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MRI-ultrasound fusion biopsy for prediction of final prostate pathology

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Abstract

PURPOSE—To explore the impact of MRI-ultrasound (MRI-US) fusion prostate biopsy on prediction of final surgical pathology.

MATERIALS AND METHODS—54 consecutive men undergoing radical prostatectomy at UCLA after Artemis fusion biopsy (Eigen, Grass Valley, CA) were included in this prospective IRB-approved pilot study. Using MRI-US fusion, tissue was obtained from a 12-point systematic grid (mapping biopsy, MBx) and from regions of interest detected by multi-parametric MRI (targeted biopsy, TBx). A single radiologist read all MRIs, and a single pathologist independently re-reviewed all biopsy and whole-mount pathology, blinded to prior interpretation and matched specimen. Gleason score (GS) concordance between biopsy and prostatectomy was the primary endpoint.

RESULTS—Mean age was 62 years, with median PSA 6.2 ng/ml. Final GS at prostatectomy was 6 (13%), 7 (70%), and 8–9 (17%). A tertiary pattern was detected in 17 (31%) men. 32/45 (71%) high-suspicion (image grade 4–5) MRI targets contained prostate cancer (CaP). The per-core cancer detection rate was 20% by MBx and 42% by TBx. The highest Gleason pattern at prostatectomy was detected by MBx in 54%, TBx in 54%, and the combination in 81% of cases.

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FINANCIAL CONFLICT OF INTEREST: None

17% were upgraded from fusion biopsy to final pathology; one case (2%) was downgraded. The combination of TBx and MBx was needed to obtain the best predictive accuracy.

CONCLUSIONS—In this pilot study, MR-US fusion biopsy allowed for prediction of final prostate pathology with greater accuracy than that reported previously using conventional methods (81% versus 40–65%). If confirmed, these results would have important clinical implications.

Keywords

prostatic neoplasms; magnetic resonance imaging; ultrasonography; biopsy; prostatectomy

INTRODUCTION

Accurate determination of whole-organ pathology is an important unmet need in men diagnosed with prostate cancer (CaP). Conventional biopsy may under-estimate final surgical pathology in 30%–43% of cases[1,2]. Knowledge of actual pathology would help improve prediction of risk and clarify treatment alternatives[3–5], particularly in selection of candidates for active surveillance[6]. Improved diagnostic confidence would reduce patient anxiety, facilitate decision-making, and increase patient satisfaction[7].

Targeted biopsy using MRI-ultrasound (MRI-US) fusion improves detection of clinically significant CaP[8,9]. As even small foci of high-grade cancer confer poor pathologic outcomes[10–12], the ability to sample the highest-grade CaP at biopsy is important and may be improved with MRI-guidance[13]. In this study, we examined the impact of MRI-US fusion biopsy on prediction of final pathology following prostatectomy.

MATERIAL AND METHODS

Study population

276 men underwent MRI-US fusion biopsy between April 2010 and March 2013, as part of a prospective Institutional Review Board-approved study. 75 underwent active treatment as of May 2013, and 54 of these men elected radical prostatectomy (RP) performed at UCLA (University of California, Los Angeles) with biopsy and RP slides available for review. These 54 men were subjects of the current study. Clinical, biopsy, MRI, and histo-pathological characteristics are presented in Supplemental Table 1. Reporting is adherent to the Standards of Reporting for MRITargeted biopsy studies (START) criteria[14].

Multi-parametric MRI

Subjects underwent multi-parametric MRI (mp-MRI) via a 3.0 T Siemens Magnetom Trio without endorectal coil, including T2-weighted, diffusion-weighted, and dynamic contrast-enhanced imaging. Mp-MRI was performed 1–8 weeks prior to fusion biopsy and reviewed on an Invivo DynaCAD or iCAD VersaVue workstation by a single uro-radiologist with 9 years of prostate MRI experience (DM). MRI was performed at least 3 months after any prior biopsy. Suspicious regions of interest (ROIs) were scored on a scale between 1–5, with higher scores indicative of higher CaP suspicion (Table 1), which is similar to the European PI-RADS[15].

MRI-US fusion biopsy

The fusion biopsy protocol has been described previously[9]. Before biopsy, patients received a cleansing enema and prophylactic oral ciprofloxacin as well as intramuscular ceftriaxone. Biopsies were performed transrectally, under local anesthesia, in an outpatient setting by a single urologist (LM). The MRI was loaded into the Artemis device (Eigen, Grass Valley, CA). A transrectal ultrasound (TRUS) scan (Hitachi Hi-Vision 5500) was performed, and a 3D prostate reconstruction was generated by the device, utilizing an algorithm incorporating both rigid and elastic registration.

