Magnetic resonance imaging-directed transrectal ultrasonography-guided biopsies in patients at risk of prostate cancer

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OBJECTIVE

To evaluate whether using endorectal-coil magnetic resonance imaging (erMRI) before transrectal ultrasonography (TRUS)-guided biopsies of the prostate increases the yield of cancer in a high-risk population, and in a subset analysis to compare the yield with high-field (3 T) vs lower field (1.5 T) MRI.

PATIENTS AND METHODS

Between March 2003 and November 2005, 26 consecutive patients had erMRI before their TRUS biopsy of the prostate (median age 62 years, range 32–76). The median prostate-specific antigen (PSA) level was 8.40 (2.1–85.9) ng/mL. All patients had at least one previous negative prostate biopsy (median 3, range 1–12). Twenty-three patients had at least one risk factor for prostate cancer (family history, high PSA velocity, low percentage of free PSA, prostatic intraepithelial neoplasia or atypical small acinar proliferation on previous biopsy). MRI studies consisted of T2-weighted and dynamic contrast-enhanced (DCE) imaging studies.

RESULTS

There was a close correlation between T2-weighted and DCE images (85% agreement, $P < 0.001$). Neither T2-weighted nor DCE imaging correlated with a higher yield for cancer on final biopsy (T2, positive predictive value, PPV, 20%, negative PV, NPV, 14%, $P = 0.21$; DCE, PPV 21%, NPV 15%, $P = 0.26$). Combining the two methods did not improve the cancer yield. There was no significant difference in the probability of cancer based on 1.5 T or 3 T imaging (17% vs 16%, $P = 0.88$).

CONCLUSION

Although erMRI before TRUS-guided biopsies tended to give higher cancer yields the difference was not statistically significant. Reasons for this might include suboptimal localisation of the MRI findings and the biopsy location. Better methods for fusing MRI and TRUS images are presently being developed at our institution to allow more accurate targeting.

KEYWORDS

prostate cancer, prostate biopsy, MRI, ultrasonography, cancer

INTRODUCTION

Patients with persistently negative biopsies despite persistent or worsening risk factors for cancer pose a diagnostic challenge. The main concern in this population is to miss a window of opportunity where curative treatment remains possible. Standard, systematic repeated prostate biopsies do not give a greater detection rate [1], yet risk complications and discomfort to the patient. Attempts to improve detection rates have included taking more biopsies [2,3], and using prostate imaging to better locate a target for biopsy [4–7].

Endorectal-coil MRI (erMRI) of the prostate has received attention as a potential targeting method for prostate cancer. A wide range of accuracy, sensitivity, specificity and predictive values was reported using various groups of patients and protocols [8–10]. Recent reports suggested that MRI might be a better imaging method than TRUS in a high-risk population with previous negative biopsies [4–7]. However, only T2-weighted imaging or spectroscopy results were reported for these patients and no dynamic contrast-enhanced (DCE) MRI was assessed. Furthermore, all imaging studies reported to date used 1.5 T MRI.

DCE MRI has been reported to discriminate between normal tissue and cancer in the prostate peripheral zone (PZ) [11,12]. This provides a rationale to test the role of DCE in prostate cancer targeting during diagnostic biopsies. Furthermore, recent reports using 3 T MRI compared to whole-mount specimens reported a significant correlation for prostate cancer location [13], although the significance of this finding is uncertain in a population in whom prostate cancer has not yet been identified.

The purpose of the present study was to assess the performance of erMRI using T2-weighted and DCE imaging before TRUS-guided prostate biopsy for cancer detection in patients with at least one previous negative prostate biopsy.

PATIENTS AND METHODS

Between March 2003 and November 2005, 26 consecutive patients had erMRI before TRUS-guided biopsies of the prostate (median age 62 years, range 32–76); their median PSA level was 8.4 (2.1–85.9) ng/mL. All patients had at least one previous set of prostate biopsies that were negative for cancer (median 3, range 1–12 biopsy procedures),

and patients with previous positive biopsies for cancer were excluded. Twenty-three patients had at least one risk factor for prostate cancer. This study was approved by the Institutional Review Board of the National Cancer Institute. Table 1 shows the patients' demographics.

