Published in final edited form as:
J Urol. 2013 January ; 189(1): 86–91. doi:10.1016/j.juro.2012.08.095.

Targeted Biopsy in the Detection of Prostate Cancer using an Office-Based MR-US Fusion Device

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Abstract

Purpose—Targeted biopsy of lesions identified on MRI may enhance detection of clinically relevant prostate cancers (CaP). We evaluate CaP detection rates in 171 consecutive men using MR-US fusion prostate biopsy.

Materials and Methods—Subjects underwent targeted biopsy either for active surveillance (N=106) or persistently elevated PSA but negative prior conventional biopsy (N=65). Before biopsy, each man had a multiparametric MRI at 3.0-Tesla. Lesions on MRI were outlined in 3D and assigned increasing cancer suspicion levels (image grade 1–5) by a uroradiologist. The Artemis biopsy tracking system was used to fuse the stored MRI with real-time ultrasound (US), generating a 3D prostate model on-the-fly. Working from the 3D model, transrectal biopsy of target lesions and 12 systematic biopsies were performed under local anesthesia in the clinic.

Results—171 subjects (median age 65) underwent targeted biopsy. At biopsy, median PSA = 4.9 ng/ml and prostate volume = 48 cc. A targeted biopsy was three times more likely to identify cancer than a systematic biopsy (21% vs. 7%). CaP was found in 53% of men, 38% of whom had Gleason ≥7. 38% of men with Gleason ≥7 cancers were detected only on targeted biopsies. Targeted biopsy findings correlated with level of suspicion on MRI. 15 of 16 men (94%) with an image grade 5 target (highest suspicion) had CaP, including 7 with Gleason ≥7.

Conclusions—Prostate lesions identified on MRI can be accurately targeted using MR-US fusion biopsy by a urologist in clinic. Biopsy findings correlate with level of suspicion on MRI.

Keywords

Prostatic neoplasms; magnetic resonance imaging; ultrasonography; biopsy

Introduction

Biopsy detection of prostate cancer (CaP) remains imperfect, limited by both over-detection of indolent tumors and under-detection of clinically relevant cancers. Nearly 50% of

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currently detected CaP cases may be insignificant,[1] while 22% to 47% of saturation or template biopsies reveal cancer after initial negative biopsy.[2] In addition, studies showing an approximately 25% to 40% rate of upgrading on final surgical pathology indicate that conventional prostate biopsy often fails to detect the highest grade lesion.[3] Thus, current methods of prostate biopsy, largely unchanged since 1989, deserve reevaluation.

Magnetic Resonance Imaging (MRI) offers potential to improve CaP diagnosis. Stronger magnets and multiparametric protocols have improved the utility of prostate MRI since its initial description in 1982. Compared to Transrectal Ultrasound (TRUS), MRI provides superior resolution and may even be used to assign CaP grade.[4–6] Turkbey et al at the National Institutes of Health (NIH), recently described a 98% positive predictive value for prostate MRI and found improved sensitivity for higher grade tumors and those >5 mm in diameter.[7] Such preferential diagnosis of clinically significant tumors comprises a potential advantage of MRI. While technology exists to biopsy prostate tumors under direct MRI-guidance,[8] such procedures are time-consuming, costly, and impractical in most settings. Magnetic Resonance-Ultrasound (MR-US) systems that fuse stored MR images with real-time ultrasound combine the resolution of MRI with the ease and practicality of ultrasound,[9–11] offering a savings in time and cost, while potentially retaining the accuracy of MR-guided biopsy. However, these systems have been limited by need for monitored anesthesia care[9] or a trans-perineal approach and general anesthesia.[10]

We previously described the initial clinical use of MR-US fusion using a mechanically-assisted prostate biopsy device (Artemis; Eigen, Grass Valley, CA), permitting targeted prostate biopsy under local anesthesia.[11] This technology, validated in phantom studies in 2008,[12] (1) enables office-based transrectal biopsy of prostate lesions via MR-US fusion, (2) maps the precise location of systematic biopsies to ensure thorough sampling of the entire organ, and (3) tracks biopsy-site locations, permitting accurate return to the same location within the prostate in cases when re-biopsy is necessary. We now report CaP detection rates in 171 consecutive outpatients undergoing MR-US fusion biopsy.

