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Prostate Cancer

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

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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.
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 $\geq$3 + 4 or Gleason 6 with maximal cancer core length $\geq$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.

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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) ≥4 mm, (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

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.