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Magnetic Resonance Imaging/Ultrasound–Fusion Biopsy Significantly Upgrades Prostate Cancer Versus Systematic 12-core Transrectal Ultrasound Biopsy

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Abstract

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Author contributions

Peter A. Pinto had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Siddiqui, Rais-Bahrami, Stamatakis, Vourganti, Nix, Choyke, Wood, Pinto.
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Background—Gleason scores from standard, 12-core prostate biopsies are upgraded historically in 25−33% of patients. Multiparametric prostate magnetic resonance imaging (MP-MRI) with ultrasound (US)-targeted fusion biopsy may better sample the true gland pathology.

Objective—The rate of Gleason score upgrading from an MRI/US-fusion-guided prostate-biopsy platform is compared with a standard 12-core biopsy regimen alone.

Design, setting, and participants—There were 582 subjects enrolled from August 2007 through August 2012 in a prospective trial comparing systematic, extended 12-core transrectal ultrasound biopsies to targeted MRI/US-fusion-guided prostate biopsies performed during the same biopsy session.

Outcome measurements and statistical analysis—The highest Gleason score from each biopsy method was compared.

Interventions—An MRI/US-fusion-guided platform with electromagnetic tracking was used for the performance of the fusion-guided biopsies.

Results and limitations—A diagnosis of prostate cancer (PCa) was made in 315 (54%) of the patients. Addition of targeted biopsy led to Gleason upgrading in 81 (32%) cases. Targeted biopsy detected 67% more Gleason ≥4 + 3 tumors than 12-core biopsy alone and missed 36% of Gleason ≤3 + 4 tumors, thus mitigating the detection of lower-grade disease. Conversely, 12-core biopsy led to upgrading in 67 (26%) cases over targeted biopsy alone but only detected 8% more Gleason ≥4 + 3 tumors. On multivariate analysis, MP-MRI suspicion was associated with Gleason score upgrading in the targeted lesions ($p < 0.001$). The main limitation of this study was that definitive pathology from radical prostatectomy was not available.

Conclusions—MRI/US-fusion-guided biopsy upgrades and detects PCa of higher Gleason score in 32% of patients compared with traditional 12-core biopsy alone. Targeted biopsy technique preferentially detects higher-grade PCa while missing lower-grade tumors.

Keywords

Image-guided biopsy; Targeted biopsy; Magnetic resonance imaging; Prostate cancer; Prostatic neoplasms/diagnosis; Prostatic neoplasms/pathology; Prostatic neoplasms/ultrasonography

1. Introduction

Pathologic grading of prostate cancer (PCa) based on biopsy Gleason score (bGS) plays an important role in clinical decision making. Unfortunately, a number of studies have identified a poor correlation between the Gleason score identified on prostate biopsy and that found in the prostatectomy specimen, with rates of Gleason score upgrading between 21% and 54% [1–3]. Cookson and colleagues have also reported a discrepancy of two or more grades in 26% of cases [4]. The challenge is that surgical-specimen Gleason scores are obtained too late (after the surgery) to influence decision making, algorithms, and triage that involve surgery.

Multiparametric prostate magnetic resonance imaging (MP-MRI) has emerged as an accurate modality in detecting PCa. Lesions identified on MP-MRI correlate with tumor

location on radical prostatectomy specimens [5]. A similar study found that the level of radiologic suspicion based on MP-MRI findings correlates with the D'Amico risk stratification [6].