A 12-point systematic mapping biopsy (MBx) plan (bilateral medial/lateral, apex/mid/base), was scaled onto the 3D prostate reconstruction by the device, along with any ROIs. Targeted biopsy (TBx) cores were obtained, followed by MBx. Targets were biopsied at 3 mm intervals based on prior work on registration accuracy with the device[16].

Histopathology

Patients underwent RP at UCLA a mean of 2.7 months following fusion biopsy. Each prostate was sectioned at 4–5 mm intervals. Using a whole-mount technique, tissue slices were then formalin-fixed, paraffin-embedded, and microtome-cut. After study conclusion, a single pathologist (DL), blinded to clinical information, prior interpretation, and matched specimen, re-reviewed all biopsy and whole-mount materials.

Gleason scoring was performed according to the 2005 International Society of Urological Pathology (ISUP) consensus recommendations[17]. For needle biopsies, the primary Gleason pattern and highest-grade Gleason pattern comprised the Gleason score (GS). For RP specimens, GS was assigned based on primary and secondary patterns, with a tertiary pattern assessment, if present; in cases with multiple tumor foci, a separate GS was assigned to each focus and the highest-grade tumor was used for this analysis.

Statistical analysis

Patient characteristics such as age, PSA, prostate volume and previous biopsy results were analyzed using descriptive statistics. GS concordance between biopsy (TBx, MBx, and combined) and final whole-mount was the primary endpoint. We used three different measures of concordance: highest Gleason pattern overall; the conventional Gleason score; and sum of primary and tertiary Gleason pattern, if present. The Goodman-Kruskal gamma statistic (γ) was used as a measure of correlation between biopsy and whole-mount results; this non-parametric statistic tests the relationship between ordinal variables, with $\gamma=1$ indicative of perfect concordance. Correlations between variables were examined using the non-parametric Spearman correlation coefficient. Biostatistician co-author FD performed statistical calculations.

RESULTS

Patient characteristics are shown in Supplemental Table 1. Mean age of the patients was 62 years (inter-quartile range, IQR=57–66); median PSA was 6.2 ng/ml (IQR=5.0–10.9). 38/54 (70%) men had previously undergone conventional TRUS biopsy. Of the 38, 15 had not yet

been diagnosed with CaP despite one or more prior biopsies (range=1–8), and 23 had previously been diagnosed with low-grade, low volume disease, including 18 initially referred for active surveillance. 18/23 (78%) of these men with prior CaP diagnosis were upgraded by fusion biopsy: 10 (43%) men were upgraded from GS 3+3=6 to 3+4=7; 7 (30%) from GS 3+3=6 to primary Gleason 4; and 1 (4%) from GS 3+4=7 to primary Gleason 4. 7 men were upgraded by TBx alone, and 8 by MBx alone.

Mp-MRI revealed 101 ROIs, of which 58 (57%) were found to be CaP positive on targeted biopsy. At each biopsy session, a mean of 18 cores was obtained (IQR=15–20), including a mean of 5.9 TBx cores (IQR=4–8). Overall, TBx cores were more likely to reveal CaP than MBx cores (42% versus 20%). Biopsy data for 31 of these men have been reported previously[9,18].

The mp-MRI grading system is depicted in Table 1. Higher lever of suspicion on MRI yielded higher cancer detection rates; CaP was found by TBx in 69% of MRI grade 4 targets and 75% of grade 5 targets. Cross tabulation of cancer detection by Gleason grade, biopsy modality, and MRI suspicion is provided in Table 2. In men with highly suspicious ROIs (MRI grade 4–5), the detection rate of GS ≥7 CaP by TBx alone was 13/36 (36%); in men with less suspicious ROIs (MRI grade 2–3) the detection rate of such CaP by TBx alone was only 1/18 (5.5%) (p=0.02, Fisher's exact test). GS ≥7 detection rates by MBx alone were not related to ROI level of suspicion 7/36 (19%) high suspicion versus 8/18 (44%) low suspicion) (p=0.11). 9/54 (17%) men were diagnosed with GS ≥7 by MBx but had no CaP detected by TBx; analysis of this subgroup revealed 4 were "near-misses", where the tumor was located within the same sextant at RP.

