Patient selection determines the prostate cancer yield of dynamic contrast-enhanced magnetic resonance imaging-guided transrectal biopsies in a closed 3-Tesla scanner

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OBJECTIVE

To evaluate the cancer yield of transrectal prostate biopsies in a 3-T magnetic resonance imaging (MRI) scanner in patients with elevated prostate specific antigen (PSA) levels and recent negative transrectal ultrasonography (TRUS)-guided prostate biopsies.

PATIENTS AND METHODS

Between July 2004 and November 2005, patients with at least one previous negative prostate biopsy within the previous 12 months had MRI-guided biopsy of the prostate in a 3-T MRI scanner. Patients with previous positive biopsies for cancer were excluded. Target selection was based on T2-weighted imaging and dynamic contrast-enhanced (DCE) imaging studies.

RESULTS

Thirteen patients were eligible; their median (range) age was 61 (47–74) years and PSA value 4.90 (1.3–12.3) ng/mL. Most patients had one previous negative biopsy (range 1–4). Four patients had a family history of prostate cancer. There were 37 distinct targets based on T2-weighted imaging. Fifteen of 16 distinct DCE abnormalities were co-localized with a target based on T2-weighted imaging. Despite this correlation, only one of 13 patients had a directed biopsy positive for cancer. Including systematic biopsies, two of 13 patients had a biopsy positive for prostate cancer. One patient had prostate intraepithelial neoplasia and one had atypical glands in the specimen.

CONCLUSION

The prostate-cancer yield of transrectal biopsies in a 3-T MRI scanner, among patients with recent negative TRUS-guided prostate biopsies, is similar to repeat systematic TRUS-guided biopsy. DCE correlates with T2-imaging but does not appear to improve prostate cancer yield in this population.

KEYWORDS

dynamic contrast enhancement, PSA level, TRUS, image-guided, biopsy

INTRODUCTION

PSA testing has allowed the early detection of impalpable prostate cancer, and in turn, early detection has lowered the incidence of advanced disease with extracapsular extension [1]. However, PSA levels can be elevated for benign reasons, e.g. BPH or prostatitis, and consequently, some patients without prostate cancer have elevated PSA levels.

However, systematic TRUS-guided biopsies, due to sampling error, risk missing prostate cancer. Persistently elevated PSA values despite previous negative biopsies pose a diagnostic challenge for physicians, and an emotional challenge for patients, who must live with the uncertainty of harbouring a potential cancer that might continue to grow and become more difficult to treat.

Standard repeat prostate biopsies, up to 2 years after the first biopsy, yield prostate cancer in about a quarter of patients [2,3]. Attempts to improve detection rates have included taking more core biopsies [4,5] and using prostate-imaging studies to better locate and guide biopsies [6–9].

MRI is a potential method to locate prostate cancer; a wide range of accuracy, sensitivity, specificity and predictive values have been reported using various patient groups and protocols [10,11]. Recent reports suggested that MRI might be a better imaging method than TRUS in high-risk patients with previous negative biopsies [6–9]. In these previous studies, only T2-weighted or spectroscopy results using 1.5-T MRI were reported.

Dynamic contrast-enhanced (DCE) MRI has been reported to allow discrimination between normal tissue and cancer in the prostate peripheral zone (PZ) [12,13]. Recent reports using 3-T MRI compared with whole-mount specimens reported a significant correlation for prostate cancer location [14].

The purpose of the present study was to assess the prostate cancer yield of MRI-guided transrectal biopsy in a closed-bore 3-T scanner, using T2-weighted and DCE imaging, in patients with at least one previous negative prostate biopsy in the preceding 12 months.

PATIENTS AND METHODS

Between July 2004 and November 2005, patients with at least one previous prostate biopsy negative for cancer within the previous year had MRI-guided biopsy of the prostate in a 3-T scanner. Patients with previous positive biopsies for cancer were excluded. This study was approved by the Institutional Review Board of the National Cancer Institute.