The ability to detect, delineate, and measure PCa on magnetic resonance imaging (MRI) has led to the development of three MRI-guided prostate biopsy methods: cognitive fusion, direct MRI-guided biopsy, and several methods of MRI/ultrasound (MRI/US)-fusion-guided biopsy [7]. Cognitive fusion involves an estimation of the location of the lesion on the part of the transrectal ultrasound (TRUS) operator and varies greatly with expertise. Direct MRI-guided biopsy is time consuming and resource costly. In contrast, MRI/US-fusion-guided biopsy is an outpatient procedure, in which prebiopsy MRI of the prostate is segmented, registered, and fused with real-time ultrasound using electromagnetic tracking or mechanical-arm navigation and a digital overlay. This method integrates well with current workflow patterns of TRUS-guided biopsy yet provides a platform for a targeted approach to prostate biopsy based on MRI-identified targets and lesions [8]. MRI/US-fusion-guided biopsy has the potential to offer improved diagnostic information over 12-core biopsy alone. To study whether MRI/US fusion results in more accurate biopsies, the correlation was assessed between the Gleason scores detected on MRI/US-fusion biopsy and those found on a standard 12-core TRUS biopsy performed during the same biopsy session.

2. Patients and methods

2.1. Study population

Subjects were enrolled in a prospective trial assessing MRI/US-fusion-guided prostate biopsy with electromagnetic tracking at the US National Cancer Institute and the US National Institutes of Health between August 2007 and August 2012 (ClinicalTrials.gov identifier: NCT00102544). Institutional review board approval was obtained and all subjects provided written informed consent. During the study period, a total of 671 MRI/US-fusion-guided prostate biopsies were performed, including 89 repeated biopsies in patients on active surveillance. For patients who had multiple MRI/US-fusion biopsies, the first biopsy session was used for this analysis. The resultant study cohort represents initial fusion-biopsy sessions of 582 consecutive subjects, 320 of which had a prior negative prostate biopsy. Patient demographics and prebiopsy prostate-specific antigen (PSA) level, prostate size, number of MP-MRI lesions, and MP-MRI cancer-suspicion score per lesion [9] were noted, as were final pathology for standard and targeted biopsies.

2.2. Imaging

All patients initially underwent a diagnostic MP-MRI of the prostate, including triplanar T2-weighted, dynamic contrast-enhanced, diffusion-weighted imaging, and MR spectroscopy sequences performed on a 3.0T MRI scanner (Achieva; Philips Healthcare, Andover, MA, USA,) with a 16-channel cardiac surface coil (SENSE; Philips Healthcare, Andover, MA, USA) positioned over the pelvis and an endorectal coil (BPX-30; Medrad Inc., Pittsburgh, PA, USA), as previously described [10,11]. These diagnostic MP-MRI studies underwent blinded, centralized radiologic evaluation to identify lesions if present and to assign PCa suspicion scores to each lesion (low, moderate, and high) according to previously described

criteria [9]. Two genitourinary radiologists (B.T. and P.L.C.) with 7 yr and 13 yr, respectively, of experience interpreting prostate MRI performed independent review and formed consensus reads of all MP-MRI in this series.

2.3. Biopsy protocol

Subjects with lesions suspicious for PCa on MP-MRI underwent prostate biopsy as previously described [12]. A standard 12-core TRUS-guided biopsy was performed (blinded to the MRI target lesions) in conjunction with a fusion biopsy using the prebiopsy MP-MRI images, which were segmented (organ was outlined), registered, and fused with the TRUS images. Lesions suspicious for cancer identified on MRI were semiautomatically displayed on the real-time TRUS image. All target lesions were sampled once in both axial and sagittal planes, with at least two core biopsies per target. Real-time electromagnetic tracking integrated into the biopsy platform allowed for localization and mapping of needle trajectories for both the standard and targeted biopsies (Philips Healthcare, Andover, MA, USA; and Northern Digital Inc., Ontario, Canada). The median time from MRI to biopsy was 39 d. One genitourinary-expert pathologist reviewed all pathologic specimens. The process of obtaining an MRI/US-fusion-guided biopsy from image acquisition to biopsy is outlined in Figure 1.

2.4. Data analysis

The Student *t* test and Pearson χ^2 or Fisher exact test were used to determine differences between continuous and categorical variables, respectively. Logistic regression models were used for univariate and multivariable analysis. JMP Pro v.10.0 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

3. Results

Patient demographics of the study cohort are shown in Table 1. The mean age of the patient population was 61.3 yr and mean prebiopsy PSA level was 9.9 ng/ml. The mean number of targeted biopsies per patient was 5.7, and, accordingly, the mean total number of biopsies including the standard 12-cores was 17.7. Abnormal findings on TRUS were observed in 79 (14%) of subjects.