Characteristic	Value
Median (range) age, years	62 (32–76)
Ethnicity, n	
White	18
African-American	6
Hispanic	1
Asian	1
Family history of prostate cancer	
None	13
One relative	7
More than one relative	2
Unknown	4
Median (range):	
PSA before biopsy, ng/mL	8.40 (2.1–85.9)
previous biopsies	3 (1–12)
prostate volume on MRI, mL	54.9 (11.9–133.0)
Significant findings on previous biopsies, n	
PIN	4
ASAP	6
N patients with palpable nodule on DRE	5
MRI field strength, T	
3	15
1.5	11

TABLE 1
The demographics of the patients

For MRI we used the 1.5 T or 3 T scanner, depending on the date of enrolment. The 3 T system was an Intera scanner (Intera Philips Medical System, Best, the Netherlands), used with a SENSE cardiac surface coil positioned over the pubic symphysis and an endorectal coil (BPX-15, Medrad, Indianola, PA, USA) in the rectum. After a DRE the endorectal coil was inserted and instilled with Fluorinert (3M, St Paul, MI, USA) to ≈60 mL. T2-weighted fast spin-echo images were obtained in three planes at a resolution of $0.46 \times 0.6 \times 3.0$ mm (field of view, FOV, 140 mm, matrix 234×304, repetition time, TR/time to echo, TE 8852/120 ms). DCE images were acquired during a single-dose injection with gadolinium-DTPA (Magnevist, Berlex Laboratories, Wayne, NJ, USA) at 3 mL/s with an injector (Spectrix MR Injection System, Medrad, Pittsburg, PA, USA). The DCE acquisition consisted of a 10-slice three-dimensional gradient echo with a temporal resolution of 3.1 s with a TR/TE of 5.5/2.1 ms, 15° flip angle, 26 cm FOV, number of signal averages of two, sensitivity encoding factor of 4 and resolution of $0.86 \times 1.18 \times 6.0$ mm

The 1.5 T system was a General Electric (GE Healthcare, Waukesha, WI, USA) 1.5 T scanner; T2-weighted images were obtained in three planes with a slice thickness of 3 mm (FOV 140 mm, matrix 256×256, TR/TE 4000/109). DCE was obtained using the same injection specifications as above (28 cm FOV, matrix 256×256, TR/TE 5000/2000 ms, slice thickness 7 mm).

MRI was interpreted exclusively by two dedicated radiologists (P.C., O.I.) who were unaware of the pathological diagnosis at the time of their final report. Suspicious areas were defined as hypo-intense regions on T2-weighted MRI and abnormally enhancing regions on DCE imaging. Abnormalities were reported separately for the T2-weighted and DCE images according to standard sextant anatomy. Any suspicion of extracapsular extension or seminal vesicle invasion was recorded, and laterality was noted in these cases. Prostate volume was measured based on MRI using maximum measurements in the coronal and axial views, according to the ellipsoid formula [14].

TRUS-guided biopsies were taken under monitored and controlled anaesthesia, and the supervision of one urologist (J.C.). Patients received peri-operative oral fluoroquinolones and a saline enema before biopsy. For TRUS we used an ultrasound scanner with harmonic and power Doppler imaging capabilities (EUB-6500, Hitachi Medical Systems, Twinsburg, Ohio, USA) with a biplanar 5–9 MHz endorectal biopsy probe (EUP-CC531). After reviewing the MRI films, the urologist taking the biopsy attempted to locate the abnormality reported on MRI using TRUS with power Doppler, harmonic imaging and frequency manipulations. Targeted biopsies were obtained when discrete lesions in the region of the MR abnormality were identified. When no abnormality was noted on TRUS, the approximate MR region of interest was biopsied and sent to pathology labelled by the sextant. Twelve cores were taken according to standard sextant anatomy, unless a target lesion was identified by TRUS, in which case this lesion was sampled as an additional biopsy (Fig. 1). A sextant was considered positive for cancer if either of the two biopsies sampling it was positive for cancer.