Two sets of MR images were acquired for each patient; a diagnostic image set was obtained before the biopsy procedure, and a second MR image set was taken during the biopsy procedure. All MRI was done on a 3-T scanner (Intera Philips Medical System, Best, the Netherlands) with combined SENSE cardiac surface-coil positioned over the pubic symphysis, and an endorectal coil. Diagnostic MR images were obtained using a commercial endorectal coil (BPX-15, Medrad, Indianola, PA, USA). After a DRE the endorectal coil was inserted and inflated with an electrically insulating and inert perfluorocarbon (Fluorinert, 3M Inc., St Paul, MN, USA) to ≈ 60 mL. The endorectal coil used for the second MRI image set, obained during the intervention, was a rigid custom-built single-loop coil. Each imaging set consisted of T2-weighted fast spin-echo and DCE images; the former were obtained in three planes at a resolution of $0.46 \times 0.6 \times 3.0$ mm (field of view 140 mm, matrix 234×304, TR/TE 8852/120 ms). DCE images were acquired during a single dose injection of Gd-DTPA (Magnevist; Berlex Laboratories, Wayne, NJ, USA) at a rate of 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 field of view, two signal averages, SENSE factor of 4 and resolution of $0.86 \times 1.18 \times 6.0$ mm.

Diagnostic MRI was interpreted exclusively by one experienced radiologist (P.C.); suspicious areas were defined as hypo-intense regions on T2-weighted imaging 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 volumes were calculated based on MRI using maximum measurements in the coronal and axial views, according to the ellipsoid formula [15]. MR abnormalities identified in the diagnostic images before biopsy were qualitatively and manually correlated to the abnormalities found during biopsy.

The procedure and customized equipment for MRI-guided biopsy were described previously [16,17]. Oral fluoroquinolones were given before biopsy, and patients also received a saline enema and lorazepam.

Targeted biopsies were obtained when discrete MR abnormalities were identified. In all, 10 cores were procured from each patient. Each target area of interest was biopsied twice (once for pathological evaluation and once for a research tissue bank). The location of the biopsy needle was verified by MR scans for all targeted biopsies. Occasionally, the needle missed the target lesion due to prostate deformation or targeting inaccuracy. This situation was detected in the MRI confirmation images taken during the biopsy procedure. In this case, a second biopsy was taken with the needle position verified, and sent to pathology instead of banked for research, thus assuring that every targeted biopsy core sent to pathology was procured from the targeted abnormality. In addition, two biopsies were obtained from a mirrored position in the contralateral prostate.

Single biopsies of the remaining four sextants were taken to fulfil the need for systematic biopsy of all sextants, and were sent for pathological evaluation. All DCE and all areas of T2 abnormalities were targeted for biopsy. The impetus for selecting each target was noted by 'DCE', 'T2', 'both', or 'systematic.' Biopsies taken only to fulfil the need to sample each sextant were designated 'systematic.'

Descriptive statistics (mean, median, range) were used to describe the patient characteristics, and the rate of positive biopsy as a percentage of the group.

RESULTS

In all, 13 patients were eligible, with a median (range) age of 61 (47–74) years and a PSA level of 4.9 (1.3–12.3) ng/mL. The modal (range) number of previous negative biopsy procedures was 1 (1–4). Four patients had a family history of prostate cancer. The median (range) diagnostic imaging and biopsy procedure time was 100 (80–185) min.

There were 37 distinct targets based on T2-weighted imaging and 16 based on DCE imaging. Fifteen of 16 distinct DCE abnormalities were sufficiently close to a target based on T2-weighted imaging to be considered co-localized by the radiologists.