The rate of Gleason score upgrading with targeted MRI/US-fusion-guided prostate biopsy was compared with standard 12-core biopsy alone. The cohort was divided into *clinically significant* high-grade (Gleason score ≥4 + 3) and *clinically insignificant* low-grade (Gleason score ≤3 + 4) subcohorts in accordance with the Standards of Reporting for MRI-targeted Biopsy Studies (START) working group recommendations [13]. A distribution of bGS as seen on standard 12-core biopsy versus MRI/US-fusion guided biopsy can be seen in Table 2. Gleason score upgrading was observed in 81 cases (32% of the 255 PCa cases diagnosed on 12-core biopsy alone). Targeted biopsies resulted in 43 (22% of 198 cases) additional cases of Gleason ≤3 + 4 PCa and 38 (67% of 57 cases) additional cases of clinically significant PCa (Gleason ≥4 + 3) (Table 3).

In contrast, we examined the converse scenario of additional cases of PCa diagnosed by standard extended 12-core TRUS biopsy versus the targeted biopsy alone. Gleason score

upgrading was found in 67 patients (26% of 253 cases) by 12-core biopsies when compared with targeted biopsies alone. An additional 60 of 165 cases (36%) of Gleason ≤3 + 4 PCa cases and 7 of 88 cases (8%) of additional Gleason ≥4 + 3 PCa were diagnosed by 12-core biopsies when compared with the targeted biopsy platform alone (Table 3).

The distribution of bGS diagnosed by targeted biopsy was examined for each given 12-core bGS (Fig. 2a). Of note, one patient (1% of all bGS ≥8) had a bGS ≥8 PCa by 12-core biopsy but had no cancer detected on targeted biopsy. In addition, 15 patients (15% of all bGS 7) with bGS 7 PCa on 12-core had no cancer detected on targeted biopsy (14 of these 15 were bGS 3 + 4). Conversely, 14 patients (17% of subjects with bGS ≥8) with no cancer on the 12-core biopsy were diagnosed with bGS ≥8 by targeted biopsy, and an additional 21 patients (21% of subjects with bGS 7) with no cancer on 12-core biopsy were diagnosed with bGS 7 PCa (18 of these 21 were bGS 3 + 4) (Fig. 2b). Overall, 17 patients with Gleason score ≥4 + 3 disease (5% of all patients with cancer and 18% of patients with bGS ≥4 + 3) would have been misdiagnosed as having no cancer if they had been assessed by the standard 12-core biopsy alone. Figure 3 demonstrates the distribution of cases missed by 12-core biopsy and targeted biopsy.

Potential predictors of Gleason score upgrading on targeted biopsy were assessed. Using univariate analysis, decreased prostate volume, higher PSA level, higher number of lesions on MRI, and higher MRI suspicion level were all associated with Gleason score upgrading by MRI/US-fusion-guided biopsy and remained significant on multivariate analysis. MRI suspicion had the strongest association with Gleason score upgrading by targeted biopsy (odds ratio [OR]: 1.7; $p = 0.04$) but higher PSA level, lower prostate volume, and more lesions on MRI were also significantly associated with Gleason score upgrading (Table 4). The number of biopsy cores performed may be an important confounder, and further controlling for number of total cores resulted in the number of lesions on MRI no longer being associated with Gleason score upgrading ($p = 0.6$). PSA level, prostate volume, and MRI suspicion (OR: 1.7; $p < 0.05$), however, remained associated with Gleason score upgrading by targeted biopsy (Table 5). Last, we also examined maximal percent cancer-positive cores and found a significant difference between targeted biopsy and 12-core biopsy cores (47.5 ± 35.1% for targeted, 9.2 ± 20.3% for random; $p < 0.0001$).