The patient depicted in Figure 1 demonstrates a situation in which fusion biopsy yielded GS 3+3=6 from MBx but GS 4+5=9 from TBx. Final pathology revealed GS 4+3 with a tertiary Gleason 5 pattern. Comparison by conventional GS would deem this case to be downgraded from fusion biopsy (from GS 4+5=9 to 4+3=7). However, analysis of Gleason score that utilizes the primary plus highest Gleason pattern (analogous to the grading scheme for needle biopsies) demonstrates concordance between biopsy and RP (4+5=9), as does analysis of highest Gleason pattern overall (Gleason pattern 5). All three methods of analysis are reported to provide a more complete understanding of biopsy concordance.

Gleason scores from MBx, TBx and final whole-mount pathology are presented in Supplemental Table 2. The higher GS obtained from either MBx or TBx determined the combined fusion biopsy GS; this combined GS was then compared to whole-mount prostatectomy GS. Final GS was: 6 (7/54, 13%), 3+4 (23/54, 43%), 4+3 (15/54, 28%), and ≥8 (9/54,17%). A tertiary Gleason pattern was assigned in 17/54 (31%).

When considering the highest overall Gleason pattern, either MBx or TBx alone yielded a concordance rate of 54%; when both biopsy modalities were combined, concordance was 81% (Table 3). Conventional Gleason score analysis revealed a concordance rate of 72%. Finally, analysis of the primary plus highest-grade pattern yielded concordance in 76%. The combination of TBx (γ=0.43–0.47) and MBx (γ=0.49–0.58) was needed to obtain the best predictive accuracy (γ=0.86–0.97).

When considering the conventional Gleason score, upgrading was seen in 7% of cases. When considering the highest Gleason pattern overall, the upgrading rate was 17%. Correlation between clinical variables (age, PSA, biopsy grade, prostate volume, MRI grade, number of biopsy cores, peripheral versus transitional zone location) and risk of upgrading at prostatectomy were examined using the non-parametric Spearman correlation, and no significant associations were found. Of upgraded cases, none were upgraded by more than one Gleason pattern. Two cases were upgraded from GS 3+3 (1 to GS 3+3+4, 1 to GS 3+4=7). The remaining cases were upgraded from a highest Gleason pattern at biopsy of 4 to a tertiary pattern of 5 at RP. Only 1 case was downgraded on final pathology, where a small focus of Gleason pattern 5 was identified on needle biopsy but whole-mount pathology only revealed GS 4+3=7.

DISCUSSION

Gleason score is commonly used to risk-stratify patients, inform prognosis, and direct clinical decision-making[3,4]. However, Gleason score concordance from conventional biopsy to prostatectomy is poor[1,2,19,20]. Upgrading at final diagnosis is most often attributed to sampling error[1,21] and observer variability among pathologists[22]. Gleason score at RP is commonly accepted as the definitive index of cancer severity and has been studied extensively in postoperative nomograms[4].

Pathologic upgrading has been shown to be associated with adverse outcomes, including higher rates of biochemical recurrence[5]. This finding is particularly concerning in the context of active surveillance or radiation therapy, where treatment choices are based on biopsy grade alone and the true underlying pathology remains unknown. Accurate risk-stratification at diagnosis is important, as most active surveillance protocols exclude the presence of Gleason pattern 4 or 5 disease[6]. Biopsy GS also informs treatment decisions in radiation therapy, including eligibility for brachytherapy, need for pelvic node irradiation, and the use of androgen deprivation[23].

In the current study, fusion biopsy identified the highest-grade Gleason pattern at prostatectomy in 81% of cases. Taking into account tertiary Gleason patterns, three measurements of biopsy concordance were used, and concordance ranged from 72–81%, with an upgrading rate between 7–22%. This represents an improvement over concordance and upgrading rates for conventional biopsy reported in the available literature[1,2,19,20]. Concordance was best when comparing the highest-grade component between biopsy and prostatectomy, consistent with our hypothesis that fusion biopsy facilitates detection of the highest-grade cancer.