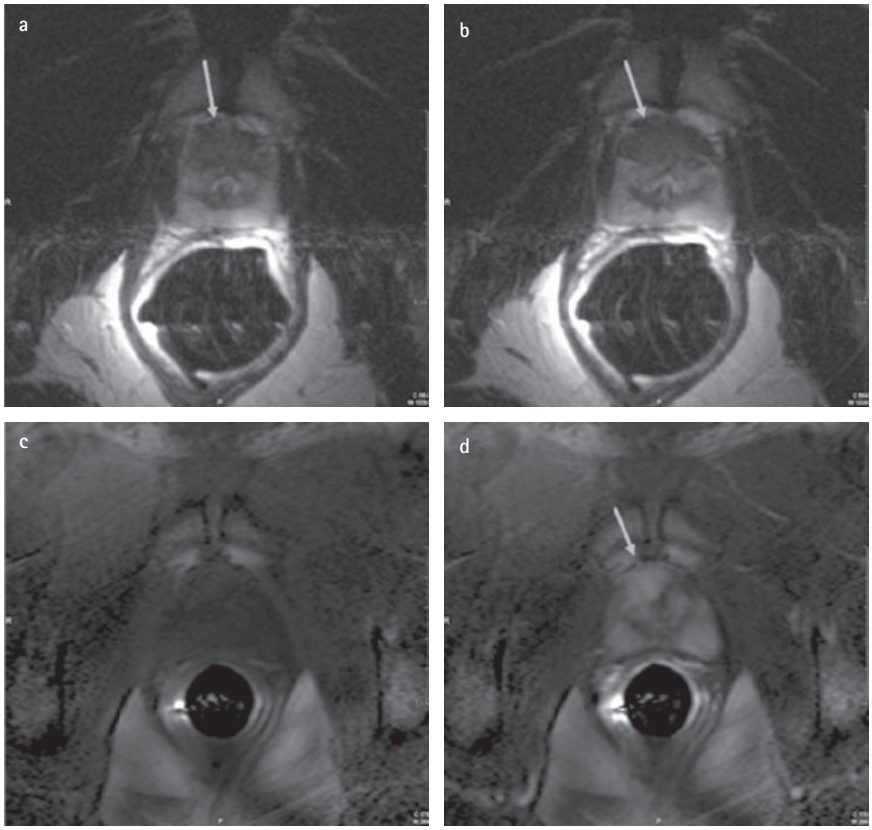
However, only one of 13 patients had a positive biopsy using a co-localized T2 and DCE abnormality. This positive targeted biopsy, Gleason score 4 + 4 = 8, was in the anterior PZ (Fig. 1). One of 13 patients had a positive systematic biopsy; this biopsy, Gleason score 3 + 3 = 6, was from a random site (no DCE or T2 abnormality) in the PZ. Also, on systematic biopsy, one patient had prostate intraepithelial neoplasia and one had atypical glands in the targeted specimen.

DISCUSSION

The prostate cancer yield of targeted transrectal biopsies in a 3-T MRI scanner, among patients with recent negative TRUS-guided prostate biopsies, was only one of 13. Including systematic biopsies, the cumulative prostate cancer yield was only 15%, and similar to repeat systematic TRUS-guided biopsy [2,3]. Although neither appeared predictive of prostate cancer, DCE findings, when present, were highly correlated (94%) with T2 abnormalities.

Microvessel density (MVD) studies in prostate cancer have shown greater vascularity in prostate tumours than in surrounding benign prostate tissue [18,19]. Siegal *et al.* [18] reported the highest MVD within the tumour in 13 of 14 prostatectomy specimens. There were significant differences between the edge of the tumour and 2.5 mm within the benign

FIG. 1. Prostate cancer depicted on both T2-weighted and DCE-MRI. Images from a 46-year-old man (PSA level 5.3 ng/mL) with one previous negative TRUS-guided biopsy. (a,b) T2-weighted transverse image shows an homogenous low signal-intensity lesion on the right anterior PZ (arrow). Three-dimensional fast field-echo T1-weighted images before (c) and after (d) contrast agent injection show an area of focal enhancement in the right anterior PZ corresponding to the tumour. A Gleason score 8 tumour was present at biopsy.



periphery, between the benign and malignant tissue at the border, and between cancer at the edge and 2.0 mm within the neoplasm. In a study of 75 prostatectomy specimens, Bono *et al.* [19] found that MVD was positively associated with a higher pathological stage and risk of progression of the disease.