4. Discussion

There has been considerable concern regarding overdiagnosis and subsequent overtreatment of men with clinically indolent PCa; thus, better characterization of PCa is highly desirable [14]. MRI/US-fusion-guided, targeted biopsies may potentially offer such an improvement [15]. An initial cohort in this same clinical trial previously demonstrated that MRI/US-fusion-guided targeted biopsy increased cancer detection rates significantly compared with standard 12-core TRUS biopsy alone, especially in lesions with a high level of suspicion on the MRI [12]. Studies have found that MRI/US-fusion biopsy detected PCa in 34–37% of patients with prior negative TRUS biopsies, with one-third of these patients harboring high-grade cancer defined as Gleason score of ≥8 [10,16]. In this study, the rate of Gleason score upgrading by targeted biopsy versus standard, extended 12-core biopsies was characterized.

Use of the targeted biopsy as an adjunct to the standard 12-core biopsy resulted in a 32% rate of Gleason score upgrading compared with the 12-core biopsy alone. We also found that a large number of bGS ≥4 + 3 PCa (17 patients, 18% of patients with Gleason ≥4 + 3) would have been diagnosed as no cancer based solely on the 12-core biopsy data. To assess the utility of the standard 12-core biopsy in conjunction with the fusion-guided biopsies, we also examined the rate of Gleason score upgrading by 12-core biopsy when compared with target biopsy alone. Standard-template 12-core biopsies detected some tumors not picked up on targeted biopsy, which is consistent with prior findings, although most of these were bGS ≤3 + 4. Our current practice is to add fusion biopsies to the standard 12-core biopsy, rather than replacing the standard 12-core altogether. There was a 26% rate of Gleason score upgrading with 12-core biopsies compared with targeted biopsies; most of these cancers (46 of 67 patients [69%]) were upgraded from no cancer on targeted biopsy to bGS 6 cancer on 12-core biopsy.

These data thus support the use of MRI/US-fusion targeted biopsy in the diagnosis of clinically significant high-grade disease without significantly adding to the diagnosis of low-grade, clinically indolent disease. Furthermore, improved targeting with the MRI/US fusion resulted in significantly longer cancer core lengths. Although core length was not incorporated into the definitions of clinically significant and insignificant disease in this study, which was focused on Gleason score upgrading, maximum cancer-core length has been recommended by experts as an important variable to incorporate into the measure of clinical significance of PCa [13]. The fusion platform was more useful in patients with high suspicion levels as judged on MP-MRI, as well as in patients with higher PSA levels, and smaller prostates. This raises the question of whether targeted biopsies could be performed in lieu of the standard 12-core biopsy. Although in our study the 12-core biopsy increased the rate of diagnosis of Gleason 6 PCa, which may be an undesirable result, it did have significant utility in the diagnosis of Gleason grade 7 PCa (37% increased rate of diagnosis compared with targeted biopsy alone). Most of these were bGS 3 + 4 (14 of 15 patients). Further research is needed and adding the fusion biopsy to the standard 12-core biopsy remains our current practice in most patients until the emergence of more clear data. Of interest also was a subcohort of seven patients in which 12-core biopsy detected clinically significant bGS ≥4 + 3 PCa not detected on targeted biopsy. Review of these patients could not definitively demonstrate failure to diagnose on MP-MRI versus targeted biopsy technique; perhaps poor image registration or targeting was the cause for this discordance. This finding raises the larger question of interest regarding imaging-guided modalities of whether upgrading was generally due to improved targeted sampling of areas of tumor that were only partially sampled on 12-core biopsy or due to improved localization on imaging of tumor that would have otherwise not been sampled altogether. Our brief review of the data suggests both scenarios may play a factor, but this question was outside the scope of this study, and clearly future, dedicated studies are needed to address this significant question.

