256 × 192). MRI studies were performed at 1.5 T (312 patients) and 3 T (76 patients).

**MRI Interpretation**

Three radiologists retrospectively and independently interpreted the MRI studies, which were archived in a picture archiving and communication system (Centricity®). Reader 1 was a fellowship trained body radiologist who had read only about 50 prostate MRI examinations before this study. Reader 2 was a body imaging fellow with a special interest and dedicated training in prostate imaging, who had read approximately 500 prostate MRI examinations. Reader 3 was a fellowship trained genitourinary radiologist who had interpreted more than 5,000 prostate MRI examinations. Readers were aware that the patients had low risk features on initial clinical evaluation and biopsy but were unaware of their PSA levels, the number(s) or location(s) of initial positive biopsies and the confirmatory biopsy findings. For each patient, each reader independently assigned a score for the presence of tumor on MRI on a 1 to 5 index scale (1—definitely no tumor, 2—probably no tumor, 3—indeterminate, 4—probably tumor, 5—definitely tumor) using previously published criteria (figs. 1 to 3).\textsuperscript{19} If a score of 4 or greater was assigned, the reader also recorded the number of lesions per patient, the maximum diameter of the largest lesion and lesion laterality (unilateral or bilateral), as well as the likelihood of ECE and SVI (using the same 5-point scale).
Histopathological Analysis and Image Correlation

For all patients initial biopsy was performed at a referring institution and confirmatory biopsy was performed at our institution within the following 6 months. There were 55 patients (14%) who had more than 1 prostate biopsy before the confirmatory biopsy, and of these patients 3 had more than 1 positive biopsy before confirmatory biopsy. The confirmatory biopsy included a standard 12-core biopsy, in which samples were obtained from the medial and lateral aspects of the base, middle and apical portions of the prostate bilaterally. In addition, 2 biopsy samples were obtained from the transition zone for a total of 14 cores. At the discretion of the urologist performing the procedure, samples were also obtained from suspicious lesions identified on digital rectal examination, transrectal ultrasound or MRI. All biopsy specimens were reviewed at our institution by a dedicated genitourinary pathologist. In the patients who underwent radical prostatectomy within 6 months of prostate MRI, pathology findings were compared with those from confirmatory biopsy.

Reference Standards

Confirmatory prostate biopsy was used as the reference standard to identify patients for whom the NCCN Prostate Cancer Guidelines recommended active surveillance. All biopsy specimens were reviewed at our institution by a dedicated genitourinary pathologist. In the patients who underwent radical prostatectomy within 6 months of prostate MRI, pathology findings were compared with those from confirmatory biopsy.
itive cores), and the NCCN very low risk category included patients with no Gleason score 7 or greater cancer in the confirmatory biopsy, no more than 3 cores involved by cancer and no single core with 50% or more involvement by cancer.

Statistical Analysis
Clinical and demographic data were summarized using descriptive statistics. Inter-reader agreement was assessed using weighted kappa statistics with Fleiss-Cohen (quadratic) weights and interpreted based on the table provided by Landis and Koch.19,20 Measures of diagnostic accuracy for predicting confirmatory biopsy findings, including sensitivity, specificity, positive predictive value and negative predictive value, were estimated at a per patient level at every possible cutoff of the 1 to 5 suspicion scale. Performance was also evaluated using the empirical ROC and AUC. AUCs for reader performance were calculated separately for 1.5 and 3 T MRI studies, and for MRI studies obtained before January 1, 2007 and on or after that date (which coincided with the last major software upgrade at our institution).

Multivariate logistic regression was used to evaluate associations between MRI features and confirmatory biopsy findings using odds ratios with p <0.05 considered significant. All statistical analyses were performed with SAS® 9.2 software.

RESULTS
Pathological Findings
Confirmatory biopsy findings fit the NCCN criteria for low risk disease in 309 of 388 patients (80%) and the NCCN criteria for very low risk disease in 239 of 388 patients (62%). In 124 patients (32%) no cancer was identified on confirmatory biopsy. In 79 patients disease was upgraded on confirmatory biopsy (ie there was at least 1 core with Gleason score 7 or greater cancer). Confirmatory biopsy included targeted cores of lesions detected by transrectal ultrasound, MRI or digital rectal examination in 70 of 388 patients (18%). Prostatectomy was done within 6 months of MRI in 129 patients (33%). In 84 of these 129 patients (65%) prostatectomy showed higher grade disease than did initial biopsy, and for 51 of the 84 patients (61%) confirmatory biopsy also showed higher grade disease than did initial biopsy.

MRI Score
An MRI score of 2 or less was associated with a high negative predictive value (0.96–1.0) for upgrading on confirmatory biopsy and a high negative predictive value (0.77–0.98) for non-very low risk features on confirmatory biopsy. For all readers an MRI score of 5 was associated with high sensitivity (0.87–0.98) for upgrading on confirmatory biopsy and high sensitivity (0.88–0.99) for non-very low risk features on confirmatory biopsy. Table 1 summarizes the measurements of diagnostic accuracy for predicting confirmatory biopsy findings at different cutoff points. AUCs did not differ significantly between 1.5 and 3 T MRI studies (p = 0.16–0.30) or between MRI studies obtained before January 1, 2007 and those obtained on or after that date (p = 0.26–0.73).

