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Value of Targeted Prostate Biopsy Using Magnetic Resonance–Ultrasound Fusion in Men with Prior Negative Biopsy and Elevated Prostate-specific Antigen

Geoffrey A. Sonn[a,*], **Edward Chang**[a], **Shyam Natarajan**[b,c], **Daniel J. Margolis**[d], **Malu Macairan**[a], **Patricia Lieu**[a], **Jiaoti Huang**[e], **Frederick J. Dorey**[f], **Robert E. Reiter**[a], and **Leonard S. Marks**[a]

Geoffrey A. Sonn: gsonn@mednet.ucla.edu

[a]Department of Urology, University of California, Los Angeles, Los Angeles, CA, USA

[b]Department of Biomedical Engineering, University of California, Los Angeles, Los Angeles, CA, USA

[c]Center for Advanced Surgical and Interventional Technology, University of California, Los Angeles, Los Angeles, CA, USA

[d]Department of Radiology, University of California, Los Angeles, Los Angeles, CA, USA

[e]Department of Pathology, University of California, Los Angeles, Los Angeles, CA, USA

[f]Department of Orthopedic Surgery, University of California, Los Angeles, Los Angeles, CA, USA

Abstract

Background—Conventional biopsy fails to detect the presence of some prostate cancers (PCas). Men with a prior negative biopsy but persistently elevated prostate-specific antigen (PSA) pose a diagnostic dilemma, as some harbor elusive cancer.

Objective—To determine whether use of magnetic resonance–ultrasound (MR-US) fusion biopsy results in improved detection of PCa compared to repeat conventional biopsy.

*Corresponding author. UCLA, Urology, 924 Westwood Blvd., Suite 1050, Los Angeles, CA 90036, USA. Tel. +1 310 794 3070; Fax: +1 310 794 3060.

Author contributions: Geoffrey A. Sonn 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: Sonn, Chang, Dorey, Marks.
Acquisition of data: Chang, Natarajan, Margolis, Macairan, Lieu, Huang, Reiter.
Analysis and interpretation of data: Sonn, Chang, Dorey, Marks.
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Design, setting, and participants—In a consecutive-case series, 105 subjects with prior negative biopsy and elevated PSA values underwent multiparametric magnetic resonance imaging (MRI) and fusion biopsy in an outpatient setting.

Intervention—Suspicious areas on multiparametric MRI were delineated and graded by a radiologist; MR–US fusion biopsy was performed by a urologist using the Artemis device; targeted and systematic biopsies were obtained regardless of MRI result.

Outcome measurements and statistical analysis—Detection rates of all PCa and clinically significant PCa (Gleason ≥3 + 4 or Gleason 6 with maximal cancer core length ≥4 mm) were determined. The yield of targeted biopsy was compared to systematic biopsy. The ability of an MRI grading system to predict clinically significant cancer was investigated. Stepwise multivariate logistic regression analysis was performed to determine predictors of significant cancer on biopsy.

Results and limitations—Fusion biopsy revealed PCa in 36 of 105 men (34%; 95% confidence interval [CI], 25–45). Seventy-two percent of men with PCa had clinically significant disease; 21 of 23 men (91%) with PCa on targeted biopsy had significant cancer compared to 15 of 28 (54%) with systematic biopsy. Degree of suspicion on MRI was the most powerful predictor of significant cancer on multivariate analysis. Twelve of 14 (86%) subjects with a highly suspicious MRI target were diagnosed with clinically significant cancer.

Conclusions—MR-US fusion biopsy provides improved detection of PCa in men with prior negative biopsies and elevated PSA values. Most cancers found were clinically significant.

Keywords

Magnetic resonance imaging; Prostate biopsy; Prostate cancer; Ultrasound

1. Introduction

Prostate needle biopsy, when performed by the conventional method [1], may fail to detect the presence of cancer. The false-negative rate of ultrasound-guided systematic biopsy may be as high as 47% [2]. Men with prior negative biopsies and persistently elevated serum prostate-specific antigen (PSA) levels, a group numbering in the millions, constitute a diagnostic dilemma [3,4]. Repeated biopsy sessions and PSA-related anxiety will follow in many of these men. In fact, 38% of Medicare patients undergo a repeat biopsy within 5 yr of an initial negative biopsy [5]. Attempts to reduce the false-negative rate by additional sampling, anterior sampling, and apical sampling have been only marginally successful [6,7]. Transperineal template biopsy may detect additional prostate cancer (PCa) [1,8], both serious and trivial, but it requires general anesthesia and risks increased morbidity [2,9].

