Original Article

Prostate Cancer Detection With Magnetic Resonance-Ultrasound Fusion Biopsy: The Role of Systematic and Targeted Biopsies

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BACKGROUND: The current study was conducted to evaluate the performance of magnetic resonance (MR)-ultrasound-guided fusion biopsy in diagnosing clinically significant prostate cancer (csCaP). **METHODS:** A total of 1042 men underwent multiparametric MR imaging (mpMRI) and fusion biopsy consecutively in a prospective trial (2009-2014). An expert reader graded mpMRI regions of interest (ROIs) as 1 to 5 using published protocols. The fusion biopsy device was used to obtain targeted cores from ROIs (when present) followed by a fusion image-guided, 12-core systematic biopsy in all men, even if no suspicious ROI was noted. The primary endpoint of the study was the detection of csCaP (ie, Gleason score $\geq$ 7). **RESULTS:** Among 825 men with $\geq$ 1 suspicious ROI of $\geq$ grade 3, 289 (35%) were found to have csCaP. Powerful predictors of csCaP were ROI grade (grade 5 vs grade 3: odds ratio, 6.5 [$P<.01$]) and prostate-specific antigen density (each increase of 0.05 ng/mL/cc: odds ratio, 1.4 [$P<.01$]). Combining systematic and targeted biopsies resulted in the detection of more patients with csCaP (289 patients) than targeting (229 patients) or systematic (199 patients) biopsy alone. Among patients with no suspicious ROI, 35 (16%) were found to have csCaP on systematic biopsy. **CONCLUSIONS:** In this prospective trial, MR-ultrasound fusion biopsy allowed for the detection of csCaP, with a direct relationship noted with ROI grade and prostate-specific antigen density. The combination of targeted and systematic biopsy detected more csCaP than either modality alone; systematic biopsies revealed csCaP in 16% of men with no suspicious MRI target. The advantages of this new biopsy method are apparent, but issues of cost, training, and reliability await resolution before its widespread adoption. ***Cancer*** **2015;000:000–000.**
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KEYWORDS: biopsy, cancer staging, diagnostic imaging, magnetic resonance imaging, prostate cancer.

INTRODUCTION

Targeted prostate biopsy using multiparametric magnetic resonance imaging (mpMRI) to guide tissue sampling can improve the detection of prostate cancer (CaP).[1-3] This has been demonstrated in biopsy-naive men,[4] men with prior negative biopsies,[5,6] and those considering active surveillance of their CaP.[7,8] However, many studies favoring the new technology are limited by small sample sizes or variable protocols, and the value of guided biopsy has been questioned.[9-11] Furthermore, to our knowledge, the predictive value of a "normal" mpMRI and the significance of "normal" regions on mpMRI have not been adequately evaluated.

The negative predictive value (NPV) of mpMRI is critical because of claims that mpMRI may have stand-alone usefulness as a cancer screening tool for men with an elevated prostate-specific antigen (PSA) level or abnormal digital rectal examination.[12] In preliminary studies from our institution, approximately 28% of prostate tumors with a Gleason score (GS) $\geq$ 7 went undetected by mpMRI, based on whole-mount prostatectomy specimens.[13] The key questions are whether a "normal" mpMRI should preclude immediate biopsy and, if guided biopsy is performed, whether targeting alone can suffice.

To evaluate these questions, a prospective trial was designed in which men with a clinical suspicion of CaP underwent mpMRI before biopsy. All participants underwent systematic biopsy (SB) and, when indicated by the mpMRI, targeted biopsy (TB). The inclusion of both biopsy methods was uniformly applied to a large sample, partial subsets of which have been reported previously.[3,5,7,14] The study design, which mandated both SB and TB in all participants

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DOI: 10.1002/cncr.29874, **Received:** October 20, 2015; **Revised:** December 2, 2015; **Accepted:** December 14, 2015, **Published online** Month 00, 2015 in Wiley Online Library (wileyonlinelibrary.com)

TABLE 1. Image Grading System for ROIs Found on mpMRI

Image Grade	T2-Weighted Imaging	ADC on DWI[a]	DCE
1	Normal	$>1.2\times10^{-3}$ mm^2/s	Normal
2	Faint decreased signal	1.0-1.2 $\times10^{-3}$ mm^2/s	Mildly abnormal
3	Moderately dark nodule	0.8-1.0 $\times10^{-3}$ mm^2/s	Moderately abnormal
4	Intensely dark nodule	0.6-0.8 $\times10^{-3}$ mm^2/s	Highly abnormal
5	Dark nodule with mass effect	$<0.6\times10^{-3}$ mm^2/s	Profoundly abnormal

Abbreviations: ADC, apparent diffusion coefficient; DCE, dynamic contrast enhancement; DWI, diffusion-weighted imaging; mpMRI, multiparametric magnetic resonance imaging; ROI, region of interest.
[a] Receives double weight for final grade assessment.

regardless of MRI findings, allowed for the critical appraisal of whether SB may no longer be necessary or even desirable.[1] We hypothesized that the combination of both TB and SB (CB) would identify more cases of clinically significant CaP (csCaP) than either modality alone.