We found higher level of MRI suspicion yielded higher cancer detection rates, consistent with earlier studies[24,25]. 13/16 (36%) of men with a highly suspicious mp-MRI were diagnosed with GS ≥7 only by TBx, and TBx diagnosed CaP more efficiently, as the per-core CaP detection rate was 20% by MBx compared to 42% by TBx. However, 9/54 (17%) of men had no CaP by TBx but GS ≥7 by MBx. 4 of these were “near-misses” of tumor within the same sextant, which may be reflective of registration accuracy. The remaining false negatives (5/54, 9%) may reflect the underlying limitation of mp-MRI, as sensitivity

for GS ≥7 tumor detection may only be as high as 85–88%[26]. Furthermore, of 18/23 men upgraded by fusion biopsy from conventional biopsy, 7 were upgraded by Tbx only and 8 by MBx only, highlighting the importance of using both modalities. Thus, the best predictive accuracy was obtained with the combination of both TBx and Mbx.

In a review of studies between 1983–2000 encompassing more than 2,600 men undergoing conventional biopsies, King, et al. found biopsy concordance rates between 28–68% and upgrading as high as 57% at final pathology. In the King review, the weighted mean concordance and upgrading rates were 42% and 43%, respectively[1]. As extended biopsy schemes became more widely utilized, a reduction in the sampling error inherent with the traditional sextant biopsy resulted. By 2008, a meta-analysis of nearly 15,000 men by Cohen, et al. reported 63% concordance, with a 30% upgrading rate[2]. Studies focusing on the benefit of extended biopsy (≥10 cores) found concordance rates between 63–76%[19,20].

Despite the utilization of extended and saturation biopsy schemes, upgrading remains a common occurrence. Numao, et al. investigated a saturation biopsy approach and found that a 26-core combined trans-perineal/trans-rectal biopsy resulted in a 27% upgrading rate. They reported a high-grade agreement rate of 92% when combining Gleason patterns 4 and 5[27]. However, this approach subjected the patient to risks of both the transperineal and transrectal approaches, and patients required general or spinal anesthesia. A similar analysis in the current study yields 96% agreement for Gleason 4/5 but was performed in the office setting under local anesthesia.

Most studies reported do not take into account tertiary Gleason score assignment, which has only recently been shown to enable better estimates of prognosis[10,17]. Pan, et al. retrospectively studied patients with tertiary Gleason 4 or 5 CaP (<5% of tumor volume) compared to those without a tertiary pattern. They demonstrated that the tertiary component had a marked adverse effect on biologic behavior; these tumors were often of higher pathological stage and had higher rates of progression than those without high-grade tertiary patterns[11]. Patel, et al. found men with GS 7 and tertiary pattern 5 had comparable risk of PSA failure to men with GS 8–10 after RP or radiation[12]. The incidence of a tertiary Gleason grade reported here is somewhat higher than reported by others (31% versus 20%)[10], perhaps because the present cohort contains few low risk patients.

Targeted biopsy may enable more accurate sampling of the highest-grade tumor component. MRI-US fusion biopsy studies have demonstrated higher cancer detection rates than conventional biopsy, with increased proportions of clinically significant, high-grade CaP and decreased proportions of low-grade CaP[8,9,28]. In the current study, 28% were diagnosed by fusion biopsy following prior negative conventional biopsies and 33% were upgraded from initial diagnosis. Thus, in nearly two-thirds of these men, the diagnosis of CaP would have been under-graded or missed entirely without the use of fusion biopsy.

In this pilot study, the concordance of pathologic results from fusion biopsy and RP is examined. The fusion biopsy technique revealed the highest-grade tumor component in the prostatectomy specimen in 81% of cases. Our multi-faceted analysis of biopsy concordance, incorporating tertiary pattern scores, offers more complete insight than would be offered by

a single measurement. As inter-observer variability and pathologist experience in Gleason grading have been documented[22,29], we employed blinded review of all specimens by a single observer experienced in genitourinary pathology.

This study is limited by a relatively small sample size, and results should be confirmed with a larger cohort. This patient sample contains few GS 6 patients. While the paucity of low-risk patients undergoing prostatectomy reflects a shift toward active surveillance in contemporary urologic practice, it does limit how these results may be generalized. Others have described “cognitive fusion”, i.e., using standard TRUS and knowledge of MRI lesion location, to manually target additional cores[30]. The present study was not designed to examine the relative merits of cognitive and software-based fusion. Although the combination of TBx and MBx increased concordance with final pathology, some patients were still upgraded. Spatial relationships of CaP on imaging, whole-mount, and biopsy site are important subjects of future study.