Targeted prostate biopsy, which uses findings from magnetic resonance imaging (MRI) to guide needle aiming, may help to establish a correct diagnosis for men in this group [10]. The technology involves either direct in-bore biopsy, performed by a radiologist [11–14], or fusion biopsy, wherein the MRI features are combined with ultrasound guidance in a traditional urologic biopsy suite [15–20]. Using one such fusion device (Artemis, Eigen, Grass Valley, CA, USA), we found that level of suspicion on MRI correlated with biopsy diagnosis of cancer; when MRI indicated a focus of greatest suspicion, cancer was diagnosed by fusion biopsy in 15 of 16 men [21].

In the present study, we sought to test the value of an office-based fusion device in the detection of PCa in men with prior negative biopsies and persistently elevated PSA levels. Conduct of the present study and preparation of this report were guided by conclusions from a recent international conference on this subject [22].

2. Material and methods

2.1. Study design

Subjects were culled from a prospective trial of magnetic resonance– ultrasound (MR–US) fusion biopsy at the University of California, Los Angeles (UCLA), which was approved in advance by the UCLA Institutional Review Board. Those included in the present study were all 105 men with one prior negative prostate biopsy or more and persistently elevated serum PSA levels who underwent multiparametric MRI (mpMRI) and MR–US fusion biopsy between March 2010 and August 2012. Prior biopsies were performed by US board-certified urologists during the previous 7 yr; 94% included ≥12 cores, and five men had a saturation biopsy with >20 cores. The Artemis device was used for fusion. Biopsy was performed in all men regardless of MRI result.

The primary outcome was detection of all cancers. Secondary outcomes included detection of clinically significant cancer (defined below), cancer detection stratified by MRI result, and comparison of targeted versus systematic cores. Partial data from 65 men in the present study were reported elsewhere [21].

2.2. Multiparametric magnetic resonance imaging

In brief, subjects underwent mpMRI on a Siemens TrioTim Somatom 3-Tesla (Siemens Medical Solutions, Malvern, PA, USA) magnet using a multichannel external phased-array coil. The MRI protocol was recently published [19,21]; delineation of lesions and assignment of image grade (1–5) was by a uroradiologist with 10 yr of experience reading prostate MRI (DM). The MRI image grading system is detailed in Table 1 [21]. MRI was performed 1 to 3 wk before biopsy.

2.3. Magnetic resonance imaging-ultrasound fusion biopsy procedure

Delineated MR images were recorded on CD and entered into the Artemis device at the outset of a conventional transrectal ultrasound (TRUS) biopsy session. Fusion of MRI and real-time ultrasound was performed as described previously [19]. Subjects underwent sampling of 12 systematic biopsy sites that were preselected by the Artemis device and were independent of the MRI result. Men with image grade ≥2 targets on MRI also received targeted biopsies, obtaining one core approximately every 3 mm of the longest axis of the lesion, prior to systematic sampling [19]. All biopsies were performed by a single urologist (LSM) with a conventional reusable spring-loaded gun and 18-G needles. An example of the fusion biopsy method is shown in Figure 1.

2.4. Definition of tumor clinical significance

Several biopsy-based definitions of *tumor significance* were used [23], including (1) Epstein criteria (Gleason >6 or Gleason 6 with >50% PCa per core or >2 cores PCa), (2) Gleason 3 + 4 or Gleason 6 with maximal cancer core length (MCL) ≥4mm, (3) Gleason 4 + 3 or MCL ≥6 mm, (4) Gleason ≥7 cancers, and (5) Gleason ≥8 cancers. Definition 2 was selected for the figures in an effort to incorporate both grade and volume into the definition of *significance*. For volume, maximum cancer core length was used instead of number of cores containing PCa to avoid the bias associated with obtaining multiple cores from the same tumor.