Other MRI Findings
The readers detected at least 1 lesion in 27% to 52% of patients. In the majority of cases, the lesions were unilateral according to readers 1 and 3 and bilateral according to reader 2. All readers suspected ECE in approximately 4% of patients and SVI in less than 1%.

Multivariate Analysis
Multivariate logistic regressions showed that for all readers, MRI scores were significantly associated
with confirmatory biopsy findings (table 2). For reader 1, lesion size was associated with the NCCN low risk category (OR 0.92, 95% CI 0.85–0.99, p = 0.03). No other MRI features were associated with confirmatory biopsy findings for any readers.

### Inter-reader Agreement

Agreement on MRI score was fair between reader 1 (least experienced) and reader 2 (intermediate experience) (weighted kappa 0.31), and between reader 1 and reader 3 (most experienced) (weighted kappa 0.38). Agreement was substantial between readers 2 and 3 (weighted kappa 0.61).

### DISCUSSION

Among patients initially diagnosed with clinically low risk prostate cancer, those with tumors not clearly visualized on MRI were significantly more likely to demonstrate low risk features on confirmatory biopsy, while patients with tumors clearly visualized on MRI were significantly more likely to have

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**Table 1. Measurements of accuracy of MRI for predicting confirmatory biopsy features consistent with NCCN risk categories**

<table>
<thead>
<tr>
<th>Cutoff</th>
<th>Specificity Value (95% CI)</th>
<th>Sensitivity Value (95% CI)</th>
<th>Pos Predictive Value Value (95% CI)</th>
<th>Neg Predictive Value Value (95% CI)</th>
<th>AUC Value (95% CI)</th>
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<tr>
<td><strong>Prediction of NCCN low risk features on confirmatory biopsy</strong></td>
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<tr>
<td>Reader 1:</td>
<td>2 or Less 1.00 (0.95, 1.00) 0.06 (0.03, 0.09) 0.21 (0.17, 0.26) 1.00 (0.81, 1.00) 0.69 (0.63, 0.75)</td>
<td>3 or Less 0.65 (0.53, 0.75) 0.67 (0.61, 0.72) 0.33 (0.26, 0.41) 0.98 (0.83, 0.92)</td>
<td>4 or Less 0.37 (0.26, 0.48) 0.87 (0.83, 0.91) 0.43 (0.31, 0.55) 0.84 (0.80, 0.88)</td>
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<tr>
<td>Reader 2:</td>
<td>2 or Less 1.00 (0.95, 1.00) 0.20 (0.16, 0.25) 0.24 (0.20, 0.29) 1.00 (0.94, 1.00) 0.79 (0.74, 0.84)</td>
<td>3 or Less 0.89 (0.85, 0.95) 0.56 (0.51, 0.62) 0.34 (0.28, 0.41) 0.95 (0.91, 0.96)</td>
<td>4 or Less 0.44 (0.33, 0.56) 0.90 (0.86, 0.93) 0.54 (0.41, 0.66) 0.96 (0.92, 0.99)</td>
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<tr>
<td>Reader 3:</td>
<td>2 or Less 0.95 (0.88, 0.99) 0.32 (0.27, 0.37) 0.26 (0.21, 0.32) 0.96 (0.90, 0.99) 0.76 (0.70, 0.81)</td>
<td>3 or Less 0.57 (0.45, 0.68) 0.82 (0.77, 0.86) 0.44 (0.34, 0.54) 0.88 (0.84, 0.92)</td>
<td>4 or Less 0.22 (0.13, 0.32) 0.98 (0.96, 0.99) 0.74 (0.52, 0.90) 0.83 (0.79, 0.87)</td>
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<tr>
<td><strong>Prediction of NCCN very low risk features on confirmatory biopsy</strong></td>
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<tr>
<td>Reader 1:</td>
<td>2 or Less 0.97 (0.93, 0.99) 0.05 (0.03, 0.09) 0.37 (0.32, 0.42) 0.77 (0.50, 0.93) 0.61 (0.56, 0.67)</td>
<td>3 or Less 0.52 (0.43, 0.60) 0.68 (0.61, 0.73) 0.48 (0.40, 0.56) 0.71 (0.65, 0.77)</td>
<td>4 or Less 0.28 (0.21, 0.36) 0.88 (0.84, 0.92) 0.57 (0.45, 0.69) 0.68 (0.63, 0.73)</td>
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<tr>
<td>Reader 2:</td>
<td>2 or Less 0.99 (0.96, 1.00) 0.25 (0.19, 0.31) 0.43 (0.38, 0.49) 0.98 (0.91, 1.00) 0.79 (0.75, 0.83)</td>
<td>3 or Less 0.81 (0.73, 0.87) 0.63 (0.57, 0.69) 0.56 (0.49, 0.63) 0.85 (0.79, 0.90)</td>
<td>4 or Less 0.37 (0.29, 0.45) 0.90 (0.91, 0.97) 0.80 (0.68, 0.89) 0.72 (0.67, 0.77)</td>
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<tr>
<td>Reader 3:</td>
<td>2 or Less 0.94 (0.89, 0.98) 0.38 (0.32, 0.44) 0.47 (0.41, 0.53) 0.92 (0.85, 0.97) 0.76 (0.71, 0.80)</td>
<td>3 or Less 0.49 (0.40, 0.56) 0.87 (0.82, 0.91) 0.68 (0.58, 0.77) 0.75 (0.68, 0.80)</td>
<td>4 or Less 0.15 (0.10, 0.22) 0.99 (0.97, 1.00) 0.91 (0.72, 0.99) 0.67 (0.62, 0.72)</td>
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* Reader 3 did not identify SVI in any of the patients.
disease upgraded on confirmatory biopsy. In addition, our results confirm the importance of confirmatory biopsy in patients being evaluated for AS. Among the patients who underwent prostatectomy within 6 months of MRI, the surgicopathological Gleason score was higher than that of the initial biopsy in 65%, but was higher than that of the confirmatory biopsy in only 26%, suggesting that confirmatory biopsy provided a better estimate of the total tumor burden than did the initial biopsy. The clinical and demographic characteristics of our study population are similar to those of patients undergoing AS in all the largest published series. This suggests that by predicting the findings of confirmatory biopsy, MRI could aid the identification of suitable candidates for AS. Our results also confirm prior reports on the importance of training and experience for accurate interpretation of prostate MRI. Measurements of diagnostic performance were consistently lowest for the least experienced reader, while agreement was moderate to substantial between the 2 more experienced readers, although only slight to fair between the least experienced reader and either of the other readers. These results suggest that MRI of the prostate, if read by radiologists with appropriate training and experience, could help determine AS eligibility and obviate the need for confirmatory biopsy in substantial numbers of patients.