MATERIALS AND METHODS

Study Design

Subjects included all men who underwent MR-ultrasound fusion biopsy between September 2009 and February 2015 for either: 1) an elevated PSA level or abnormal digital rectal examination or 2) confirmation of low-risk CaP for patients considering active surveillance. For patients who underwent >1 fusion biopsy, results from their first biopsy were assessed. The study was approved in advance by the Institutional Review Board of the University of California at Los Angeles (UCLA).

Multiparametric MRI

Subjects underwent mpMRI on a Siemens TrioTrim/Somatom 3-Tesla magnet (Siemens Medical Solutions USA Inc, Malvern, Pa) with a transabdominal external phased array coil. Regions of interest (ROIs) were delineated and graded as 1 to 5 using a scoring system established before the Prostate Imaging Reporting and Data System (PI-RADS) was described.[2] The UCLA scoring system incorporates T2-weighted imaging, diffusion-weighted imaging, and dynamic contrast enhancement (Table 1).[2] We defined the primary ROI based on the highest ROI grade, then the lowest apparent diffusion coefficient from the diffusion-weighted imaging, and then the largest diameter in millimeters.

MR-Ultrasound Fusion Biopsy

Figure 1 shows the steps in the process of fusion biopsy. MRI images were transferred electronically to an Artemis fusion device (Eigen, Grass Valley, Calif) immediately before a transrectal ultrasound was performed. The fusion of MR and real-time ultrasound images was then completed.[2] Men with ROIs underwent TB, with approximately 1 core per 3 mm of the longest ROI axis. After TB was obtained, patients underwent 12-core SB via a scalable grid incorporated into the software of the Artemis device.

The primary outcome of interest was the detection of csCaP, defined here as any tumor with a GS $\geq$7.[15] We compared the performance of different fusion biopsy strategies (ie, TB alone, SB alone, or CB) in detecting csCaP among patients with $\geq$1 ROI of $\geq$ grade 3.

Statistical Analysis

Descriptive statistics were performed to summarize clinical, radiographic, and biopsy characteristics. Chi-square and Fisher exact tests were used to evaluate the association between clinical characteristics and the presence of csCaP. The McNemar test was used to compare the performance of different biopsy strategies and the detection of: 1) csCaP; 2) low-risk CaP (ie, GS 3 + 3 = 6); and 3) high-risk CaP (ie, GS $\geq$ 8). Multivariable logistic regression models were used to estimate odds ratios (OR) for the presence of csCaP based on pertinent covariates. The efficacy of the logistic model was estimated using the area under the receiver operating characteristic curve and the goodness of fit was estimated using the Hosmer-Lemeshow test. Chi-square and Fisher exact tests were also performed to assess the relation between covariates and the presence of CaP among patients with a negative MRI (ie, no ROIs of $\geq$grade 3). The tests were 2-sided and considered to be statistically significant at $P<.05$. Statistical analysis was performed using Stata 11 statistical software (StataCorp, College Station, Tex).

RESULTS

Table 2 lists the characteristics of the analytic cohort. Among 1042 patients, 324 (31%) had csCaP found on fusion biopsy (289 with at least 1 suspicious ROI and 35 with a normal mpMRI). A total of 825 patients (79%) had $\geq$ 1 ROI of $\geq$ grade 3, and 217 patients (21%) had