DCE-MRI studies are thought to be sensitive to the increased MVD and permeability of cancer. Using DCE-MRI, Padhani *et al.* [21] discriminated between cancer and no cancer in the PZ but not in the transitional zone [12]; this is consistent with the positive finding on targeted biopsy in our study (Fig. 1).

The value of DCE was tested in the present patients with the rationale that increased MVD in prostate cancer might result in contrast enhancement and better tumour localization, but DCE imaging did not contribute to enhanced cancer detection in the present study.

Previous studies using T2 and/or MR spectroscopy assessed the cancer yield of MRI-guided prostate biopsy in a known or high-risk population [8,9,20,21]. Sensitivities and specificities for T2-weighted imaging with or without spectroscopy in these studies were 42.9–85% and 22–97.9%, respectively, when considered for each core. MR spectroscopy was not done in all patients in the present study. Overall, although there were too few patients for statistical analysis, the contribution of MRI spectroscopy to T2 imaging in the present study was not obvious.

Two previous studies reported on prostate biopsies taken in closed-bore MRI scanner; Beyersdorff *et al.* [7] found prostate cancer in five of 11 patients with elevated PSA levels and an abnormality on 1.5-T MRI before biopsy. Similarly, Anastasiadis *et al.* [21] reported a 56% incidence of prostate cancer by MRI-guided biopsy in a 1.5-T scanner in 27 patients with elevated PSA levels and/or a suspicious finding on DRE.

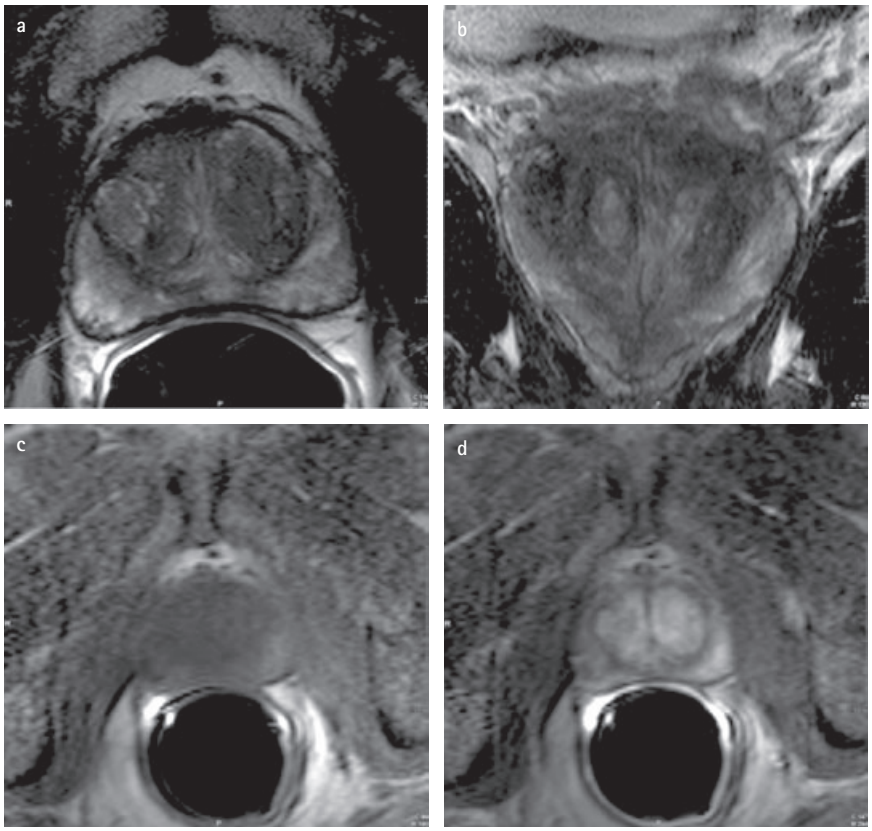
The detection of prostate cancer in about half the patients in these two previous MRI-guided biopsy studies is considerably higher than in the present study. This discrepancy might result from differences in the populations. Beyersdorff *et al.* [7] included patients with elevated PSA levels who had not yet been biopsied. Therefore, the pre-test probability of having prostate cancer was higher than in the present patients who had a recently negative prostate biopsy. Anastasiadis *et al.* [21], while requiring at least one former negative TRUS biopsy, noted that the length of time from the previous biopsy 'varied'.