CONCLUSIONS

Use of MR-US fusion biopsy allowed for prediction of final prostate pathology with greater accuracy than that reported using conventional methods. If confirmed, improved knowledge of final pathology by fusion biopsy would have important clinical implications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS AND ACRONYMS

CaP	prostate cancer
MBx	systematic mapping biopsy
TBx	targeted biopsy
MRI-US	magnetic resonance imaging-ultrasound
GS	Gleason score
RP	radical prostatectomy
Mp-MRI	multiparametric MRI
ROI	region of interest
TRUS	transrectal ultrasound

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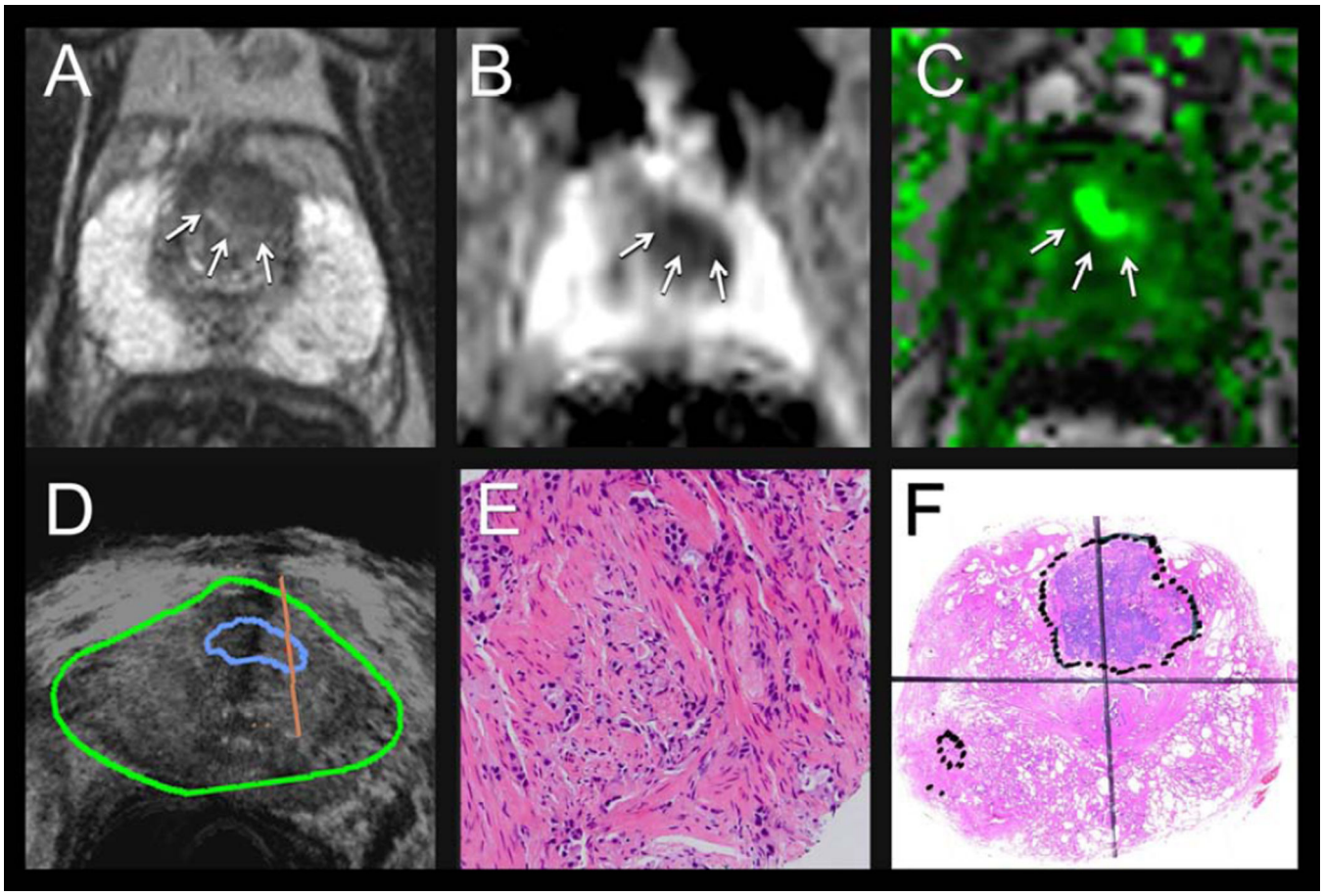

Figure 1.