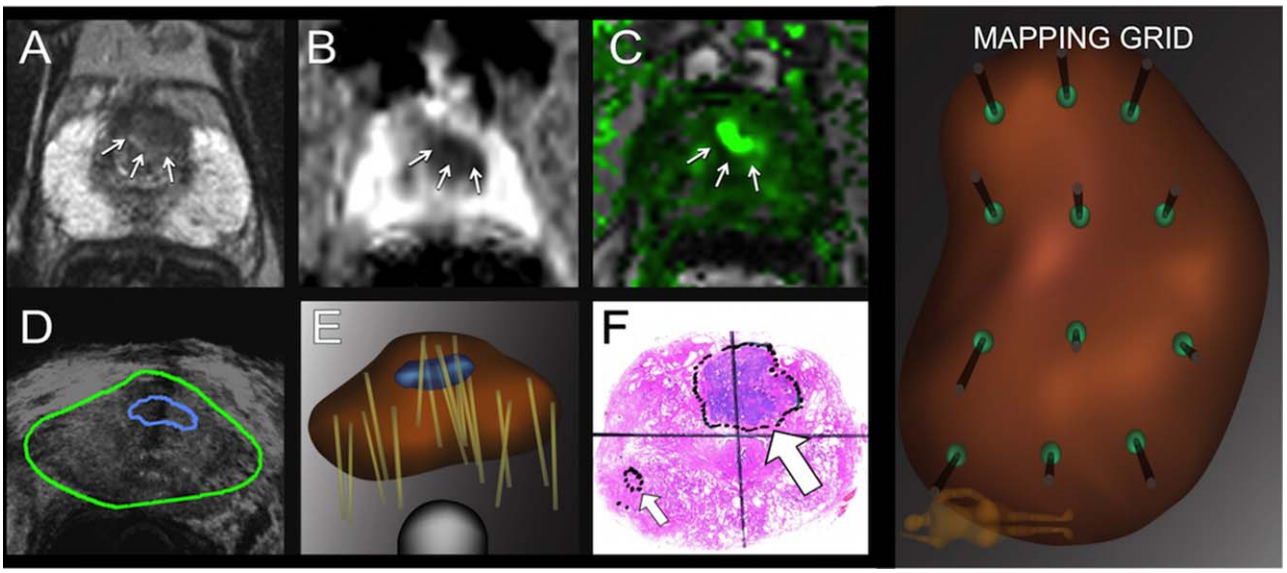

Figure 1. Pathway for the performance of magnetic resonance (MR)-ultrasound-guided fusion biopsy in a sample patient. From the multiparametric MR imaging (mpMRI), a region of interest (ROI) (arrows) was identified on 3 sequences: (A) T2-weighted imaging, (B) diffusion-weighted imaging, and (C) dynamic contrast enhancement. (D) MR images were coregistered with real-time transrectal ultrasound in the image fusion device. (E) Biopsies (tan lines) were performed on a 3-dimensional reconstruction of the prostate made by the fusion device; the model incorporated the ROI (in blue) as an anterior target. Targeted and systematic cores were obtained. (F) The radical prostatectomy specimen processed with whole-mount sectioning shows the index tumor corresponding to the ROI (large arrow). The small arrow points to a secondary lesion. Men with no suspicious ROIs on mpMRI had systematic biopsies taken via a 12-point scalable grid, performed with the fusion biopsy device (systematic grid, coronal view).

no suspicious lesions noted on MRI. The median time to biopsy after mpMRI was 20 days (interquartile range, 7-43 days). Men were divided nearly evenly into those with no prior biopsy (32%), those with a prior negative biopsy (31%), and those with a previously positive biopsy (ie, active surveillance patients) (37%). With regard to the maximum ROI grade, 42% had a low-suspicion grade 3 lesion, 29% had a moderate-suspicion grade 4 lesion, and 8% of patients had a high-suspicion grade 5 ROI.

The performance of CB compared with SB only or TB only is detailed in Figure 2. Among 825 patients with $\geq$ 1 ROI of $\geq$ grade 3, CB identified 289 cases of csCaP (vs 229 cases for TB only and 199 cases for SB only [$P<.001$]). The CB approach also identified more high-risk CaP cases (ie, those with a GS of $\geq$8) compared with either approach alone (89 cases vs 74 for TB only [$P<.001$] and 51 cases for SB only [$P<.001$]). A total of 204 men were diagnosed with GS 6 disease using CB (vs 208 with SB only [$P<.001$] and 131 with TB only [$P<.001$]). Thus, adding SB to TB resulted in 60 additional csCaP diagnoses (7% of the ROI cohort), 15 additional high-risk CaP cases (2% of the ROI cohort), and 73 additional GS 6 cases (9% of the ROI cohort) that would have otherwise been undiagnosed if only the ROIs were targeted. Using the CB approach, the number needed to biopsy to identify 1 additional case of csCaP or high-risk CaP was 14 and 55, respectively. Thus, the CB approach would result in 1 additional low-risk CaP case per csCaP cases, and 5 additional low-risk CaP cases per high-risk CaP cases. In a separate analysis, the number of targeted cores taken was found to be related to the detection rate of csCaP (OR, 1.44; $P<.001$), but the number of systematic cores was not (OR, 0.93; $P>.05$).

Figure 3 displays the relationship between ROI grade and the presence of csCaP among the 825 men with an ROI of $\geq$grade 3. The presence of csCaP was found to be directly related to ROI grade. Approximately 80% of men with a grade 5 ROI had evidence of GS $\geq$7 CaP (vs 24% for those with a grade 3 ROI; $P<.001$). The CB approach outperformed TB or SB alone for all ROI grades (all $P<.001$). There was a direct association noted with ROI size and the presence of GS $\geq$7 CaP (24% for ROIs $<$ 8 mm vs 41% for ROIs $>$ 14 mm, or 1.04 per mm [$P<.001$]).