Sextants on T2-weighted and DCE images were dichotomized (positive or negative for cancer) and then compared with sextant biopsy results, which were also dichotomized as positive or negative for cancer. The Generalized Estimating Equation (GEE)/logistic regression [15] was used to examine the ability of MRI to predict a positive biopsy result. The GEE method accounts for the potential correlation in sextant measurements on the same subject. A Wald test was used to test for the significance of a particular MRI predictor. $P < 0.05$ was considered to indicate statistical significance and all reported tests were two-sided.

The sensitivity and specificity were estimated across sextants (e.g. sensitivity was defined as the proportion of sextants that tested positive, based on MRI criteria among sextants that were positive on biopsy). The bootstrap [16] was used to estimate 95% CIs corresponding to the sensitivity and specificity estimates, using a percentile interval with 5000 bootstrap samples.

RESULTS

In all, 11 patients had 1.5 T MRI and the other 15 had 3 T MRI before biopsy; Table 2 shows the overall MRI T2-weighted and DCE imaging

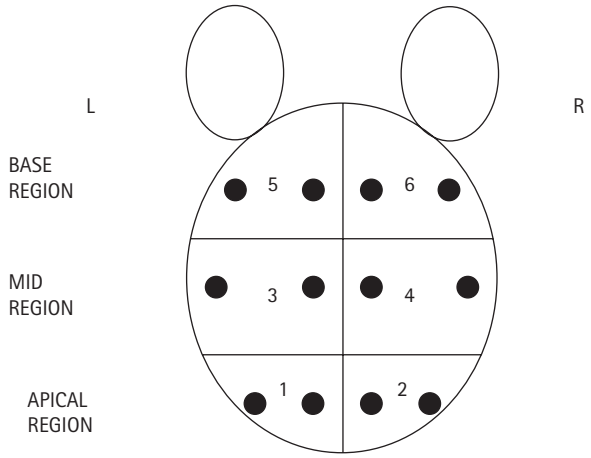


FIG. 1.
The MRI and sextant biopsy scheme: Abnormalities on T2-weighted MRI and DCE MRI were separately noted according to standard sextant anatomy, with suspicion of seminal vesicle invasion recorded separately. Two biopsies were taken per sextant, i.e. one medial and the other lateral. Refer to the text for the targeted biopsy scheme.

TABLE 2 Overall MRI findings compared biopsy findings (location by sextant histological correlation not considered). The biopsy is considered positive if any sextant-specific biopsy is positive. Likewise, the overall MRI T2-weighted or MRI DCE findings are positive if any of the sextant measurements are positive

	T 2/DCE findings		
Biopsy	+ve	−ve	Total
MRI T 2:			
Positive	13	1	14
Negative	10	2	12
Total	23	3	26
MRI DCE:			
Positive	10	4	14
Negative	8	4	12
Total	18	8	26

Feature	N
Clinical stage	
T1c	11
T2	3
Gleason score	
5	1
6	6
7	3
8	2
9	2
Mean (range) PSA before biopsy, ng/mL	19.1 (2.3–85.9)
Median (range) previous biopsies	3 (1–12)

TABLE 3
Clinical features of patients with cancer found on biopsies

Number of			Biopsy	
patients	T 2	DCE	+ve	−ve
2	Normal	Normal	0	2
6	Abnormal	Normal	4	2
1	Normal	Abnormal	1	0
17	Abnormal	Abnormal	9	8

TABLE 4
Overall results of T 2 and DCE imaging for biopsy (location by sextant correlation not considered)

findings for the biopsy outcome per patient, regardless of correspondence between the sextant sample and imaging of the biopsy. In all, 23 patients had at least one positive finding on T2-weighted MRI and 18 had one positive finding on DCE imaging; 14 patients (54%) had a biopsy result positive for cancer (Table 3 shows the clinical characteristics).