Materials and Methods

Patients

171 consecutive outpatients, clinical stage T1c, undergoing MR-US fusion biopsy from March 2010 to September 2011 provided informed consent. The University of California Los Angeles (UCLA) Institutional Review Board approved this study. Patients were scheduled for MRI-US fusion biopsy for two different indications: (1) persistently elevated PSA but prior negative TRUS biopsy, (2) active surveillance yearly protocol biopsy. All MRIs were followed by fusion biopsy regardless of the MRI result. Ten men underwent multiple fusion biopsy sessions according to the UCLA active surveillance protocol. For the purpose of this study, only the most recent biopsy result was used for analysis.

Multiparametric MRI

Subjects underwent multiparametric MRI on a Siemens TrioTim Somatom 3T (Siemens Medical Solutions, Malvern, PA) magnet with high-performance gradients using a multi-channel external phased-array coil. Following the latest international recommendations on prostate MRI for detection purposes, no endorectal coil (ERC) was used.[13] MRI was performed 1–3 weeks before biopsy. The MRI and biopsy protocol were described previously.[11] In brief, the protocol included T2 weighted imaging (T2WI), diffusion weighted imaging (DWI) and dynamic contrast-enhanced (DCE) imaging. Each parameter was interpreted by a uroradiologist (DJAM) with 8 years of experience reading prostate MRI who was blinded to clinical data, including the location of prior positive biopsies. Suspicious

regions of interest (ROI) were identified on a DICOM workstation (CADstream; Merge Healthcare, Chicago, IL). Each ROI (i.e. lesion or target) was assigned an image grade on a 1–5 scale ranging from normal to highly suspicious and outlined in 3D on an open-source workstation (Osirix, www.osirix-viewer.com). This previously published classification system has been updated (Table 1).[11]

MR-US Fusion Biopsy Procedure

Each patient received ciprofloxacin for 1 day, a cleansing enema, and IM ceftriaxone prior to biopsy, followed by 3 days of ciprofloxacin. The MRI with documented ROIs was loaded into the image processing component of the Artemis device (Eigen, Grass Valley, CA), a 3D ultrasound-guided prostate biopsy system. The left lateral decubitus position was used. After insertion of the standard ultrasound probe (Hitachi Hi-Vision 5500 [Hitachi Medical Systems America, Twinsburg, OH], 7.5 MHz end-fire) and administration of peri-prostatic 1% lidocaine, the tracking arm was attached to the ultrasound probe. Figure 1 A–F demonstrates workflow in a representative patient. During scanning of the prostate, the US feed is captured by the device and reconstructed as a 3D prostate model on the monitor. The stored MRI data set was manually aligned and automatically fused with the real-time US, overlaying the ROIs on the virtual 3D prostate model. A systematic array of 12 preselected biopsy sites, generated by the Artemis device and independent from MRI result, was loaded along with the ROI targets identified on MRI. A multi-panel image was generated on the monitor showing real-time US, the corresponding axial and sagittal MR images, and the virtual 3D model. Working from the 3D model (panels D&E), transrectal biopsies of target lesions and 12 systematic biopsies were performed by a single urologist (LSM) with a conventional reusable spring-loaded gun and 18G needles in the urology clinic. Targets were biopsied at 3mm intervals, based on prior experience demonstrating 1.2 ± 1.1 mm tracking accuracy on repeat biopsy.[11] Discordance from the 3D model due to patient or prostatic movement was corrected using a motion compensation function in the biopsy tracking software. All biopsies were performed on outpatients under local anesthesia in the UCLA Clark Urology Center.

Statistical Analysis

Descriptive statistics were used to analyze patient characteristics such as age, PSA, prostate volume and previous biopsy results. Comparison of cancer percentages within groups was made using the Chi-square statistic. Ninety-five percent confidence intervals based on the exact binomial distribution are presented in parentheses where appropriate. Comparison of tumor length between systematic and targeted cores was made using a simple t-test. The results of the fusion biopsies were stratified according to the MRI scoring system (image grade 2–5). The non-parametric Spearman rank correlation was used to assess the relationship between image grade and the presence of cancer. A statistician (FD) performed all calculations.