Table 3 lists the results from our multivariable regression models estimating the relation between clinical factors and the presence of csCaP on fusion biopsy. The strongest predictor of csCaP on fusion biopsy was ROI

TABLE 2. Patient Characteristics (N = 1042)

	Prior Negative Biopsy (N = 324)	Biopsy-Naive (N = 328)	Prior Positive Biopsy (N = 390)
Covariate	No. (%)	No. (%)	No. (%)
Median age at biopsy (IQR), y	65.7 (59.3-70.2)	64.4 (58.5-69.4)	65.1 (59.6-69.5)
Race			
White	248 (77)	270 (82)	312 (83)
African American	17 (5)	18 (5)	24 (6)
Asian	35 (11)	22 (7)	24 (6)
Hispanic/Latino	14 (4)	9 (3)	22 (6)
Other/unknown	10 (3)	10 (3)	7 (2)
Median PSA (IQR), ng/mL	7.6 (5.0-11.5)	5.8 (4.4-8.1)	4.8 (3.0-6.9)
Median prostate volume (IQR), cc	57.7 (39.8-83.5)	45.0 (33.0-61.5)	43.0 (32.3-60.4)
Median time between MRI to biopsy (IQR), d	21 (7-43)	19 (7-43)	20 (8-49)
Median maximum diameter of ROI (IQR), mm	11.0 (9.0-14.5)	11.0 (8.0-14.0)	10.0 (8.0-14.0)
No. of ROI ≥ grade 3			
0	48 (15)	45 (14)	85 (22)
1	162 (50)	186 (56)	183 (47)
2	98 (30)	81 (25)	98 (25)
3	16 (5)	17 (5)	23 (6)
Maximum ROI grade			
No lesion/1-2	59 (18)	56 (17)	102 (26)
3	148 (46)	129 (39)	158 (41)
4	87 (27)	109 (32)	105 (27)
5	30 (9)	35 (11)	24 (6)
Median ADC of index ROI (IQR)	982 (871-1096)	985 (875-1104)	999 (870-1126)
Anterior lesion	100 (31)	148 (45)	130 (33)

Abbreviations: ADC, apparent diffusion coefficient; IQR, interquartile range; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; ROI, region of interest.

grade, in which men with a grade 5 ROI were found to have 9 times the odds of csCaP compared with men with grade 3 ROI (OR, 9.05; 95% confidence interval, 4.96-16.50). The presence of csCaP was found to be directly related to age, PSA, PSA density, and number of targeted cores and inversely related to prostate volume. Adding ROI size to the model did not appear to significantly alter the area under the receiver operating characteristic curve and the effect of ROI size was no longer statistically significant ($P = .115$).

Compared with men with prior negative biopsies, those undergoing their first prostate biopsy had a 2-fold risk of csCaP (OR, 2.0; 95% confidence interval, 1.39-2.86). Nearly 3 of 4 patients with a prior negative conventional biopsy who had either a negative MRI (79%) or a ROI < grade 3 (70%) were found to have a negative fusion biopsy. Conversely, the majority of patients with grade 5 ROIs had csCaP (83% of biopsy-naive men, 72% of men with prior negative biopsies, and 76% of men with prior positive biopsies). The summary of cancer detection stratified by biopsy indication (biopsy-naive, prior negative biopsy, and prior positive biopsy) and biopsy strategy based on mpMRI findings is shown in Table 4.

Among 217 men who did not have any suspicious lesions noted on MRI, fusion biopsy demonstrated CaP and csCaP in 93 patients (43%) and 35 patients (16%), respectively. The presence of any CaP within the setting of a normal mpMRI was directly associated with age and inversely associated with prostate volume ($P<.05$), and it was most common among men with prior positive biopsies (59% vs 21% of men with prior negative biopsies; $P<.05$). Age and PSA density were found to be directly associated with csCaP in the setting of a normal mpMRI ($P<.05$), and csCaP was most common among men who had previously positive biopsies (22% vs 9% for men with a prior negative biopsy; $P = .05$).

