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An Initial Negative Round of Targeted Biopsies In Men With Highly Suspicious Multiparametric MR Findings Does Not Exclude Clinically Significant Prostate Cancer – Preliminary Experience

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Abstract

Background—Targeted prostate biopsies are changing the landscape of prostate cancer (PCa) diagnosis with the degree of suspicion on multiparametric MRI (mpMRI) being a strong predictor of targeted biopsy outcome. Data regarding the rate and potential causes of false-negative magnetic resonance imaging-transrectal ultrasound (MRI-TRUS) fusion targeted biopsy in patients with highly suspicious mpMRI findings are lacking.

Objectives—To determine the rate of clinically significant PCa detection in repeat targeted biopsy or surgery in patients with highly suspicious mpMRI findings and an initial negative MRI-TRUS fusion targeted biopsy.

Materials and Methods—In this single center, retrospective study of prospectively generated data, men with highly suspicious lesions (Likert 5 score) on mpMRI and an initial negative MRI-TRUS fusion targeted biopsy were reviewed. The rate of PCa detection in a subsequent MRI-TRUS fusion targeted biopsy or radical prostatectomy was determined. Tumors in the intermediate and high risk groups according to the National Comprehensive Cancer Network criteria were considered clinically significant.

Results—32 men with 38 Likert 5 lesions were identified. Repeat targeted biopsy or surgery detected cancer in 42% (16/38) of the Likert 5 lesions with initial negative targeted biopsy. Most of these cancers were intermediate (69%; 11/16) or high risk (25%; 4/16) tumors.

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Conclusion—A negative round of targeted biopsies does not exclude clinically significant PCa in men with highly suspicious mpMRI findings. Patients with imaging-pathology disagreement should be carefully reviewed and considered for repeat biopsy or strict surveillance.

Keywords

prostate cancer; diagnosis; early detection; biopsy; magnetic resonance imaging

1. Introduction

Targeted prostate biopsies are changing the landscape of prostate cancer (PCa) diagnosis and have shown to improve the detection of clinically significant PCa[1]. Software-based magnetic resonance imaging-transrectal ultrasound (MRI-TRUS) fusion systems that overlay MRI findings on the TRUS screen distinguish themselves by combining efficiency and lower cost compared to direct, in-bore MRI guidance, and by improved accuracy compared to cognitive MRI-TRUS image fusion[2].

The performance of software-based MRI-TRUS fusion is dependent on the acquisition of high quality multiparametric MR images, adequate MR interpretation, MR image segmentation (i.e., prostate contouring and target delineation), ultrasound (US) image segmentation of prostate boundaries, fusion of magnetic resonance (MR) and US images, precise target sampling based on navigation of fused images, adequate tissue samples and sound histological interpretation[3]. Deficiencies in one or more of these multiple steps may compromise the accuracy of targeted biopsies using this approach.

The degree of suspicion on multiparametric MRI (mpMRI) is the strongest predictor of a positive targeted biopsy with positive rates of 70-90% when the MRI findings are highly suspicious for PCa (i.e., PI-RADS or Likert scores of 5) [4-11]. Thus, a negative targeted biopsy of a highly suspicious lesion on mpMRI must be interpreted with caution and additional actions (e.g., repeat biopsy, imaging follow-up) may be required depending on the clinical context. However, data regarding the rate and potential causes of false-negative MRI-TRUS fusion targeted biopsy in patients with highly suspicious mpMRI findings are lacking.

Hence, the goal of this study was to determine the rate of clinically significant PCa detection in repeat targeted biopsy or surgery in patients with highly suspicious mpMRI findings and an initial negative targeted biopsy. Secondly, we aimed to determine potential reasons for failures and features associated with an increased risk of a falsely negative targeted biopsy.

2. Materials and Methods

This Institutional Review Board-approved and Health Insurance Portability and Accountability Act-compliant study is a retrospective collection and analysis of prospectively generated clinical, imaging and histopathological data.

2.1. Patient eligibility

All patients without previous diagnosis of PCa who underwent prostate mpMRI for cancer detection in our institution between February 2013 and December 2015 were reviewed. Men with highly suspicious mpMRI findings (i.e., at least one Likert scale score 5 lesion) followed by a targeted MRI-TRUS biopsy were eligible for this study. Indications for mpMRI included elevated prostate-specific antigen (PSA), abnormal rise in PSA and/or abnormal digital rectal exam.