2.5. Statistical analysis

Descriptive statistics were used to summarize patient characteristics such as age, ethnicity, PSA, prostate volume, PSA density, and number of prior negative biopsies. Correlations between continuous variables were made using the nonparametric Spearman rank

correlation. Univariate analysis was performed using logistic regression analysis to detect the associations between presence of any cancer; clinically significant cancer; and the demographic variables listed above, including time from previous negative TRUS biopsy, target grade, maximum target diameter, and number of cores taken. A stepwise multivariate logistic regression model was performed to find a parsimonious model that accounted for all the relationships between the covariates and clinically significant cancer. All calculations were performed using Stata v.11 software (StataCorp, College Station, TX, USA) by a biostatistician (F.D.).

3. Results

3.1. Demographics and clinical characteristics

Table 2 displays demographics and clinical characteristics. The median interval from negative biopsy to MR–US fusion biopsy was 14 mo (interquartile range [IQR]: 9–26). At prior biopsies, a median of 13 cores was obtained (IQR: 12–16). At fusion biopsy, the median PSA level was 7.5 ng/ml (IQR: 5.0–11.2) and median prostate volume was 58 ml (IQR: 39–82). Targets were identified on mpMRI in 101 of the 105 patients (maximum image grade of 1, $n = 4$; grade 2, $n = 11$; grade 3, $n = 42$; grade 4, $n = 34$; and grade 5, $n = 14$). On average, 1.3 targets were identified per patient (range: 1–3) and 4.2 cores were taken per target (range: 1–9). The mean number of biopsy cores per patient was 15.9. The mean time from probe insertion to last biopsy was approximately 20 min.

3.2. Biopsy results

Biopsies revealed PCa in 36 of 105 men (34%; 95% confidence interval [CI], 25–45). When including only those patients with a highly or very highly suspicious MRI (maximum image grade 4–5), the cancer yield was 24 of 48 men (50%). A strong relationship existed between target image grade and biopsy yield (Fig. 2). The proportion of PCa deemed clinically significant varied from 31% to 72% depending on the definition of *significance* (Table 3). The detection of clinically significant cancer was independent of both the number of prior biopsies (Table 4) and the interval from prior negative biopsy to fusion biopsy (data not shown). In 16 of the 36 men with PCa, the index lesion was located in the anterior region of the prostate.

3.3. Systematic versus targeted biopsies

Ninety-seven men had at least one targeted biopsy, and 102 men had systematic biopsies. Eight men did not have targeted biopsies, because no appreciable target was seen on MRI ($n = 6$) or because of technical difficulties with the biopsy device ($n = 2$). Three men did not have systematic cores because of intolerance of additional biopsies after completion of the targeted cores. Of these, one had no cancer and two had clinically significant cancer on targeted biopsy.

We also evaluated the overall diagnostic rate and the hypothetical rate if only targeted cores or only systematic cores were considered. Based on targeted cores only, 24% of men were diagnosed with PCa. When considering systematic cores only, 27% were diagnosed. For targeted biopsies, PCa was present in 5 of 228 (2%) cores from image grade 2 or 3 targets, 23 of 195 (12%) from image grade 4 targets, and 57 of 94 (61%) from image grade 5 targets. To increase the probability of finding clinically significant cancer to 95% (definition 2), 175 cores would need to be taken for grade 2–3 targets, 15 for grade 4 targets, and only 3 for grade 5 targets.

Targeted biopsy detected more clinically significant cancers and fewer insignificant cancers than systematic biopsy using each of the five definitions of PCa *significance*. Using

definition 2 [23], 21 of the 23 men (91%) diagnosed with cancer on targeted biopsies had clinically significant disease. In contrast, 15 of the 28 men (54%) had clinically significant cancer based on systematic biopsies. Table 5 displays the comprehensive results of targeted versus systematic biopsy using definition 2. When compared to systematic cores, targeted cores discovered 1.4 times as many clinically significant cancers but just 15% as many insignificant cancers. Figure 3 displays this relationship graphically.

3.4. Predicting biopsy results

Univariate analysis showed that age, PSA level, PSA density, prostate volume, maximum target diameter, and MRI grade were directly related to the likelihood of clinically significant cancer ($p < 0.05$). Prostate volume was inversely related ($p < 0.05$). A model based on a stepwise multivariate logistic regression analysis showed that an older age ($p = 0.025$), smaller prostate volume ($p = 0.004$), PSA density ($p = 0.077$), and image grade 5 ($p = 0.001$) were sufficient for explaining all of the statistically significant relationships among the covariates and clinically significant cancer. Image grade 5 was the most powerful predictor of significant cancer (odds ratio: 33.0). Twelve of 14 (86%) subjects with a maximum target of grade 5 were diagnosed with clinically significant cancer. Of the two without significant cancer, one had Gleason 7 disease on repeat targeted biopsy, and one had a granuloma from prior bacillus Calmette-Guérin treatment.