A limitation of this study is that it compares two biopsy modalities to each other. Ideally, the addition of final prostatectomy pathology as an end point arbitrates which lesions were most important to detect. Data acquisition to address this limitation is under way. Another limitation stems from the fact that the referral population in this study usually presented with

an elevated PSA level that had prompted prior negative biopsies. Thus, the population is skewed to patients who would be more likely to benefit from targeted biopsies. This selection bias suggests that these findings may not be generalizable to the general population of men undergoing biopsy, although this too is speculative. Last, the inclusion criteria of the trial specified patients with MRI-visible lesions, thus excluding patients with no lesions seen on MRI. Due to this limitation, although it likely applies to few subjects, we were not able to ascertain how many patients with no lesions on MP-MRI had cancer and, in particular, high-grade cancers.

5. Conclusions

In this study, the rate of Gleason score upgrading with MRI/US-fusion-guided targeted biopsies was examined and a 32% rate of increased Gleason score was found when compared with standard extended 12-core biopsy alone. The converse relationship was also examined of 12-core biopsies as an adjunct to targeted biopsies alone and found a 26% rate of Gleason score upgrading. Most of these cases were due to new bGS 6 tumors that were detected; however, seven patients were upgraded to bGS ≥4 + 3 disease. MP-MRI suspicion level was found to have a strong association with Gleason score upgrading by targeted biopsy (over 12-core biopsy). MRI/US-fusion targeted biopsy missed far fewer aggressive PCa tumors than standard biopsy. This study highlights a potentially useful role of MRI/US-fusion-guided targeted biopsies for the identification of clinically significant high-risk tumors otherwise missed by 12-core biopsy alone.

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Take-home message

Magnetic resonance imaging/ultrasound-fusion guided biopsies upgraded Gleason score in 32% of prostate cancer cases and led to a 67% rate of increased diagnosis of high-grade tumors versus 12-core biopsy alone. Targeted biopsy missed diagnosis of lower-grade tumors in 36% of cases.