There was a strong correlation between T2-weighted MRI findings and DCE findings, with 85% agreement ($P < 0.001$). Findings on T2-weighted MRI did not increase the yield of positive biopsies (T2, positive predictive value, PPV, 20% and negative PV, NPV, 14%, $P = 0.21$). Likewise, DCE imaging did not contribute to increased positive biopsy rate (PPV 21% and NPV 15%, $P = 0.26$). Combining the two methods did not give better detection (T2 + DCE, PPV 23%, NPV 15%, $P = 0.14$). Seven lesions were identified on TRUS and thought to correspond to MRI abnormalities. Four of these lesions were positive for cancer on targeted biopsies. All these lesions could have been accounted for by the standard 12-biopsy scheme, in which at least one core was positive for cancer. The respective contribution to T2-weighted and DCE imaging in positive biopsy cases is reported in Table 4. Figures 2, 3 and 4 illustrate typical false-negative, true-positive and false-positive cases.

Table 5 provides sensitivity and specificity data for MRI in the present patients. When the definition of positive MRI was widened to include adjacent sextant samples to a positive biopsy site on one side or the other, the sensitivity of DCE increased to 64% (95% CI 44–80); that of MRI became 68 (50–84)%, and either MRI or DCE being positive resulted in a sensitivity of 76 (62–90)%. This was accompanied by a corresponding decrease in specificity (data not shown).

MRI field strength did not result in a significant difference in cancer detection rate. The probability of a positive biopsy was 16% at 3 T and 17% at 1.5 T ($P = 0.88$). The probability of a positive biopsy for sextant samples which are positive on either MRI or DCE was 22% at 3 T and 14% at 1.5 T ($P = 0.38$).

Stratifying by previous number of biopsies, prostatic intraepithelial neoplasia (PIN) or atypical small acinar proliferation (ASAP) on previous biopsies, PSA level before biopsy, and

prostate volume did not improve the contribution of MRI to the diagnosis.

The erMRI images were reviewed retrospectively after unblinding to assess whether the threshold for defining a lesion was high. On this second review, sensitivities were 68%, 44% and 68%, whereas specificities were 56%, 90% and 53% for MRI, DCE and MRI + DCE, respectively. When the correlation was enlarged to include neighbouring sextant samples to account for possible targeting inaccuracies, the sensitivities increased to 88%, 68% and 88% for MRI, DCE and MRI + DCE, respectively.

DISCUSSION

MRI for the detection and staging of prostate cancer has great potential clinical use. Unfortunately attempts at correlating and confirming the findings of MRI with tissue histology have been difficult, particularly among undiagnosed patients before biopsy. Four studies describe the contribution of erMRI to the diagnosis of prostate cancer in a high-risk population [4–7]. Two of them used T2-weighted MRI exclusively [5,6] and the other two used T2-weighted MRI and MRI spectroscopy. To our knowledge, ours is the first study using DCE imaging and erMRI before repeat prostate biopsies.

Sensitivities and specificities for T2-weighted MRI with or without spectroscopy in the previous studies were 43–85% and 22–98%, respectively, when considered on a core-by-core basis. Comparison of the data among studies is difficult, given that the biopsy schemes varied, as did the imaging parameters and thresholds for MRI spectroscopy. The contribution of MRI spectroscopy did not seem to be very well defined, although some patients with positive biopsies had anatomically corresponding suspicious findings on MRI spectroscopy only.