68 year-old man with PSA 8.3 ng/ml who underwent multi-parametric MRI: (**A**) T2-weighted, (**B**) diffusion-weighted, and (**C**) dynamic contrast-enhanced imaging. He then underwent fusion biopsy (**D**). Mapping biopsy revealed Gleason 3+3, but (E) targeted biopsy revealed Gleason 4+5. Reduced from ×20. (**F**) Gleason score on whole-mount prostatectomy specimen was Gleason 4+3 with tertiary pattern 5. Fusion biopsy, which included the MRI-targeted region of interest, predicted the highest Gleason grade at final pathology. Reduced from ×1.

Table 1

MRI grading criteria and protocol

Grade	T2WI	DCE	ADC
1	Normal	Progressive (type I)	>1400
2	Indistinct, wedge-shaped, highly heterogeneous, or encapsulated border (transitional zone)	Early with plateau (type II) or progressive but intense (>200%)	1200–1400
3	Masslike but faint or slightly heterogeneous	Early with washout (type III) or early/plateau and intense	1000–1200
4	Blurred borders or uniform low signal with distinct borders	Early and intense with washout (type III and >200%)	800–1000
5	Invasive into capsule or other compartment	Early & intense with immediate washout	<800

T2WI: T2-weighted imaging (Siemens SPACE, TR/TE 3800–5040/101 ETL 13, 14 cm FOV, 256 × 256 matrix, 1.5 mm contiguous slices), **DCE**: dynamic contrast-enhanced imaging curve type (Siemens TWIST, TR/TE 3.9/1.4 ms, 12° flip angle, 26 × 26 cm FOV, 160 × 160 matrix, 3.6 mm slices, 4.75 s/acquisition over 6 minutes with 15 second injection delay); **ADC** (μm^2 /s): apparent diffusion coefficient from diffusion-weighted imaging (echoplanar, TR/TE 3900/60, 21 × 26 cm FOV, 130 × 160 matrix, 3.6 mm slices, 4 NEX, b-values 0, 100, 400, 800 s/mm2). An overall suspicion score is given by the following formula, weighted toward the ADC score: (ADC*2 + T2 + DCE)/4. Peripheral gland lesion scores are rounded up, and central gland lesions are rounded down. The UCLA grading system was originally described in 2011[16]. The present modified system, which is similar to PI-RADS[15], is reprinted with permission[9].

Table 2

Cross tabulation of mapping and targeted biopsy, N (%)

	Mapping biopsy		
Targeted biopsy	**No cancer**	**GS 6**	**GS ≥7**
MRI grade 2–3			
No cancer	0 (0)	1 (2)	4 (7)
GS 6	0 (0)	1 (2)	4 (7)
GS ≥7	0 (0)	1 (2)	7 (13)
MRI grade 4–5			
No cancer	0 (0)	0 (0)	5 (9)
GS 6	2 (4)	0 (0)	2 (4)
GS ≥7	7 (13)	6 (11)	14 (26)

GS, Gleason score. For example, of men with a MRI grade 4 or 5 target, 7 men were found to have GS ≥7 cancer by targeted biopsy but no cancer by systematic mapping biopsy.

Table 3

Prediction of final pathology by fusion biopsy, N (%)

	Mapping biopsy		Targeted biopsy		Combined	
Highest Gleason pattern						
Concordant	29 (54%)	γ=0.49	29 (54%)	γ=0.47	44 (81%)	γ=0.97
Upgraded	25 (46%)		24 (44%)		9 (17%)	
Downgraded	0 (0%)		1 (2%)		1 (2%)	
Gleason score (primary + secondary pattern)						
Concordant	27 (50%)	γ=0.54	31 (57%)	γ=0.43	39 (72%)	γ=0.86
Upgraded	21 (39%)		17 (31%)		4 (7%)	
Downgraded	6 (11%)		6 (11%)		11 (20%)	
Primary + highest-grade pattern*						
Concordant	25 (46%)	γ=0.58	28 (52%)	γ=0.45	41 (76%)	γ=0.94
Upgraded	29 (54%)		25 (46%)		12 (22%)	
Downgraded	0 (0%)		1 (2%)		1 (2%)	

Concordance rates are given according to: highest Gleason grade pattern, Gleason score, and primary plus highest-grade pattern; γ, gamma statistic value.

*A tertiary spattern, which was the highest-grade pattern, was present in 17 men.