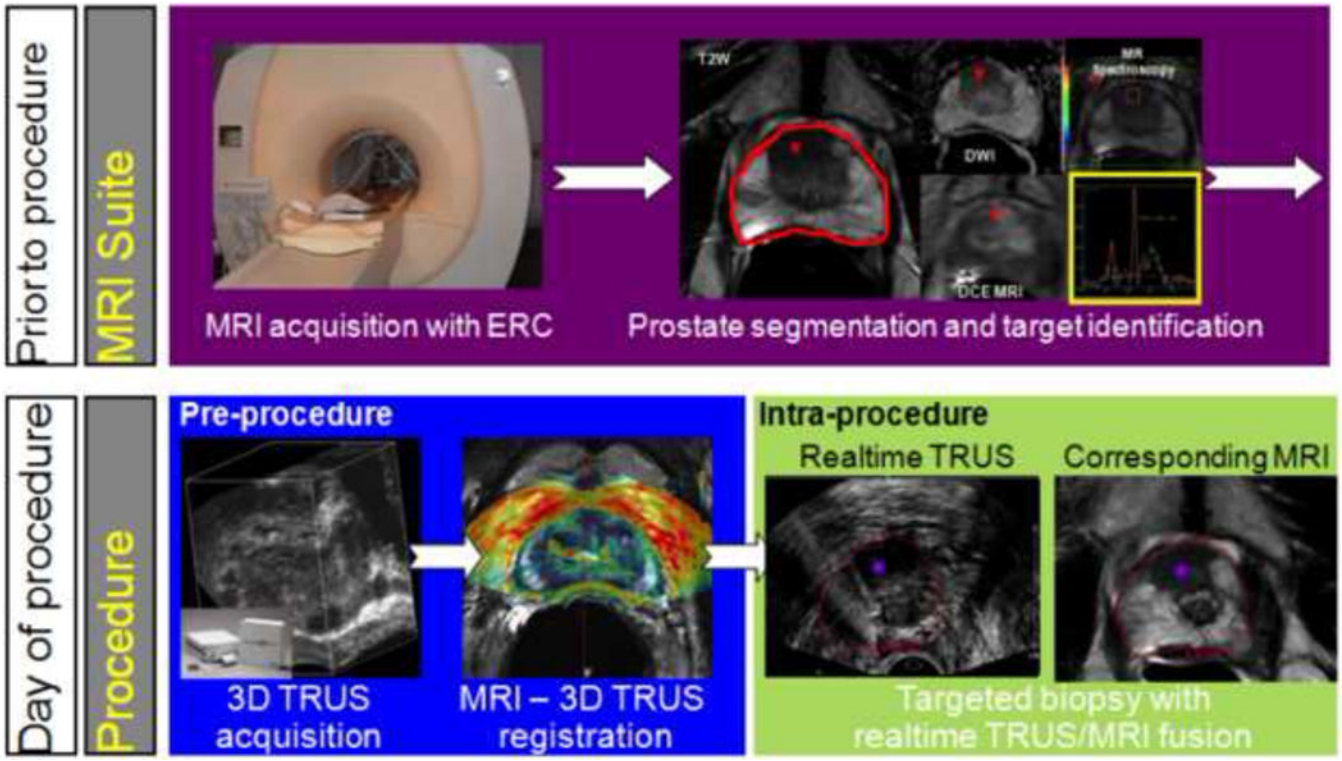

Fig. 1.

Schematic demonstrating steps to obtaining a magnetic resonance imaging/ultrasound (MRI/US)-fusion guided biopsy. ERC = endorectal coil; T2W = T2 weighted; DWI = diffusion-weighted imaging; DCE = dynamic contrast enhanced; TRUS = transrectal ultrasound; 3D = three dimensional.