4. Discussion

In the present study of men with a prior negative biopsy and persistently elevated PSA levels, a *dilemma group*, we found that MR–US fusion biopsy yielded a 34% cancer-detection rate. When highly suspicious MRI lesions were targeted, the great majority of cancers found were clinically significant, and few were insignificant. Because of these and other supporting data [15,18], fusion biopsy can now be considered for men in the dilemma group. Although experience is limited, the fusion device method compares favorably to other targeted biopsy techniques.

Repeat conventional biopsy yields a decreasing cancer rate with each subsequent biopsy session. Among the 1051 men enrolled in the European Prostate Cancer Detection study, the first repeat eight-core TRUS biopsy was positive in 10% of men, while the second repeat biopsy revealed cancer in only 4% of cases [24]. In another study of 2526 men, the yield of the first, second, third, and fourth repeat biopsy was 17%, 14%, 11%, and 9%, respectively [25]. Thus, the 34% PCa detection rate with fusion biopsy in the present study exceeds the historical detection rates obtained by conventional biopsy. This yield is obtained despite the fact that many patients were undergoing a third or fourth biopsy, in which detection rates are traditionally low. No relationship existed between number of prior biopsies and detection rate by the fusion biopsy method, suggesting that it discovers PCa that would evade detection by repeat conventional biopsy.

To improve the sensitivity of repeat biopsy, others have advocated transrectal saturation or transperineal template biopsy [2,26,27]. One study of 1056 men (median PSA level: 5.6) found a greater cancer yield for a 20- to 24-core transrectal saturation biopsy (32.7%) than a 12- to 14-core extended biopsy (24.9%). However, although the saturation technique detected more cancers, 40.1% were clinically insignificant [26]. Using transperineal template biopsy in a repeat biopsy setting, Taira et al. detected cancer in 55.5%, 41.7%, and 34.4% of first, second, and subsequent repeat biopsies, respectively. Yet, 45% of tumors were Gleason ≤6 [2]. Furthermore, transperineal template schemes are limited by a need for general anesthesia and substantial rates of complications [9,28,29].

Direct MR-guided biopsy in the dilemma group of men is reported to show cancer detection rates of 39% to 59% [11–14]. In the most recent and largest series, investigators identified 438 men with a PSA level >4.0 ng/ml (median PSA level: 11.4) and ≥1 negative TRUS biopsies who underwent mpMRI. After excluding those without a suspicious lesion on MRI, 265 underwent MR-guided biopsy. Cancer was diagnosed in 108 of 265 men (41%), with 87% of those defined as clinically significant [11]. This detection rate is comparable to the 50% rate reported here in men with a lesion graded ≥4 on MRI.

Using a different MR-US fusion biopsy platform in men with prior negative biopsies, Vourganti et al. detected cancer in 73 of 195 men (37%) with a lesion suspicious for cancer on MRI [15]. This result included 21 men with high-grade cancer (Gleason ≥8). Other important findings included identification of more significant cancers and fewer insignificant cancers with targeted versus systematic biopsies, independence between the yield of fusion biopsy and the number of prior negative biopsies, and no detection of high-grade cancers in men with a PSA density <0.15 ng/ml per ml. Our results substantiate each of these findings. The consistency of the two reports, which were obtained by two independent groups using two different technologies, strengthens the validity of the fusion biopsy concept.

In the present study, cancer yield was similar to that of direct MR-guided biopsy. MR–US fusion biopsy enables rapid acquisition of systematic biopsies in addition to targeted biopsies. The importance of retaining systematic biopsies was affirmed by the finding of significant cancer only on systematic biopsy in five of our subjects (Fig. 3). Although the false-negative rate of MRI appears to be low [30], the present data indicate that the highest sensitivity in detection of PCa is obtained by a combination of targeted and systematic biopsies, even in areas that appear normal on MRI.