DISCUSSION

Three principal findings can be derived from this prospective study of 1042 men undergoing MR-ultrasound fusion biopsy. First, 2 factors, ROI grade and PSA density, were found to be strongly and directly related to the presence of csCaP. Men with grade 5 ROIs had 9 times the odds of having csCaP compared with men with grade 3 ROIs. Second, the combination of TB and SB resulted

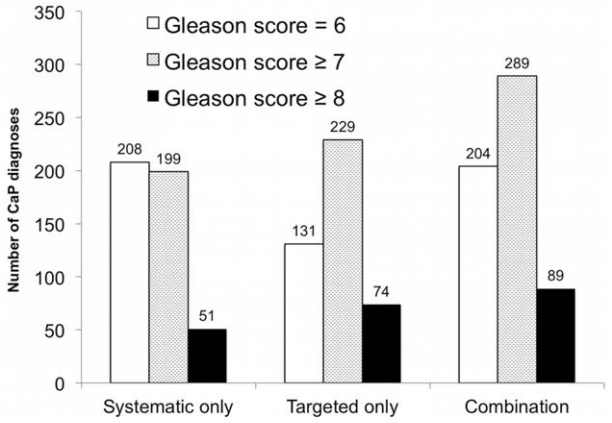

Figure 2. Diagnostic performance of systematic biopsy, targeted biopsy, and the combined approach among patients whose multiparametric magnetic resonance imaging revealed at least 1 region of interest of >grade 3 (825 patients). The number of patients diagnosed with prostate cancer (CaP) (vertical axis) versus the biopsy strategy is shown. Combining targeted and systematic biopsies resulted in the detection of 60 clinically significant CaPs that were undetected by either targeted or systematic biopsy alone (light gray bars; $P<.001$ vs systematic and targeted biopsy alone), and an additional 15 high-risk cases (black bars; $P<.001$ vs the systematic and targeted approaches).

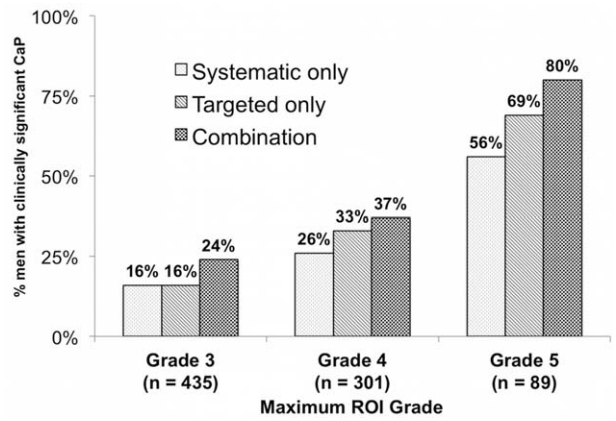

Figure 3. Relationship between region of interest (ROI) grade and the presence of cancer. This figure shows the percentage of patients with ≥1 ROI on magnetic resonance imaging (825 patients) with a diagnosis of clinically significant prostate cancer (csCaP) (289 patients; 35%) (y-axis) stratified by ROI grade (x-axis). Combination biopsy (black checked bars) outperformed systematic biopsy (dark diagonal bars) and targeted biopsy (light hatched bars) across all ROI grades ($P<.001$). Overall, 80% of patients with a grade 5 ROI were found to have csCaP (vs 24% of patients with grade 3 ROI; odds ratio, 9.05 [95% confidence interval, 4.96-16.50]).

in the detection of more csCaP cases than the use of either method alone. This difference was clinically significant: 60 men were diagnosed with csCaP on SB who would have been missed with the use of TB alone. Third, a considerable number of men with negative mpMRI findings were found to harbor potentially significant CaP: 1 in 8 men without suspicious lesions on mpMRI were diagnosed with csCaP by SB. The study design, which included SB regardless of MRI findings, thus provided a critical test of the NPV of MRI in the detection of csCaP.

In predicting csCaP from MRI findings, the ROI grade was by far the most important factor. Among patients with a grade 5 ROI, the presence of aggressive disease was the usual finding, in which 8 of 10 men with these high-suspicion regions harbored high-grade CaP. These results are concordant with several small, retrospective studies in which increasing suspicion of MRI lesions was associated with aggressive disease appearing on fusion biopsy.[2,7,16] Prior work by our group demonstrated that ROI grade is directly related to reclassification beyond the criteria of Epstein et al[15] for a small cohort of men considering active surveillance[7] and among a limited group of men with prior negative prostate biopsies.[5] The results of the current study confirmed these preliminary studies among a large cohort of men and provide helpful information for men considering fusion biopsy after mpMRI of the prostate.

Men with increased PSA density were at considerable risk of the detection of csCaP on fusion biopsy, with an OR of 1.3 per increase of 0.05 ng/mL/cc. Increased PSA density has been recognized as a risk factor for csCaP since the criteria of Epstein et al for clinically insignificant disease were established.[15] Several active surveillance protocols use elevated PSA density as an exclusion criterion for enrollment.[17,18] Other studies have shown the association with elevated PSA density and significant CaP noted on fusion biopsy.[19] Along with ROI grade, the results of the current study confirm PSA density to be an important risk factor for the presence of csCaP on fusion biopsy.