In the present study, a sensitivity for T2-weighted MRI of 40% was at the lower limit of what was reported previously, whereas specificity values were in the higher range (70%). Although contrary to the pattern in previous studies, the higher specificity in the present series might be due to the higher than expected prevalence of cancers detected in the present patients. It might also reflect a higher diagnostic threshold by the radiologists on MRI interpretation for cancer

FIG. 2. erMRI in a 66-year-old patient with a PSA level of 9.5 ng/mL. There was no low-intensity lesion on axial or coronal T2-weighted images and DCE-MRI. The biopsy result showed adenocarcinoma with a Gleason score of 8 on the right apex. (A) T2-weighted axial view and (B) coronal view. Axial views before (C) and after (D) DCE imaging.

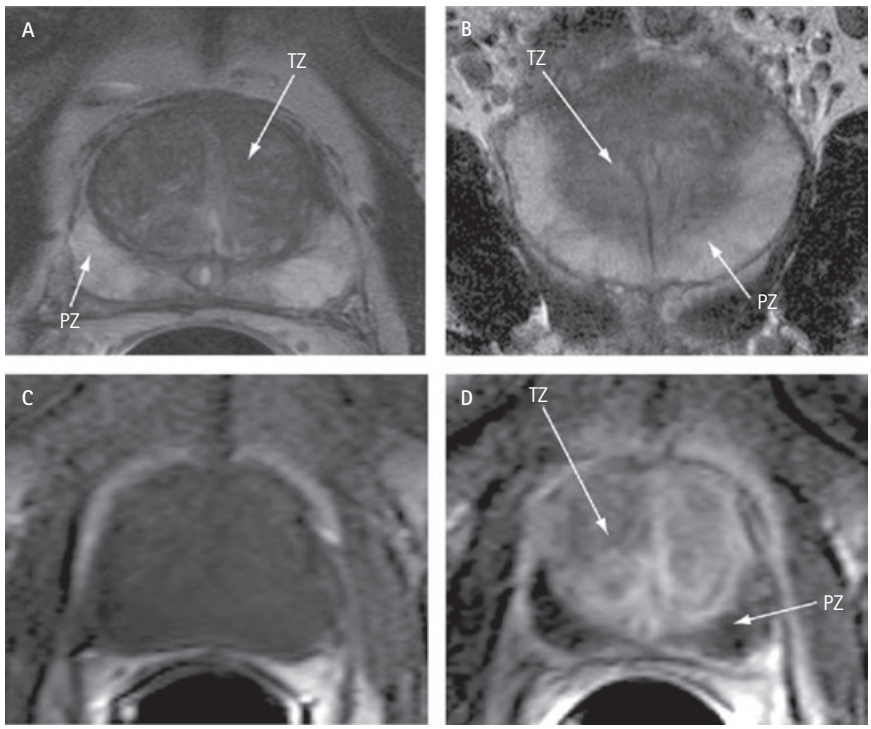


FIG. 3. erMRI in a 52-year-old patient with a PSA level of 29.3 ng/mL and a history of two previous negative biopsies. A and B, T2-weighted axial MR images show a diffuse low signal intensity in the whole PZ. Images before (C) and after (D) DCE-MRI accurately located the tumour area (arrow labelled 'Anterior PZ') on the anterior PZ, which yielded a Gleason score 7 adenocarcinoma.