This study has several limitations. First, it is a relatively small, retrospective case study. A randomized trial comparing men undergoing conventional versus fusion biopsy would provide level 1 evidence. Second, limited patient follow-up precludes comment on subsequent cancer diagnoses in the 66% of men with a negative MR–US fusion biopsy. It remains possible that some clinically significant cancers are missed on MR–US fusion biopsy, so the false-negative rate is unknown. Third, all biopsies were performed by one urologist, and all MRIs were interpreted by an experienced uroradiologist. Less experienced urologists and radiologists might not achieve the same diagnostic yield. Finally, the study uses several published definitions of PCa *significance* that were developed based on random sampling. The most appropriate definition of *clinically significant cancer* for targeted biopsy has yet to be defined.

Notwithstanding these limitations, MR–US fusion targeted prostate biopsy appears to improve the diagnostic yield over repeat TRUS biopsy in the dilemma group of men with an elevated PSA level but prior negative biopsy. Further, the new method is less likely to detect insignificant cancers than saturation techniques. The results of MR–US fusion biopsy compare favorably to those achieved by direct MR-guided biopsy but require only a single MRI and 20 min of procedure time. In terms of clinical application, cost of fusion biopsy was not analyzed, but the outpatient procedure described here should be substantially less expensive than a formal saturation biopsy, which requires anesthesia, or a direct in-bore biopsy, which requires two separate sessions of MRI.

5. Conclusions

Office-based MR–US fusion biopsy improves detection of PCa in men with prior negative biopsies and elevated PSA levels. The majority of detected cancers are clinically significant.

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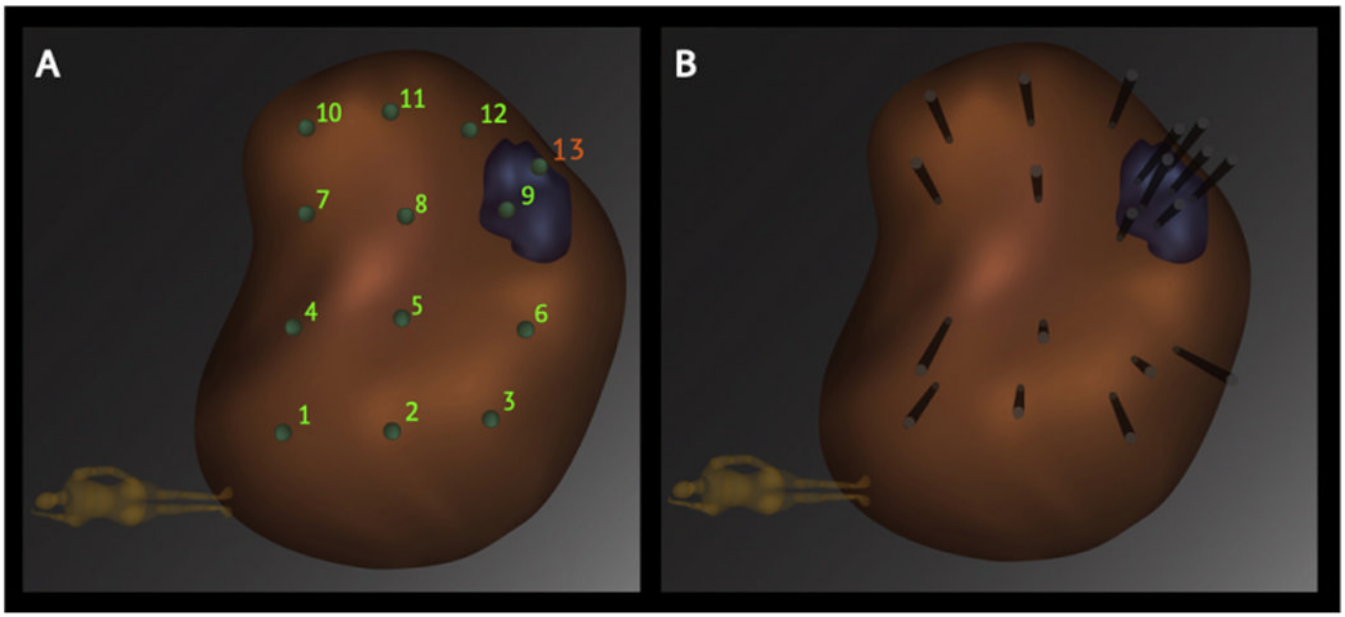

Fig. 1.