In the only published study we found that evaluated the use of T2-weighted MRI to select patients for AS, Ploussard et al reported on 96 patients who decided to pursue definitive treatment, although they were deemed eligible for AS based on stringent criteria from a single 21-core biopsy scheme (Gleason score 6 or less, fewer than 3 cores involved by cancer and tumor length per core less than 3 mm). The authors concluded that MRI findings (dichotomized as organ confined vs nonorgan confined disease) did not improve the prediction of unfavorable features at prostatectomy in the population studied. Our results are concordant with theirs, as we did not find an association between ECE or SVI (ie nonorgan confined disease) on MRI and upgrading from the NCCN low and very low risk categories at confirmatory biopsy. However, we did find an association between tumor visibility on MRI and confirmatory biopsy findings, meaning that in this clinical setting, the most important MRI finding is not whether the cancer appears organ confined, but whether it is clearly visualized.

Our study has several limitations. It is retrospective, and we chose confirmatory biopsy rather than long-term outcomes as our reference standard. However, our results could provide the foundation for a prospective study incorporating outcome data. In addition, NCCN classifications and all other predictive tools intended to define clinically significant prostate cancer are controversial. Nevertheless, many of these tools are routinely used in clinical practice (such as the D’Amico risk stratification system25 and the Epstein criteria26). Despite subtle differences between the tools and guidelines used to classify risk level and select patients for AS, no substantial differences in AS outcomes associated with their use have been reported. Furthermore, the NCCN risk assessment criteria used here, which are the only ones that include specific recommendations about suitability for AS, are part of established management guidelines.11 It should also be noted that 18% of confirmatory biopsies in our study included samples from lesions targeted based on clinical or imaging findings. Theoretically this could have improved tumor burden detection on confirmatory biopsies, although whether the initial biopsies also included targeted samples is unknown.

Another limitation of our study was the inclusion of 1.5 and 3 T MRI examinations performed during a period of 10 years. This allowed us to maximize the number of eligible patients but also introduced potential diagnostic heterogeneity. However, we found no differences in diagnostic performance between 1.5 and 3 T MRI studies, or between MRI studies obtained before or after the last major software upgrade at our institution. This suggests that technological improvements in the last decade may not have significantly affected conventional sequences such as T2-weighted imaging, which still represents the mainstay of prostate MRI. To date, the theoretical advantages of 3 T MRI for prostate cancer diagnosis have not been comprehensively validated.27 While there is currently great interest in the use of MP MRI sequences such as diffusion weighted imaging and dynamic contrast enhanced MRI, such sequences have only been clinically available for a few years. Thus, the largest published study to our knowledge of MP MRI in patients considering AS includes only 60 patients.28 We hope our study of T2-weighted MRI will serve as a basis for future studies assessing the incremental value of MP MRI in larger cohorts.

In summary, the success of active surveillance as a management strategy for prostate cancer relies primarily on the accurate identification of patients with low risk disease unlikely to progress. The fact that clear tumor visualization on MRI was predictive of upgrading on confirmatory prostate biopsy suggests that prostate MRI may contribute to the complex process of assessing patient eligibility for AS.

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