2.2. Multiparametric MRI

All MRI studies were performed in a 3 Tesla MRI scanner (Achieva or Ingenia, Philips; Best, The Netherlands) with an endorectal and a phased-array surface coil. Each MRI examination was prospectively and independently interpreted by 1 of 7 radiologists with advanced training in body MRI and not blinded to the clinical context. Our routine, clinical interpretation includes the assignment of a per-lesion score using a 1–5 Likert scale score as a subjective assessment of the likelihood of the presence of a clinically significant cancer (score 1, highly unlikely; score 2, unlikely; score 3, equivocal; score 4, likely; and score 5, highly likely), based on its appearance on T2-weighted, diffusion-weighted, and dynamic contrast-enhanced images [7, 12, 13].

2.3. Targeted MRI-TRUS Fusion Biopsy

A commercially available workstation (VersaVue, iCAD) was utilized by a radiologist to generate volumetric reconstructions of the prostate using an automated segmentation tool and to delineate the biopsy targets, the latter using a free-hand region of interest tool. These data were uploaded to the MRI-TRUS fusion system (UroStation, Koelis). Each biopsy was performed by 1 of 4 urologists with 3 years of experience with targeted biopsies using an ultrasound machine (HD9, Philips Medical Systems; Best, The Netherlands) with an endocavitary 4-9 MHz broadband curved array end-fire transducer (Philips Medical Systems) and an 18-gauge needle mounted on a reusable core biopsy system (Pro-Mag, Angiotech). The targeted biopsy generally consisted of 2 or 3 cores from each target and was performed immediately after the standard 12-core systematic TRUS biopsies. Cores from each lesion were numbered and labeled according to the target location (e.g., lesion 1, left anterior mid gland) enabling the radiology-pathology correlation in patients with multiple targets.

2.4. Standard of reference

In men who underwent surgery for cancer detected by non-targeted, systematic biopsies (performed concomitantly with the targeted session), step-sectioned radical prostatectomy specimen served as the standard of reference. In patients who did not have surgery, repeat targeted biopsy was used as the standard of reference. The decision to re-biopsy patients was at the discretion of the provider. All specimens were prospectively analyzed by 1 of 4 dedicated genitourinary pathologists using the report template recommended by the College of American Pathologists[14].

PSA, PSA density, prostate volume as measured by MRI, lesion size (greatest diameter) and location, biopsy operator experience, and number of targeted cores were recorded for each

patient as potential predictors of diagnostic performance of targeted MRI/TRUS biopsies. For lesion location, lesions in the anterior half of the prostate were considered anterior lesions. Conversely, lesions in the posterior half of the gland were considered posterior lesions. If the lesion crossed this boundary, the predominant component prevailed. At our institution, we performed 638 mpMRIs of the prostate, more than 400 MRI-TRUS fusion targeted biopsies and 333 radical prostatectomies in 2015. Two of the four operators who had performed more than 50 MRI-TRUS fusion targeted biopsies per year were considered more experienced.

Cancers were stratified into very low, low, intermediate and high-risk groups according to the version 2.2014 of the National Comprehensive Cancer Network (NCCN) guidelines[15] (Supplemental Table 1). Intermediate and high-risk groups were considered clinically significant cancers. An index lesion[16] was defined as the cancer focus with highest Gleason score in each patient or in patients with more than one lesion with the same Gleason score, the largest lesion or the one associated with extraprostatic extension if present.

Positive imaging-pathology agreement was defined as the presence of site-concordant cancer on step-sectioned radical prostatectomy specimen or, in patients who did not undergo surgery, as the presence of cancer on targeted core biopsies.

For each lesion with an initial false-negative targeted biopsy, imaging, biopsy and pathology data were reviewed by a radiologist (D.N.C.) with 4 years of experience with targeted biopsies and 12 years of experience in prostate MRI to determine the reason for failure. Inadequacies in one or more of the following steps were evaluated as the most likely explanation for failure: prostate segmentation with MRI, lesion segmentation with MRI, prostate segmentation with US, perceived target sampling during biopsy, pathologist interpretation.

2.5. Statistical analysis

Univariate and multiple analysis with logistical regression were used to identify potential parameters associated with false-negative targeted biopsies, including PSA, PSA density, lesion size, location (anterior versus posterior), number of targeted cores, prostate volume and biopsy operator experience; a significance level of 0.05 was used for statistical testing. Stepwise variable selection algorithm was used for multiple logistic regression. Odds ratios were also estimated with Wald 95% confidence interval.