Example of fusion biopsy. The patient is a 72-yr-old man with a prostate-specific antigen value of 18.2 ng/ml, a prostate volume of 75 ml, and two prior negative biopsies. (A) A three-dimensional model of the prostate (brown) was created in the Artemis device, fusing magnetic resonance imaging (MRI) and real-time ultrasound images. An optimally spaced 12-core systematic biopsy map (green spots) is automatically generated. An area of interest on MRI, assigned image grade 5 by the radiologist, is shown fused within the model (blue spot marked as a target numbered 13). In this patient, mapped spot 9 overlies the target 13. (B) A 12-core systematic biopsy was performed at mapped sites. Recorded locations of biopsy cores are shown as black cylinders. The MRI target was sampled with five targeted cores and one systematic core (mapped spot 9). All six cores showed Gleason 9 prostate cancer. Other biopsies were negative.

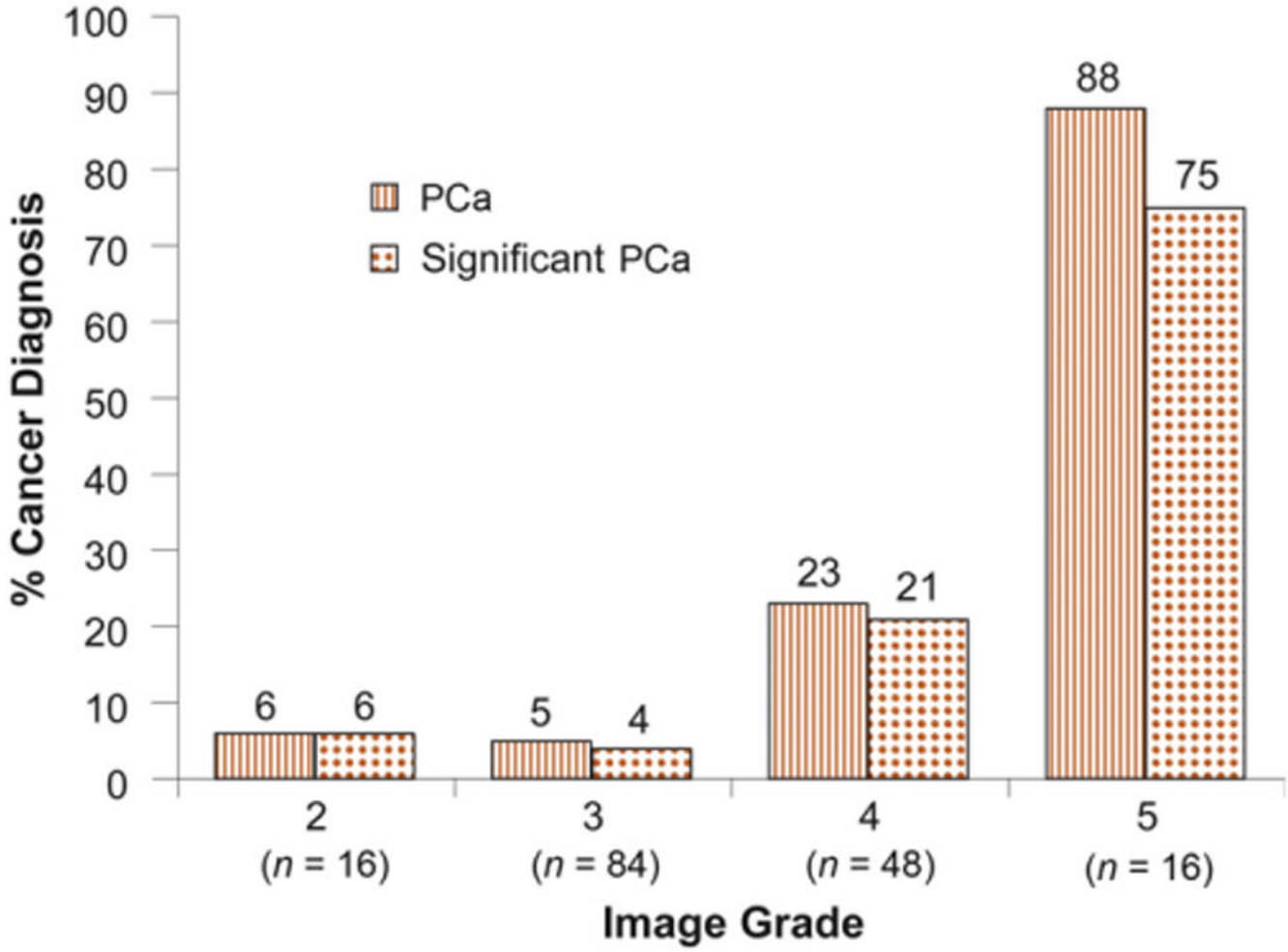

Fig. 2.

This per-target analysis shows the proportion of all cancers (hatched) and clinically significant cancers (dotted) stratified by image grade on magnetic resonance imaging scans. For example, 75% of the 16 image grade 5 targets identified in the 105 patients had clinically significant cancer identified in at least one of the targeted biopsy cores. PCa = prostate cancer.

* Targeted biopsies were not taken from men (n = 4) with a normal magnetic resonance imaging scan (image grade 1).