Results

171 subjects (median age 65) underwent fusion biopsy. At the time of biopsy, median PSA was 4.9 ng/ml and median prostate volume was 48 cc. Mean time from probe insertion to last biopsy was approximately 20 minutes. On average, 1.6 targets were identified per patient (range 0–4) and 2.2 cores were taken per target (range 1–6). 106 men underwent biopsy for surveillance, while 65 had elevated PSA but prior negative biopsies. Of 293 MRI targets, 257 (88%) were successfully sampled with at least one targeted core traversing the ROI. On average, 13.4 biopsy cores were taken per patient. No patient required hospitalization for fever or sepsis after biopsy.

Biopsies demonstrated CaP in 90 of 171 men (53%). Of these 90 men, 34 (38%) had Gleason ≥7. In subjects with ≥1 prior negative biopsy (median PSA 7.3), the rate of cancer diagnosis was 37%. In men on active surveillance (median PSA 4.1), the rate was 63%. In men with an image grade 2, 3, 4, or 5 ROI, the rate of cancer diagnosis on either targeted or systematic biopsy was 43%, 48%, 56%, and 94%, respectively. Gleason grade was ≥7 in 7%, 15%, 23% and 44% of those with an image grade 2, 3, 4, or 5 ROI, respectively (Figure 2). Prostate cancer was diagnosed on systematic biopsies in 6 of the 19 (32%) men with no ROI identified on MRI (3 Gleason 3+4, 3 Gleason 3+3).

A total of 279 targets were identified in the 171 men. The mean maximal diameter of the ROI identified on MRI was 11.4 mm (range 4–45 mm). The rate of cancer diagnosis overall and the rate of detection of clinically significant CaP increased with increasing suspicion on MRI (Figure 3).

Targeted biopsies were more likely to reveal CaP (20.8% of 486 targeted cores) than systematic biopsies (7.3% of 1741 systematic cores) (p=0.001). The mean cancer length from cancer-positive targeted cores exceeded that from systematic cores (5.1 mm vs. 3.3 mm, p=0.003). The distribution of Gleason ≥7 tumors was also greater for targeted cores compared to systematic cores, as 36% of tumors identified on targeted cores were Gleason ≥7 vs. 24% of tumors identified on systematic cores (p=0.037).

Of the 151 subjects who underwent both systematic and targeted biopsies, 84 had CaP diagnosed. Of these, 31 were detected only by systematic biopsy, 15 were detected only by MR-US targeted biopsy, and 38 were detected by both. Of the 29 men (35%) found to have Gleason ≥7 CaP, these numbers were 9 for systematic, 11 for targeted, and 9 for both. Thus, 11/29 men (38%) with Gleason ≥7 cancers were detected only on targeted biopsy.

Discussion

Our study yielded three key findings. First, we demonstrate the ability to accurately target and biopsy lesions seen on MRI using MR-US fusion technology in an office-based setting under local anesthesia. Second, the addition of targeted biopsies to systematic biopsies increases the rate of diagnosis of all cancers and, more importantly, Gleason ≥7 cancers. In fact, 38% of men with Gleason ≥7 cancers were detected only via targeted biopsies of lesions identified on MRI. Third, the level of suspicion on MRI correlated with both cancer diagnosis overall and diagnosis of Gleason ≥7 prostate cancers. Biopsies revealed CaP in 16/17 (94%) of men with an image grade 5 lesion on MRI.

Two recently published investigations utilizing different MR-US fusion devices for targeted prostate biopsy yielded similar results to ours. Pinto et al described a technique incorporating electromagnetic tracking and found cancer in 28%, 67% and 89% of men with low, moderate and high suspicion on MRI.[9] Hadaschik et al incorporated MR-US fusion technology via a transperineal approach in the operating room and found CaP in 59% of men overall, and in 96% of men with highly suspicious lesions on MRI.[10] The similarity of the above results to those presented here substantiates the advantages of image-guided targeted biopsy using MR-US fusion.