The 56% positive biopsy rate of Anastasiadis *et al.* is similar to our experience in a separate study [22] in which patients who had high PSA levels and previous biopsies more than a year previously (and were therefore ineligible for the present study) had T2 and DCE-MRI followed by a TRUS biopsy; 14 of 26 (54%) were found to have positive biopsies for prostate cancer. Given the 54% positivity rate in our complementary MRI-TRUS study [22], it is possible that the large difference in the rates of prostate cancer detection between the present and previous studies is due to patient selection.

Further arguing for the importance of patient selection (data not shown) in two studies using MRI-guided biopsies to aid external beam radiation therapy, we successfully identified the location of cancer within the prostate in eight of nine patients known to have prostate cancer. This is similar to the sensitivity and specificity for diagnostic MRI in other series of patients with known prostate cancer [14,23].

One point of agreement among all MRI-guided biopsy studies is that the imaging characteristics of prostatitis and prostate cancer are quite similar. Beyersdorff *et al.* [7] found prostatitis in six of 11 patients. Anastasiadis *et al.* [21] noted, and we concur, that 'chronic prostatitis has a very similar morphologic pattern to cancerous lesions.' In addition, we noted that haemorrhage can also mimic prostate cancer on T2-weighted scans, but not on DCE scans (Fig. 2). Thus, the overall sensitivity and specificity of MRI of the prostate depends substantially on the

FIG. 2. Haemorrhage mimicking a suspicious prostate carcinoma in a 60-year-old man with a PSA level of 4.9 ng/mL and two previous negative TRUS-guided biopsies. (a,b) Transverse and coronal T2-weighted image shows streaky low signal intensity in the entire PZ which could be due to prostatitis and/or haemorrhage. (c) Transverse three-dimensional fast field-echo T1-weighted pre-contrast image shows diffuse haemorrhage on the left PZ. (d) After injection with contrast agent the haemorrhagic regions show early enhancement.



background incidence of prostate cancer vs prostatitis and haemorrhage in the study population.

In conclusion, MRI remains a promising tool for finding and sampling cancerous regions in patients with known prostate cancer. However, as a screening tool in patients with elevated PSA levels and recent previous negative biopsy, the promise of MRI remains unfulfilled. In the present patients, DCE-MRI-directed biopsy markedly improved neither prostate cancer detection (compared with historical repeat TRUS-guided series) nor the sensitivity or specificity of T2-weighted image-directed MRI biopsy.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1 **Ward JF, Slezak JM, Blute ML, Bergstralh EJ, Zincke H.** Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome. *BJU Int* 2005; **95**: 751–6

2 **Zackrisson B, Aus G, Lilja H, Lodding P, Pihl CG, Hugosson J.** Follow-up of men with elevated prostate-specific antigen and one set of benign biopsies at prostate cancer screening. *Eur Urol* 2003; **43**: 327–32

3 **Fleshner NE, O'Sullivan M, Fair WR.** Prevalence and predictors of a positive repeat transrectal ultrasound guided needle biopsy of the prostate. *J Urol* 1997; **158**: 505–8

4 **Stewart CS, Leibovich BC, Weaver AL, Lieber MM.** Prostate cancer diagnosis using a saturation needle biopsy technique after previous negative sextant biopsies. *J Urol* 2001; **166**: 86–91

5 **Fleshner N, Klotz L.** Role of 'saturation biopsy' in the detection of prostate cancer among difficult diagnostic cases. *Urology* 2002; **60**: 93–7

6 **Yuen JS, Thng CH, Tan PH *et al.*** Endorectal magnetic resonance imaging and spectroscopy for the detection of tumor foci in men with prior negative transrectal ultrasound prostate biopsy. *J Urol* 2004; **171**: 1482–6

7 **Beyersdorff D, Winkel A, Hamm B, Lenk S, Loening SA, Taupitz M.** MR imaging-guided prostate biopsy with a closed MR unit at 1.5 T. initial results. *Radiology* 2005; **234**: 576–81