The design and findings of the current study differ somewhat from the recently published work of Siddiqui et al at the National Cancer Institute (NCI) (Table 5).[1] In the NCI study, men with a negative mpMRI (182 men) were excluded from biopsy; in the current study, all men underwent SB, even if MRI was negative. By performing SB regardless of mpMRI findings, 42% of men with no

TABLE 3. Covariates of csCaP Among Patients With an ROI ≥Grade 3 (N=825)

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]	Adjusted OR (95% CI)[b]
Age at biopsy (per 10 y)	1.46 (1.21-1.76)	1.40 (1.13-1.73)	1.63 (1.31-2.02)
PSA (per 5 ng/mL)	1.24 (1.12-1.39)	-	1.29 (1.12-1.49)
Prostate volume (per 10 cc)	0.76 (0.71-0.82)	-	0.70 (0.64-0.76)
PSA density (per 0.05 ng/mL/cc)	1.75 (1.58-1.94)	1.33 (1.23-1.43)	-
ROI grade			
Grade 3[c]	-	-	-
Grade 4	1.91 (1.38-2.63)	1.55 (1.10-2.19)	1.61 (1.14-2.27)
Grade 5	12.80 (7.28-22.41)	7.98 (4.43-14.38)	9.05 (4.96-16.50)

Abbreviations: 95% CI, 95% confidence interval; csCaP, clinically significant prostate cancer; OR, odds ratio; PSA, prostate-specific antigen; ROI, region of interest.

[a] Included covariates for age, PSA density, ROI grade, and number of targeted cores and had an area under the receiver operating characteristic curve of 0.781.

[b] Included covariates for age, PSA, prostate volume, ROI grade, and number of targeted cores and had an area under the receiver operating characteristic curve of 0.794.

[c] Reference group.

TABLE 4. Risk of CaP on Fusion Biopsy Based on mpMRI Findings and Biopsy Indication

		Fusion Biopsy Results (Systematic Plus Targeted)			
				csCaP	
Biopsy Group	Maximum ROI Grade	Negative	GS 3 + 3=6	GS 3 + 4=7	GS ≥ 4 + 3=7
Biopsy-naive (N = 328)	No lesion/grade 1-2	38 (68%)	11 (20%)	4 (7%)	3 (5%)
	Grade 3	60 (46%)	27 (21%)	32 (25%)	10 (8%)
	Grade 4	36 (33%)	28 (26%)	21 (19%)	24 (22%)
	Grade 5	1 (3%)	5 (14%)	8 (23%)	21 (60%)
Prior negative biopsy (N = 324)	No lesion/grade 1-2	47 (80%)	7 (12%)	3 (5%)	2 (3%)
	Grade 3	104 (70%)	25 (17%)	10 (7%)	9 (6%)
	Grade 4	47 (54%)	13 (15%)	15 (17%)	12 (14%)
	Grade 5	4 (13%)	2 (7%)	6 (20%)	18 (60%)
Prior positive biopsy (N = 390)	No lesion/grade 1-2	43 (42%)	38 (37%)	17 (17%)	4 (4%)
	Grade 3	51 (32%)	63 (40%)	35 (22%)	9 (6%)
	Grade 4	29 (28%)	36 (34%)	26 (25%)	14 (13%)
	Grade 5	0 (0%)	6 (25%)	9 (38%)	9 (38%)
		Fusion Biopsy Results (Targeted Alone)			
				csCaP	
Biopsy Group	Maximum ROI Grade	Negative	GS 3 + 3=6	GS 3 + 4=7	GS ≥ 4 + 3=7
Biopsy-naive (N = 328)	No lesion/grade 1-2[a]				
	Grade 3	77 (60%)	18 (14%)	28 (22%)	6 (5%)
	Grade 4	49 (45%)	19 (17%)	20 (18%)	21 (19%)
	Grade 5	2 (6%)	8 (23%)	6 (17%)	19 (54%)
Prior negative biopsy (N = 324)	No lesion/grade 1-2				
	Grade 3	124 (84%)	9 (6%)	9 (6%)	6 (4%)
	Grade 4	53 (61%)	11 (13%)	13 (15%)	10 (11%)
	Grade 5	5 (17%)	3 (10%)	5 (17%)	17 (56%)
Prior positive biopsy (N = 390)	No lesion/grade 1-2[a]				
	Grade 3	106 (67%)	34 (22%)	15 (10%)	3 (2%)
	Grade 4	46 (44%)	25 (24%)	23 (22%)	11 (11%)
	Grade 5	4 (17%)	5 (21%)	9 (37%)	6 (25%)
		Fusion Biopsy Results (Systematic Alone)			
				csCaP	
Biopsy Group	Maximum ROI Grade	Negative	GS 3 + 3=6	GS 3 + 4=7	GS ≥ 4 + 3=7
Biopsy-naive (N = 328)	No lesion/grade 1-2	38 (68%)	11 (20%)	4 (7%)	3 (5%)
	Grade 3	64 (50%)	38 (29%)	22 (17%)	5 (4%)
	Grade 4	44 (40%)	31 (28%)	19 (17%)	15 (14%)
	Grade 5	5 (14%)	4 (11%)	12 (34%)	14 (40%)
Prior negative biopsy (N = 324)	No lesion/grade 1-2	47 (80%)	7 (12%)	3 (5%)	2 (3%)
	Grade 3	113 (76%)	24 (16%)	7 (5%)	4 (3%)
	Grade 4	58 (67%)	12 (14%)	10 (12%)	7 (8%)
	Grade 5	10 (33%)	5 (17%)	4 (13%)	11 (37%)
Prior positive biopsy (N = 390)	No lesion/grade 1-2	43 (42%)	38 (37%)	17 (17%)	4 (4%)
	Grade 3	71 (45%)	54 (34%)	27 (17%)	6 (4%)
	Grade 4	46 (44%)	31 (29%)	17 (16%)	11 (11%)
	Grade 5	6 (25%)	8 (33%)	5 (21%)	5 (21%)