Other recent studies involved targeted prostate biopsy under direct MRI-guidance. Among 68 men with ≥2 prior negative TRUS biopsies and a median PSA of 13 ng/ml, Hambrock et al detected cancer in 59%.[14] Of those with cancer, 45% had Gleason ≥7. The authors contrasted these results to a reference database at their institution in which the tumor detection rate during the third TRUS biopsy session (without MRI) was just 15%. The same group published results evaluating the concordance of highest Gleason grade (HGG) from biopsy to prostatectomy specimens in 98 patients. The exact concordance rate for MR-

guided biopsy was 88% vs. 55% for TRUS-guided biopsy (p=0.001).[8] In Germany, Anastasiadis et al performed MRI-guided biopsy on men with a suspicious MRI and ≥1 prior negative TRUS biopsy. The cancer diagnosis rate in 27 men (median PSA 10.2 ng/ml) was 55%.[15]

The present study applies a 5-point semi-quantitative scoring system to assess degree of cancer suspicion to lesions seen on MRI. The scoring system is based on T2 characteristics, quantitative apparent diffusion coefficient (ADC), and DCE curve analysis (Table 1). The scoring system, similar to that used by Hambrock,[14] allows for graded levels of suspicion, as opposed to other protocols where a binary score of 'normal' or 'abnormal' was assigned.[10, 15] Thus, the present scoring system follows guidelines recently released by the European Society of Uroradiology.[13]

Targeted prostate biopsy may be useful in three key situations: active surveillance, elevated PSA but negative TRUS biopsy, and selection for focal therapy. First, while surveillance has proven to be a safe approach for low risk CaP,[16–21] utilization remains low[22] and rates of progression to active treatment in the major surveillance series range from 14–41%.[23] Targeted prostate biopsy may improve patient selection, making surveillance a more attractive option to patients while reducing progression to active treatment. Further, the tracking feature of the Artemis device allows the urologist to return to the exact area of prior positive biopsies, enabling the physician to follow individual tumors over time. Second, conventional TRUS biopsy may miss tumors in the apex and anterior prostate.[2, 24, 25] MR-US fusion targeted biopsy may identify tumors missed by TRUS biopsy, sparing patients the discomfort of numerous negative biopsies and reducing the risk of delayed diagnosis of aggressive tumors. Our 37% diagnosis rate in the prior negative biopsy population, 67% of whom had Gleason ≥7 cancers, is considerably higher than would be expected from repeat conventional biopsy[26, 27] and compares favorably with detection rates seen using saturation biopsy.[28] Third, focal therapy has become an area of keen interest. Current strategies for patient selection for focal therapy often entail perineal template mapping biopsy,[29] a more invasive, morbid, resource-intensive and expensive procedure than MR-US fusion biopsy.

This study has several limitations. First, given the low-risk patient population in our study (median PSA 4.9, all with prior biopsies), relatively few patients subsequently underwent radical prostatectomy. It remains possible that some significant tumors may be missed by both targeted and systematic biopsies. Whole-mount data would enable a more definitive analysis of the nature of lesions identified on MRI and biopsied using MR-US fusion. Second, while the yield of biopsies from image grade 5 lesions is excellent, the concordance between lower image grade lesions and biopsy histology is suboptimal. Further analysis may determine if this stems from inaccurate MR-US registration or if many abnormal areas on MRI are actually benign. Third, while some studies show a high sensitivity and specificity of contemporary multiparametric MRI,[7, 30] prostate MRI remains difficult to interpret and requires dedicated training and expertise to approach the accuracy of expert radiologists. The yield of targeted biopsies relates directly to the ability of the radiologist to accurately identify targets on MRI. Until the sensitivity of prostate MRI is confirmed, we view the ability to obtain systematic biopsies along with targeted biopsies as an advantage of MR-US fusion technology over direct MRI-guided biopsy. Finally, image fusion technology is rapidly evolving and clinical experience with fusion devices remains in its infancy; advances in hardware and software are certain to change the usability of fusion devices in the future.

In spite of these limitations, MR-US targeted prostate biopsy has the potential to improve the contemporary diagnosis and treatment of CaP. The present data, obtained using an office-based procedure under local anesthesia, demonstrate better CaP detection than with systematic biopsies alone. These results compare favorably to those obtained using

transperineal template biopsy techniques requiring general anesthesia. In contrast to direct MRI-guided biopsy, the present method allows both systematic and targeted biopsies to be obtained efficiently. Further work, including a detailed study correlating MRI, targeted biopsy results, and prostatectomy specimens, is ongoing.

