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.

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 × 0.6 × 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 × 1.18 × 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

![Table 2](image_url)

**TABLE 1** The demographics of the patients
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.
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 scheme sampled more TZ than PZ, and diluted the efficacy of DCE 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 sextant with the positive biopsy result (with 95% CI) to the DCE-positive patients was 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%.

The present study had a negative T2-weighted MRI and positive DCE (Table 4), and his pathology, as they related to MRI findings, sampling variation might be another cause. Factors such as PSA levels and previous biopsy history of two 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,

FIG. 4. cmMRI 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.

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
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<tbody>
<tr>
<td>DCE positive</td>
<td>28.0 (12.5–44.4)</td>
<td>79.3 (70.7–87.3)</td>
</tr>
<tr>
<td>T 2 positive</td>
<td>40.0 (23.8–56.4)</td>
<td>69.5 (60.6–78.9)</td>
</tr>
<tr>
<td>DCE or T 2 positive</td>
<td>40.0 (23.8–56.4)</td>
<td>66.4 (57.8–75.4)</td>
</tr>
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TABLE 5

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

1 Zackrisson B, Aus G, Bergdahl S et al. The risk of finding focal cancer (less than 3 mm) remains high on re-biopsy of patients with persistently increased prostate specific antigen but the clinical significance is questionable. J Urol 2004; 171: 1500–3
3 Fleshner N, Klotz L. Role of ‘saturation biopsy’ in the detection of prostate cancer among difficult diagnostic cases. Urology 2002; 60: 93–7

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Abbreviations: erMRI, endorectal-coil MRI; DCE, dynamic contrast-enhanced; T2, T2*, 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.