8 **Amsellem-Ouazana D, Younes P, Conquy S *et al.*** Negative prostatic biopsies in patients with a high risk of prostate cancer. Is the combination of endorectal MRI and magnetic resonance spectroscopy imaging (MRSI) a useful tool? A preliminary study. *Eur Urol* 2005; **47**: 582–6

9 **Perrotti M, Han KR, Epstein RE *et al.*** Prospective evaluation of endorectal magnetic resonance imaging to detect tumor foci in men with prior negative prostatic biopsy: a pilot study. *J Urol* 1999; **162**: 1314–7

10 **Ikonen S, Kivisaari L, Tervahartiala P *et al.*** imaging. Accuracy in differentiating cancer from other prostatic disorders. *Acta Radiol* 2001; **42**: 348–54

11 **Mullerad M, Hricak H, Kuroiwa K *et al.*** Comparison of endorectal magnetic resonance imaging, guided prostate biopsy and digital rectal examination in the preoperative anatomical localization of prostate cancer. *J Urol* 2005; **174**: 2158–63

12 **Padhani AR, Gapinski CJ, Macvicar DA *et al.*** Dynamic contrast enhanced MRI of prostate cancer: correlation with

morphology and tumour stage, histological grade and PSA. *Clin Radiol* 2000; **55**: 99–109

13 **Noworolski SM, Henry RG, Vigneron DB, Kurhanewicz J.** Dynamic contrast-enhanced MRI in normal and abnormal prostate tissues as defined by biopsy, MRI, and 3D MRSI. *Magn Reson Med* 2005; **53**: 249–55

14 **Futterer JJ, Heijmink SW, Scheenen TW *et al.*** Prostate cancer: local staging at 3-T endorectal MR imaging – early experience. *Radiology* 2006; **238**: 184–91

15 **Littrup PJ, Williams CR, Egglin TK, Kane RA.** Determination of prostate volume with transrectal US for cancer screening. Part II. Accuracy of in vitro and in vivo techniques. *Radiology* 1991; **179**: 49–53

16 **Krieger A, Susil RC, Menard C *et al.*** Design of a novel MRI compatible manipulator for image guided prostate interventions. *IEEE Trans Biomed Eng* 2005; **52**: 306–13

17 **Menard C, Susil RC, Choyke P *et al.*** An interventional magnetic resonance imaging technique for the molecular characterization of intraprostatic dynamic contrast enhancement. *Mol Imaging* 2005; **4**: 63–6

18 **Siegal JA, Yu E, Brawer MK.** Topography of neovascularity in human prostate carcinoma. *Cancer* 1995; **75**: 2545–51

19 **Bono AV, Celato N, Cova V, Salvadore M, Chinetti S, Novario R.** Microvessel density in prostate carcinoma. *Prostate Cancer Prostatic Dis* 2002; **5**: 123–7

20 **Beyersdorff D, Taupitz M, Winkelmann B *et al.*** Patients with a history of elevated prostate-specific antigen levels and negative transrectal US-guided quadrant or sextant biopsy results: value of MR imaging. *Radiology* 2002; **224**: 701–6

21 **Anastasiadis AG, Lichy MP, Nagele U *et al.*** MRI-guided biopsy of the prostate increases diagnostic performance in men with elevated or increasing PSA levels after previous negative TRUS biopsies. *Eur Urol* 2006; **50**: 738–48

22 **Lattouf JB, Grubb RL, Lee JM *et al.*** Yield of MRI directed trans-rectal ultrasound biopsies of the prostate in patients at high risk of having prostate cancer. *BJU Int* 2007; in press

23 **Futterer JJ, Heijmink SW, Scheenen TW *et al.*** Prostate cancer localization with dynamic contrast-enhanced MR imaging and proton MR spectroscopic imaging. *Radiology* 2006; **241**: 449–58

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Abbreviations: **DCE**, dynamic contrast-enhanced; **PZ**, peripheral zone; **MVD**, microvessel density.