Abbreviations: CaP, prostate cancer; csCaP, clinically significant prostate cancer; GS, Gleason score; mpMRI, multiparametric magnetic resonance imaging; ROI, region of interest.

[a] Grade 1 to 2 lesions were not consistently targeted and therefore were excluded from the current analysis.

TABLE 5. Comparison Between the UCLA and NCI Fusion Biopsy Studies

Characteristic	NCI	UCLA
Patient cohort	Only patients with ROI	All patients, including those with normal mpMRI
Patients with negative mpMRI	No	Yes (n=217; 21%)
Prior negative biopsy, no. (%)	432 (43%)	324 (31%)
Biopsy-naive patients, no. (%)	196 (20%)	328 (37%)
MRI grading system	Incorporated MR spectroscopy	Similar to PI-RADS with greater emphasis on ADC from DWI
Endorectal coil	Yes	No
MRI findings		
ROI grade	72% moderate suspicion 11% high suspicion	37% moderate suspicion 11% high suspicion
Mean no. of ROIs/MRI	2.7	1.5
% anterior ROIs	44%	36%
Fusion biopsy device	UroNav (Invivo Corporation)	Artemis (Eigen)
Systematic biopsy	Transrectal ultrasound-guided systematic biopsy performed by second urologist	Artemis-guided mapping biopsy performed by same urologist
Definition of low-risk cancer	Gleason score 3 + 3=6 and low-volume Gleason score 3 + 4=7	Gleason score 3 + 3=6

Abbreviations: ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; MR, magnetic resonance; mpMRI, multiparametric magnetic resonance imaging; NCI, National Cancer Institute; PI-RADS, Prostate Imaging Reporting and Data System; ROI, region of interest; UCLA, University of California at Los Angeles.

suspicious lesions on mpMRI were found to harbor CaP; moreover, approximately one-third of the cancers found were clinically significant, resulting in a change in management for these men. Freehand SB added very little to the detection of csCaP in the NCI study, but software-guided SB was of considerable importance to the detection of csCaP in the current study.

There are several factors that could explain these observed differences in cancer detection on SB. First, approximately 43% of the patients in the NCI study had undergone prior negative biopsy (vs 31% in the current study), indicating that more men in the NCI study had hard-to-detect tumors than in the present group. Furthermore, an anterior location was more common in the NCI study compared with the current study (44% vs 36%). Anterior tumors often go undetected by conventional SB in as many as 50% of cases.[20] Furthermore, the MRI grading systems used were not the same in the 2 studies. Neither system was the contemporary version of PI-RADS (version 2), which is now the "industry standard."[21] Another possible contributing factor to the observed differences is the technique used for SB. Freehand biopsies using transrectal ultrasound guidance, as in the NCI report, may provide different tissue findings than SBs using a defined grid or template, as in the current study. For example, conventional prostate biopsies are hampered by a risk of falsely negative results, which is reported to be as high as 47% in some series.[22] When experienced urologists performed freehand, ultrasound-guided biopsies on a phantom prostate, biopsy sites were found to be widely divergent between individual operators, were frequently clustered, and left large parts of the prostate unsampled.[23] Thus, all these factors may have played a role in the lower detection rate of the SBs noted in the NCI report.