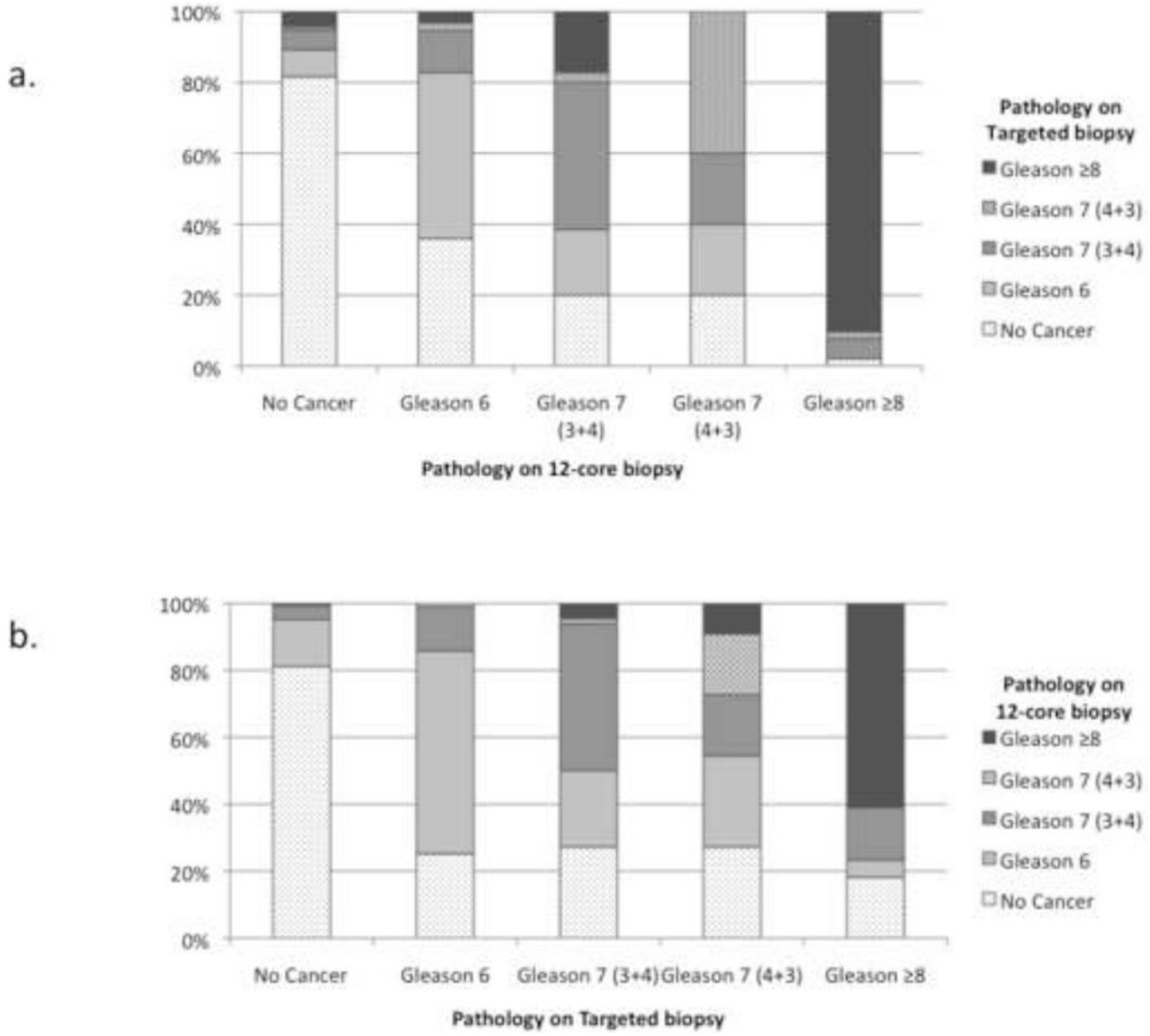

Fig. 2.

(a) Distribution of Gleason scores seen (a) on target biopsies for each given 12-core biopsy diagnosis and (b) on 12-core biopsy for each given target biopsy diagnosis.

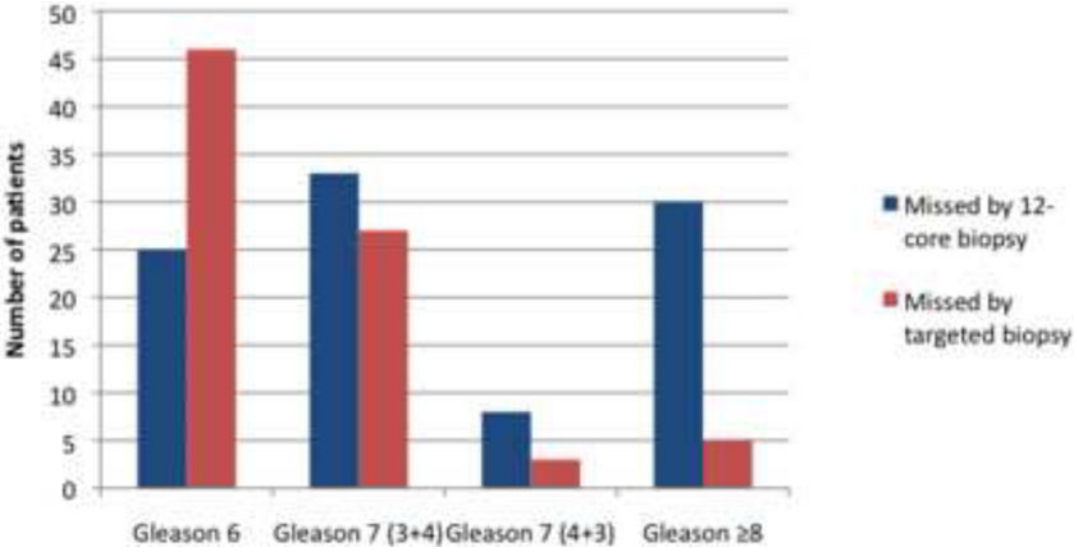

Fig. 3.
Distribution of cases missed by 12-core biopsy and targeted biopsy.