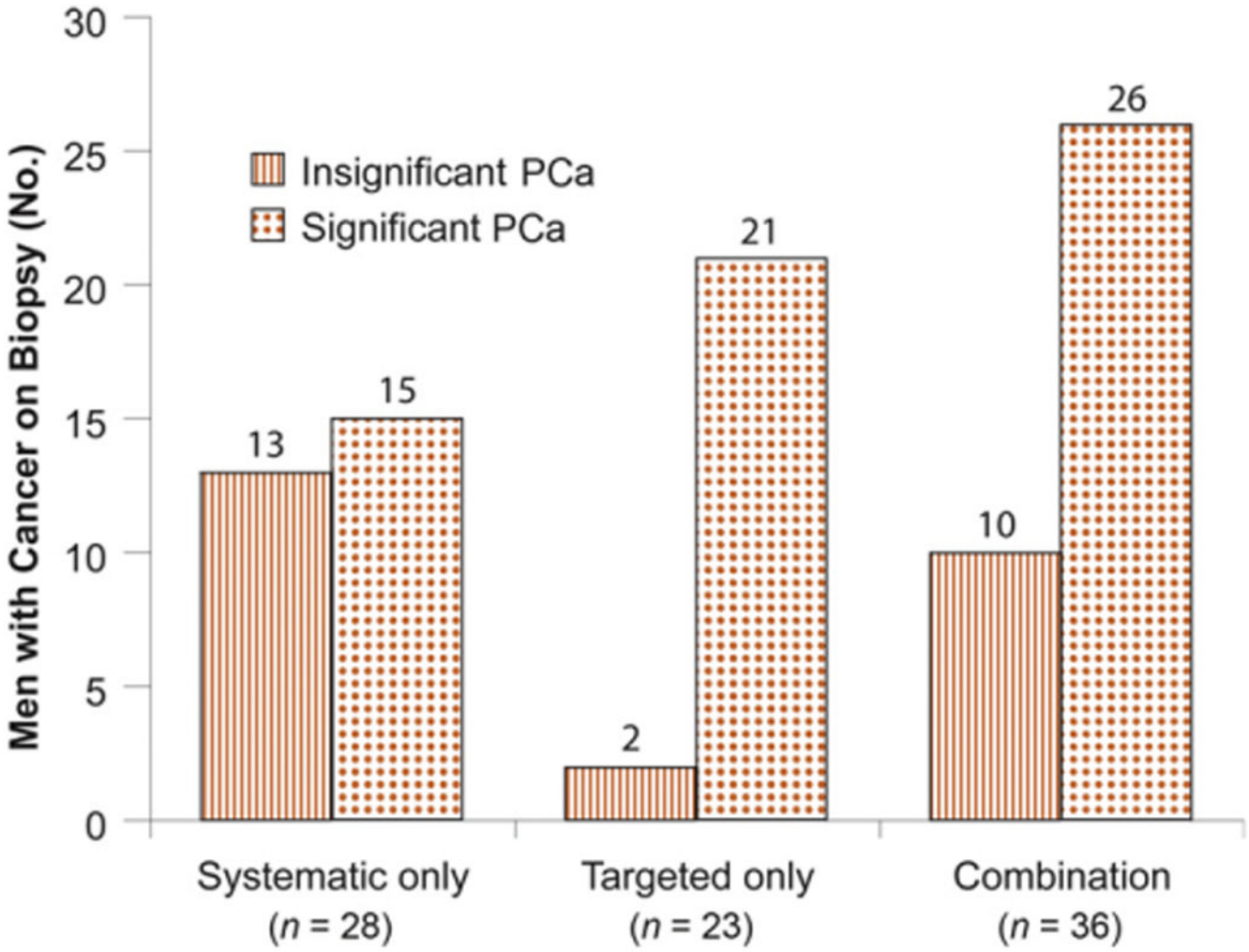

Fig. 3.

This per-patient analysis shows the number of subjects diagnosed with significant cancers (dotted) and insignificant cancers (hatched) depending on biopsy method. Clinically significant cancer was based on definition 2 (Gleason >6 or ≥4 mm maximal core length). PCa = prostate cancer.

Table 1

Classification system for targets identified on magnetic resonance imaging scans. The composite image grade is a weighted average of the individual scores.

Image grade	T_2-weighted imaging	Apparent diffusion coefficient x10-3 m^2/s)	Dynamic contrast enhancement
1	Normal	>1.4	Normal
2	Faintly decreased signal	1.2–1.4	Early or intense enhancement
3	Distinct, low signal	1.0–1.2	Early and intense enhancement or early enhancement with washout
4	Distinct, low signal with ill-defined margins	0.8–1.0	Early and intense enhancement with washout
5	Focal low signal with mass effect	<0.8	Early enhancement is intense with immediate washout.

Table 2
Demographic and clinical characteristics of 105 men who underwent fusion biopsy

Clinical characteristics	Median	IQR
Age	65	59–70
PSA	7.5	5.0–11.2
PSA density	0.13	0.08–0.23
Prostate volume	58	39–82
No. of prior TRUS biopsies	2	1–3
No. of cores in previous biopsy	13	12–16

Treatment history	No. of patients	%
TURP	2	2
5α-reductase inhibitor	23	22
HT	0	0

Prior biopsy pathology	No. of patients	%
HGPIN	12	11
ASAP	10	10

Ethnicity	No. of patients	%
Caucasian	79	75
Asian	12	11
Hispanic	8	8
African American	6	6