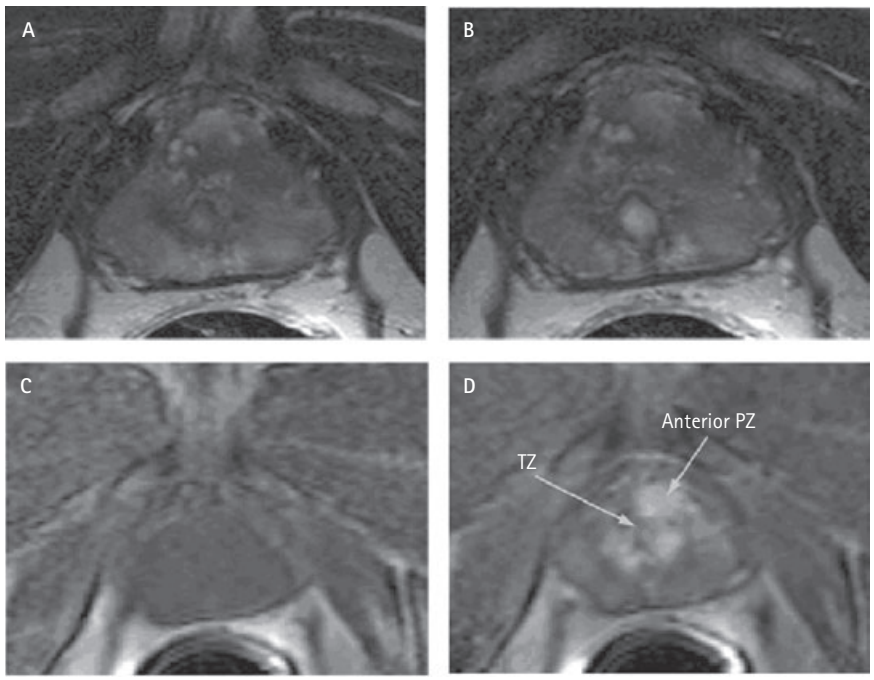
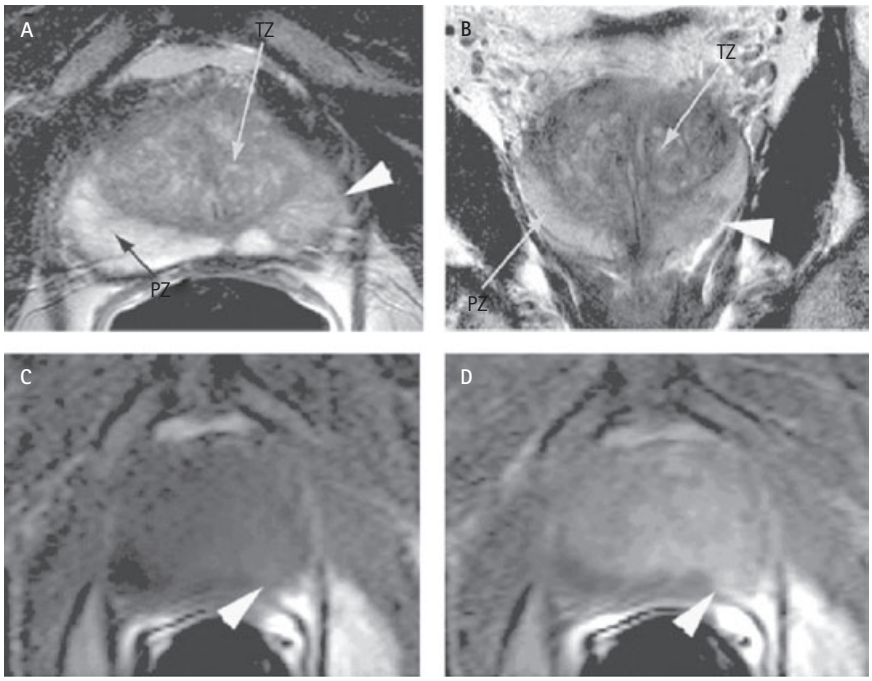


FIG. 4. erMRI in a 72-year-old patient with a PSA level of 7 ng/mL and a history of two previous negative TRUS-guided biopsies. T2-weighted images show a low-signal intensity lesion on the left apex in the axial (A) and coronal (B) views (arrowhead), and early enhancement on DCE-MRI, before (C) and after contrast (D). The repeat biopsy was negative for cancer but showed inflammation on all the specimens collected on the left side.



Test	Sensitivity, %	Specificity, %
DCE positive	28.0 (12.5–44.4)	79.3 (70.7–87.3)
T 2 positive	40.0 (23.8–56.4)	69.5 (60.6–78.9)
DCE or T 2 positive	40.0 (23.8–56.4)	66.4 (57.8–75.4)

TABLE 5 The sensitivity and specificity for MRI for the biopsy result (with 95% CI)

in this series, as might be suggested by the retrospective, unblinded review. However, this evidence should be interpreted cautiously, as it might be subject to bias. Expanding the definition of a positive MRI sextant to include sextants adjacent to the positive biopsy site resulted in a substantial increase in sensitivity, unfortunately with a corresponding decrease in specificity.