Table 1

Patient demographics, distribution of multiparametric prostate magnetic resonance imaging–assigned prostate cancer suspicion scores, and summary of fusion-guided biopsy findings

Men, no.	582
Age, yr	61.3 ± 8.4
PSA, ng/ml	9.9 ± 13.1
Suspicious DRE findings	55
Prostate volume, ml	56.4 ± 31.2
Cancer suspicion score on MP-MRI (%)	
Low	123 (21)
Moderate	370 (64)
High	89 (15)
MRI lesions per patient, no.	2.6 ± 1.3
Percent of MRI lesion unilateral (vs bilateral)	41
Men with prostate cancer, no. (on targeted or 12-core biopsy)	315
Gleason score, no. (%)	
Gleason 6	131 (42)
Gleason 7 (3 + 4)	89 (28)
Gleason 7 (4 + 3)	13 (4)
Gleason ≥8	82 (26%)
Biopsies per patient, no.	17.7 ± 3.0
Positive lesions on targeted biopsy (per patient)	1.8 ± 1.0

PSA = prostate-specific antigen; DRE = digital rectal examination; MP-MRI = multiparametric prostate magnetic resonance imaging; MRI = magnetic resonance imaging.

Continuous variables reported as mean plus or minus standard deviation.

Table 2

Comparison of biopsy results from standard 12-core biopsy versus magnetic resonance imaging/ultrasound–fusion targeted biopsies

	Standard 12-core biopsy		
MRI/US-fusion targeted biopsies	**No cancer, no.**	**Clinically insignificant disease, no.***	**Clinically significant disease, no.***
No cancer	267	60	2
Clinically insignificant disease	43	117	5
Clinically significant disease	17	21	50

MRI-US = magnetic resonance imaging/ultrasound.

*Clinically insignificant defined as Gleason score ≤7 (3 + 4) and clinically significant defined as Gleason score ≥7 (4 + 3).

Table 3

Additional utility of targeted biopsy over 12-core biopsy alone, and of 12-core biopsy over targeted biopsy alone

	PCa clinical significance*		
	Insignificant, no.	**Significant, no.**	**Total**
PCa cases diagnosed by 12-core biopsy	198	57	255
Additional PCa cases diagnosed by targeted biopsy	43	38	81
Additional percent of PCa missed by 12-core biopsy	22	67	32
PCa cases diagnosed by targeted biopsy	165	88	253
Additional PCa cases diagnosed by 12-core biopsy	60	7	67
Additional percent of PCa missed by targeted biopsy	36	8	26

PCa = prostate cancer.

* Clinically insignificant defined as Gleason score ≤7 (3 + 4) and clinically significant defined as Gleason score ≥7 (4 + 3).

Table 4

Association of patient parameters with Gleason score upgrading on targeted biopsy over 12-core biopsy

	Univariate			Multivariable		
	OR	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Age (per 10 yr)	1.1	0.8–1.5	0.5	–	–	–
Prostate volume (per 10 ml)	0.87	0.78–0.95	0.001	0.84	0.74–0.93	0.0005
PSA (per ng/ml)	1.02	1.01–1.04	0.002	1.03	1.01–1.05	0.004
MRI lesions (per lesion), no.	1.4	1.2–2.8	<0.0001	1.4	1.2–1.8	0.0005
MRI suspicion score (per suspicion increase)	2.5	1.7–3.6	<0.0001	1.7	1.02–3.0	0.04
TRUS suspicion (yes vs no)	1.3	0.7–2.6	0.5	–	–	–
DRE suspicion (yes vs no)	2.1	0.9–6.1	0.1	–	–	–

OR = odds ratio; CI = confidence interval; PSA = prostate-specific antigen; MRI = magnetic resonance imaging; TRUS = transrectal ultrasound; DRE = digital rectal examination.

Table 5

Association of patient parameters with Gleason score upgrading on target biopsy assessed while additionally controlling for total number of biopsies performed

	Multivariable		
	OR	**95% CI**	***p* value**
Prostate volume (per 10 ml)	0.83	0.74–0.93	0.0005
PSA (per ng/ml)	1.03	1.01–1.05	0.004
MRI lesions (per lesion), no.	1.3	0.8–1.9	0.2
MRI suspicion score (per suspicion increase)	1.7	1.0–3.0	<0.05
Biopsy cores (per core), no.	1.1	0.9–1.3	0.6

OR = odds ratio; CI = confidence interval; PSA = prostate-specific antigen; MRI = magnetic resonance imaging.