Conclusions

Prostate lesions identified on MRI can be accurately targeted with MR-US fusion biopsy in a clinic setting using local anesthesia. Biopsy findings correlate with the level of suspicion on MRI. Targeted prostate biopsy has the potential to improve the diagnosis of CaP and may aid in the selection of patients for active surveillance and focal therapy.

Acknowledgments

The project described was supported by Award Number R01CA158627 from the National Cancer Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

Additional support was provided by the Beckman Coulter Foundation, the Jean Perkins Foundation, and the Steven C. Gordon Family Foundation. Technical support was provided by Eigen. The authors wish to express great appreciation to Professors Jelle Barentsz of Nijmegen, NL and Aaron Fenster of London, Ont., CA, who helped stimulate our interest.

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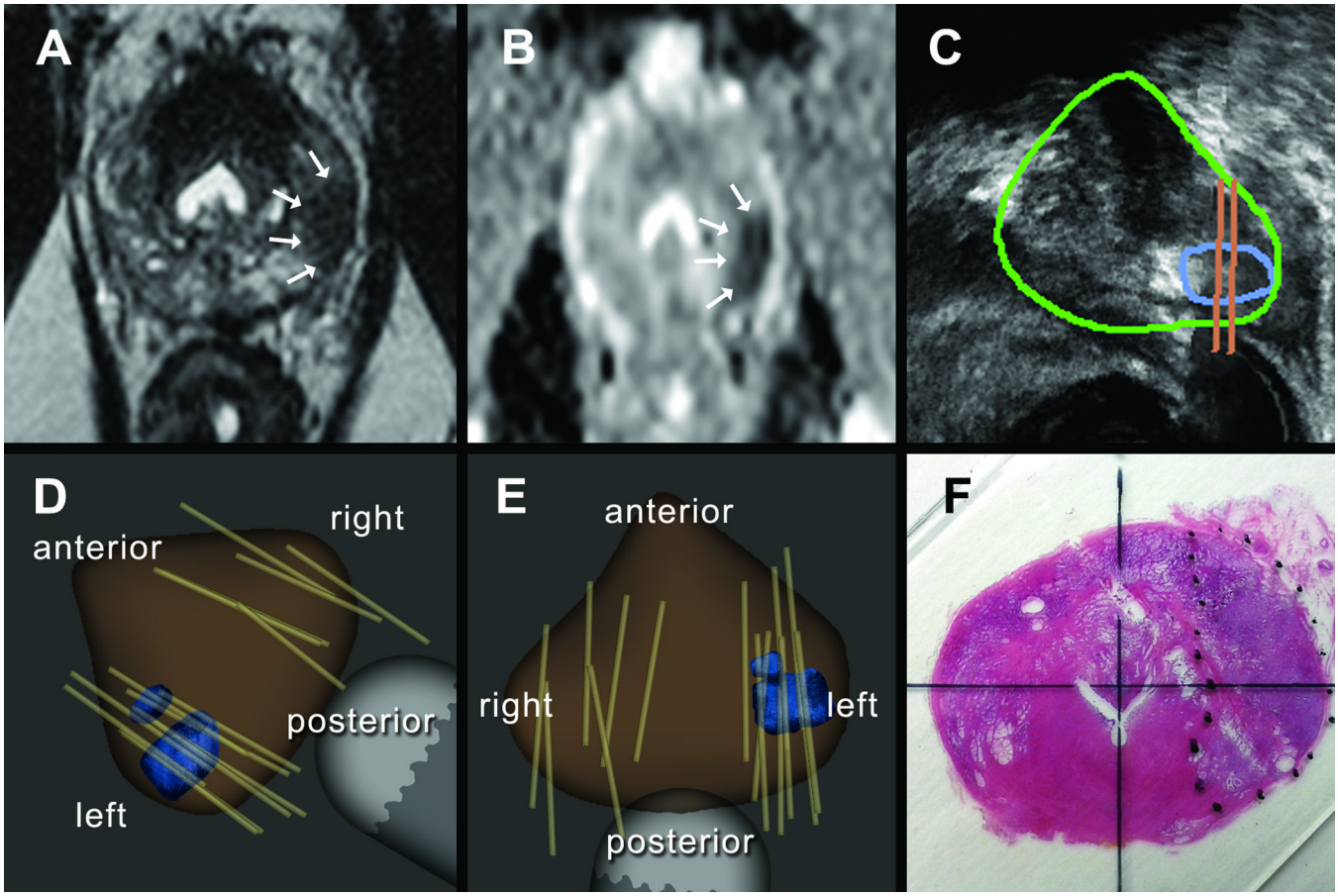
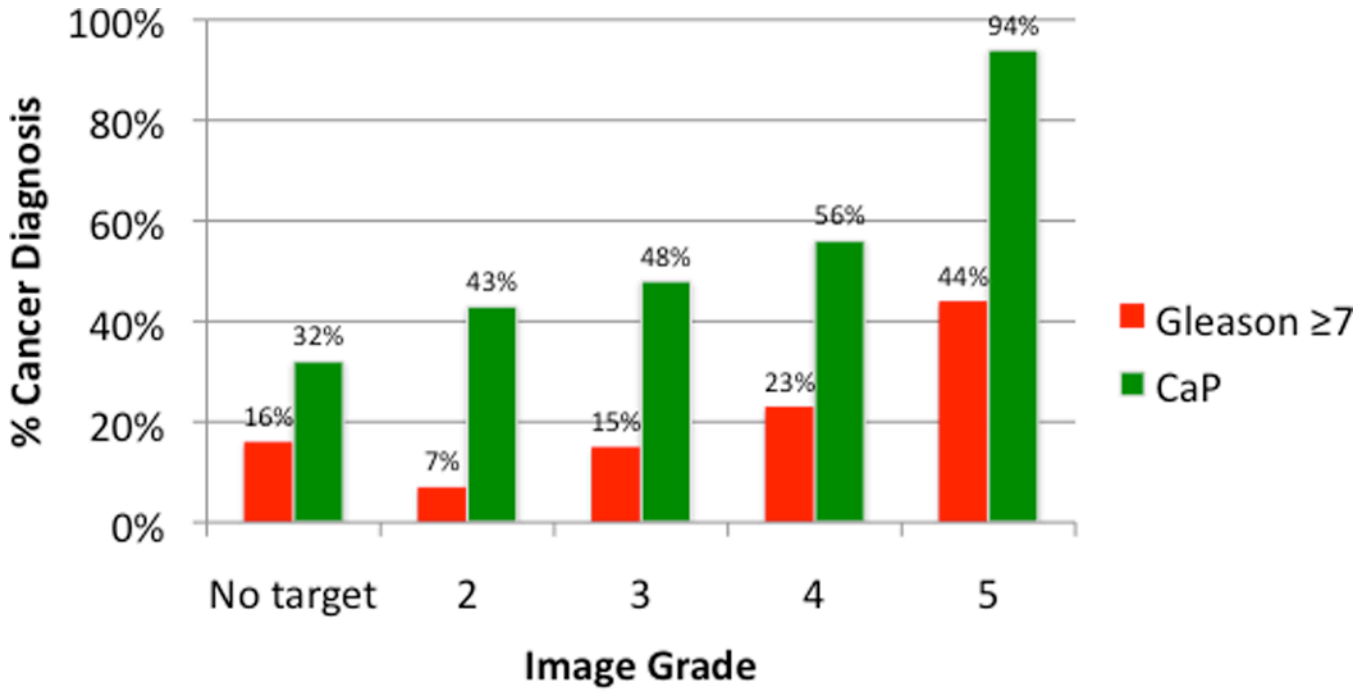