IQR = interquartile range; PSA = prostate-specific antigen; TRUS = transrectal ultrasound; TURP = transurethral resection of the prostate; HT = hormone therapy; HGPIN = high-grade intraepithelial neoplasia; ASAP = atypical small acinar proliferation of prostate.

Table 3

Number and proportion of diagnosed cancers deemed clinically significant based on a variety of published definitions [23]

Definition	Criteria	Significant PCa, no.	Men with significant PCa (*n* = 105), %	Men with PCa deemed significant (*n* = 36), %
1	Epstein criteria	24	23	67
2	Gleason 3 + 4 or MCL ≥4 mm	26	25	72
3	Gleason 4 + 3 or MCL ≥6 mm	20	19	56
4	Gleason≥7	22	21	61
5	Gleason ≥8	11	10	31

PCa = prostate cancer; MCL = maximal core length.

Percentages in column 4 are based on the total population (*n* = 105), and those in column 5 are based on patients with PCa (*n* = 36). Clinically significant cancer based on definition 2.

Table 4

Relationship between the number of prior negative biopsies and detection of all cancers and clinically significant cancers

Prior negative biopsy		Fusion biopsy results	
No. of biopsies	**No. of patients**	**Any PCa, no. (%)**	**Significant PCa, no. (%)**
1	46	17 (37)	11 (24)
2	26	7 (27)	6 (23)
3	16	6 (37)	4 (25)
≥4	17	6 (35)	5 (29)

PCa = prostate cancer.

Table 5

Cross-tabulation of biopsy results comparing systematic biopsies to targeted biopsies in 105 subjects

	Standard biopsies			No systematic cores
	No cancer	Clinically insignificant disease	Clinically significant disease	
MRI-targeted biopsies				
No cancer	63	8	2	5
Clinically insignificant disease	1	0	1	1
Clinically significant disease	5	4	10	2
No targeted cores	1	0	2	

MRI = magnetic resonance imaging.

Ninety-four men had both systematic and targeted biopsy.