Studies of microvessel density in prostate cancer reported controversial results [17–19]. The value of DCE was tested in the present patients with the rationale that increased microvessel density in prostate cancer might result in contrast enhancement and better tumour localization. Adding DCE imaging did not contribute to enhanced cancer detection over T2-weighted MRI alone in the present study. This seems to be confirmed by the high rate of agreement between these methods of imaging in the present patients, independent of final biopsy result. Such correlation between MRI and DCE suggests that the latter added little information on cancer location. Only one patient in the present study had a negative T2-weighted MRI and positive DCE (Table 4), and his imaging abnormality did not correspond to the sextant with the positive biopsy result. Padhani *et al.* [12] showed that DCE imaging can discriminate between cancer and benign lesions in the PZ but not in the transition zone (TZ). It might be that adding the median biopsies in the present scheme sampled more TZ than PZ, and diluted the efficacy of DCE discrimination in the latter. Finally, it might be that the microvessel density in the present patients is the same in benign and cancerous prostate tissue.

Data on the use of 3 T MRI for prostate cancer location in patients with prostate cancer was published recently [13]. Using whole-mount sections, the authors reported sensitivities of 50–88% and specificities of 92–96%. There was no direct comparison with 1.5 T MRI in that study. In the present patients there was no difference in cancer detection between 3 T to 1.5 T MRI using biopsies as the reference standard. Obvious causes for this discrepancy relate to sampling error as well as image-fusing inaccuracies. When comparing sextant biopsies to MRI, Wefer *et al.* [20] showed that the former might have a lower performance depending on the region of the prostate that is biopsied. This underlines the limitation of biopsies as a reference standard. Correcting for image-fusion error might significantly reduce the sampling error and allow better detection.

The present study has the limitation of being retrospective and might be under-powered to detect significant differences. While there was a trend for higher detection rates at sites of positive MRI, the differences were not clinically significant with these few patients. It is possible that with a larger study differences between 1.5 T and 3 T MRI would emerge, and the difference between the PPV and NPVs might increase. Furthermore, the lack of an accurate method of fusing MRI images with TRUS images might have reduced the accuracy of targeting suspicious lesions, thereby reducing the contribution of MRI to detection. Until such technical hurdles can be overcome, it is difficult to draw definitive conclusions as to the efficacy of MRI in the setting of a high-risk population. Finally, it is difficult to account for the unusually high positive cancer detection rate in the present patients having a repeat biopsy (54%). Our standard 12-biopsy scheme compared to a 4–10-biopsy scheme in other studies can only partly explain this discrepancy; population-sampling variation might be another cause. Factors such as PSA levels and previous biopsy pathology, as they related to MRI findings, were evaluated and were not significant.

In conclusion, using MRI in patients with previous negative prostate biopsies does not significantly increase the yield of repeat TRUS biopsy. 3 T MRI does not contribute to better detection than with 1.5 T MRI. This study underlines the need for continued investigation and development of MRI techniques to establish its role as a diagnostic and staging tool for prostate cancer. Similarly,

technologies that allow real-time targeting of prostate tumours during MRI, or that insure more accurate fusion between MRI and TRUS imaging, would help to eliminate questions of targeting error.

CONFLICT OF INTEREST

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Abbreviations: **erMRI**, endorectal-coil MRI; **DCE**, dynamic contrast-enhanced; **TZ**, **PZ**, transitional, peripheral zone; **FOV**, field of view; **TR**, repetition time; **TE**, time to echo; **GEE**, Generalized Estimating Equation; **PPV**, **NPV**, positive, negative predictive value; **PIN**, prostatic intraepithelial neoplasia; **ASAP**, atypical small acinar proliferation.