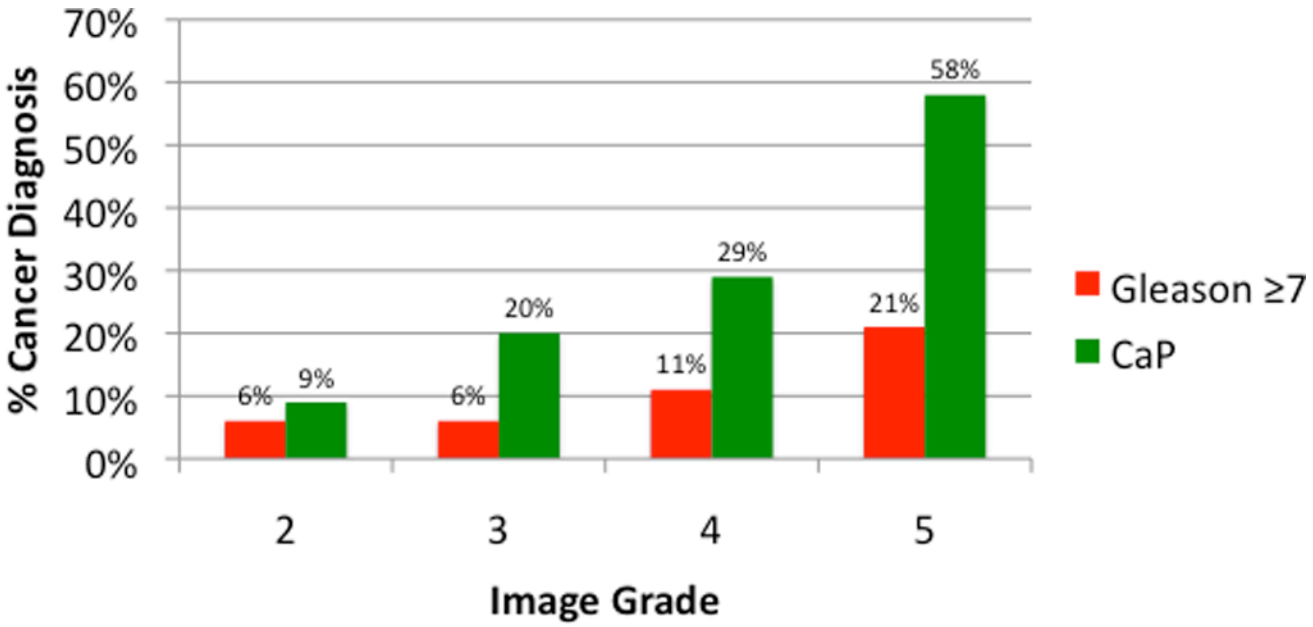
Figure 1. Sample Case

59 year old man with a PSA of 7.4 and one prior negative biopsy. **A.** T2-weighted axial MR image demonstrating a lesion in the left peripheral prostate with focal low signal. **B.** Diffusion weighted axial MR image with an ADC value of 0.562×10^{-3} m^2/s in the corresponding area. The lesion was classified as image grade 5 based on multiparametric features. The radiologist outlined the lesion in each axial image. Open-source imaging software then produced a 3D model of the prostate including the 3D target. **C.** Real-time ultrasound image of the area of interest (outlined in blue). Note the absence of ultrasound abnormality. A 3D model is generated based on ultrasound. **D and E.** The two models were then dynamically fused, generating the composite virtual 3D model seen in panel D and E. The prostate is mapped in brown and the target identified in blue (outlined by white circle). Systematic and targeted biopsies were obtained, generating the final 3D model demonstrating the location of all biopsy cores (light brown cylinders). Targeted biopsies in this patient revealed Gleason 7 CaP. **D.** Radical prostatectomy whole mount pathology confirmed the presence of a 2 cm Gleason 7 cancer in the left peripheral zone.



# Patients	19	14	61	61	16
# Any CaP	6	6	29	34	15
# Gleason ≥7 CaP	3	1	9	14	7

Figure 2.
Prostate Cancer Detection Rate in 171 men undergoing MR-US fusion biopsy.



# Targets	34	142	84	19
# Any CaP	3	29	24	11
# Gleason ≥7 CaP	2	9	9	4

Figure 3.
Prostate Cancer Diagnosis by Target for the 279 targets identified on MRI in 171 men.

Table 1
Classification system for targets identified on MRI

Modified from a previously published classification system.[11]

Image grade	T2-weighted imaging (T2WI)	Apparent Diffusion Coefficient (ADC, x10-3 m^2/s)	Dynamic Contrast Enhancement (DCE)
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	Markedly decreased signal	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.