The concept of using mpMRI to obviate prostate biopsy, if the imaging reveals no targets, should be regarded with caution.[12,24] In a recent meta-analysis, the NPV of mpMRI was found to range from 65% to 94%, depending on how that finding was validated.[25] In a retrospective study of 193 men, Itatani et al reported an NPV of 89.6% for the identification of csCaP on mpMRI.[12] However, in the series by Itatani et al, conventional transrectal ultrasound-guided biopsy was performed, which may result in a lower detection rate compared with SB. In the current study, NPVs of 56% for any cancer and 85% for csCaP were observed. These data suggest that a negative mpMRI should not routinely replace biopsy as a method with which to rule out the presence of csCaP.

The current study focused on the diagnosis of csCaP rather than high-risk CaP. Siddiqui et al found that to detect 1 additional high-risk case, 200 CBs would be required, with the implication being that SBs may be unnecessary.[1] However, high-risk cases are often of large volume and are less difficult to detect. Clinically significant tumors (ie, tumors with a GS of 7) may not always be apparent on mpMRI and are often smaller and more difficult to detect than large-volume, high-risk tumors. Furthermore, the detection of csCaP will often change patient management, at least with regard to increasing the vigilance of follow-up. Using SB as described herein, 14 CBs would be needed to detect 1 additional csCaP and 55 CBs would be needed to detect high-risk tumors (ie, those

with a GS >8). Thus, the combination of SB and TB, as described in the current study, is necessary for optimal characterization of whole-organ pathology and the assessment of biologic potential.

The findings of the current study should be interpreted within the context of some methodological limitations. First, we chose not to use an endorectal coil for the present investigation. The use of an endorectal coil for MRI is acknowledged to improve the staging of CaP. However, to the best of our knowledge, comparisons of external phased array versus endorectal coil imaging have demonstrated equivalent performance with each modality for the detection of CaP.[26,27] A recent comparison of these acquisition techniques[28] found more cancers were detected with the use of an endorectal coil than the body coil. However, in the current study, the endorectal coil provided only a 10% improvement in sensitivity for the dominant tumor (85% vs 75%), only 20 patients were included, and the MRI method was not fully multiparametric. Thus, with the goal of defining a practical diagnostic modality for widespread adoption, the choice to use the more patient-friendly body coil was a key consideration of the experimental design.

Second, we used specific institutional protocols for the grading of ROIs that may limit generalizability to other practice settings. However, our protocol varies only slightly from the validated PI-RADS grading scheme, and in-house data have shown that the UCLA grading system[2] is highly concordant with PI-RADS. In addition, the results of the current study relied on input from individual experts well versed in the execution of mpMRI and MR-ultrasound fusion biopsy, respectively. These results may not be reproducible in settings among practitioners with less experience. There also is a risk of misregistration with fusion biopsy based on several factors (eg, distortion from the transrectal ultrasound probe) that could explain differences in cancer detection rates between TB and SB. Third, our definition of csCaP as a tumor with a GS $\geq$7 may not capture truly significant disease, because there may be clinical implications of having high-volume GS 6 disease and less significance with low-volume GS 7 disease. Finally, this analysis did not consider whole-mount prostatectomy specimens, thereby precluding knowledge of the true CaP detection rate of MR-ultrasound fusion biopsy and mpMRI.[13]

These limitations aside, MR-ultrasound fusion biopsy appears to be most accurate when the targeting of specific lesions is combined with SB guided by software in the fusion device. The combined approach identifies more csCaP than TB alone and provides accurate characterization of low-risk (and likely indolent) tumors with a GS of 6. It is interesting to note that men with high-suspicion ROI and elevated PSA density are at a greatly increased risk of aggressive CaP. Finally, at this point, when biopsy is clinically indicated, a negative mpMRI should not preclude it. Template-based systematic sampling can detect cases of csCaP even when MRI indicates no suspicious targets.

FUNDING SUPPORT

Supported by the National Cancer Institute at the National Institutes of Health (grant R01CA158627), the University of California at Los Angeles Clinical and Translational Science Institute (grant UL1TR000124), the Beckman Coulter Foundation, the Jean Perkins Foundation, the Steven Gordon Family Foundation (to Leonard S. Marks), and the American Cancer Society Postdoctoral Fellowship (grant PF-14-161-01-CPHPS) (to Christopher P. Filson).

CONFLICT OF INTEREST DISCLOSURES

Daniel J.A. Margolis was supported by an institutional grant from Siemens Medical Systems for work performed outside of the current study (he is not named on the grant). Patricia Lieu and Frederick J. Dorey were supported by a grant from the American Cancer Society for work performed as part of the current study. Robert E. Reiter has received personal fees from Astellas Pharma and ImaginAb for work performed outside of the current study.

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