3. Results

A total of 122 men with 150 lesions met eligibility criteria (Figure 1), with mean and standard deviation age of 68+7 years, PSA of 9.4+7.3 ng/mL, lesion size of 15+7 mm, prostate volume of 62+30 cc and interval between initial and repeat targeted biopsy or surgery of 74+50 days. Of these biopsies, 81 % (99/122) were performed by 2 more experienced and 19% (23/122) were performed by 2 less experienced biopsy operators. Among the 32 men with 38 Likert 5 lesions who had an initial negative targeted biopsy, in 38% (12/32) pathologic correlation was available from radical prostatectomy and in 13%

(4/32) from a repeated targeted biopsy. In 50% (16/32) of the patients, only clinical follow-up data were available.

In the 32 men (38 lesions) with an initial negative round of targeted MRI-TRUS fusion biopsies, cancer was detected in 42% (16/38) of the Likert 5 lesions. Of these, 6% (1/16), 69% (11/16) and 25% (4/16) were low, intermediate and high risk tumors per NCCN criteria, respectively (Figure 2). Of the patients who underwent radical prostatectomy, the Likert 5 lesion missed by the initial targeted biopsy represented the index lesion in 75% (9/12). Post-operative staging demonstrated pT2 disease in 75% (9/12) and pT3a in 25% (3/12) of the patients.

Review of the imaging, biopsy and pathology data in the patients with false-negative targeted biopsies determined inadequate prostate segmentation with US (Figure 2) and lack of accurate target sampling (i.e., biopsy operator misperception of the anatomical relationship between the biopsy cores and the target) to be the reason for the initial false negative result in 44% (7/16) and 19% (3/16) of the lesions, respectively. In 38% (6/16) of the cases, the main contributing factor could not be established.

None of the potential predictors demonstrated an association with an increased false-negative rate except for number of targeted cores when comparing the 16 lesions with an initial false-negative targeted biopsy were compared to the 112 with an initial true-positive biopsy (Table 1).

4. Discussion

The majority of men (74%; 90/122) with Likert 5 lesions have PCa detected on initial MRI-TRUS fusion targeted biopsy. Equally relevant is that at least 42% of the Likert 5 lesions with a negative initial MRI-TRUS fusion biopsy have missed cancer, of which most represent clinically significant disease. As such, one needs to strongly consider re-biopsy in men with Likert 5 lesions and a re-evaluation of the MRI and ultrasound fusion for technical issues that may have resulted in a false-negative biopsy. Certain areas that can be improved include increasing the number of cores from the targeted lesion, improving the automated segmentation of the prostate provided by the fusion biopsy system to improve image co-registration during the time of biopsy, and further refinement of the image fusion software interface to facilitate post-biopsy verification of the core location in relation to the suspicious area.

The increased positive yield from MRI-TRUS fusion targeted prostate biopsies has resulted in an increased reliance on mpMRI and an improved detection of higher risk PCa[1]. Refinements in mpMRI, such as the use of scoring systems that ascribe a likelihood of clinical significance to the MRI findings, either by using a Likert scale or PIRADS, support an ability to correlate highly suspicious appearing lesions with higher risk cancers [4-11]. This has led some to suggest that a negative MRI-TRUS fusion targeted biopsy or even a negative mpMRI might be a sufficient means to exclude significant disease[17]. An emphasis on the improved positive biopsy yield has, however, left a gap in understanding

how to manage patients with highly suspicious mpMRI lesions that are found to be negative after a targeted biopsy session. Our study contributes to address this gap in knowledge.

To the best of our knowledge this is the first study to assess the rate of clinically significant PCa detection in repeat targeted biopsy or surgery in patients with lesions highly suspicious on mpMRI and an initial negative round of targeted biopsies. In the only study available in the literature where patients with a previous negative targeted biopsy underwent repeat targeted biopsy due to continued clinical suspicion for PCa, Chelluri et al. [18] found cancer in only 16% (21/131) of the lesions, far different from our 42% rate of detecting cancer. In the Chelluri study, most (62%; 13/21) were Gleason 3+3 tumors and these discrepant results may be explained by a lack of stratification per level of suspicion based on the mpMRI findings by these investigators. Therefore, that study conclusion that pathologically benign mpMRI lesions on initial image-guided fusion biopsy are rarely found to harbor clinically significant PCa on repeat biopsy [18] does not seem applicable to patients where imaging findings are highly concerning. The extent to which their use of a different MRI-TRUS fusion biopsy system contributed is unknown and may need to be taken into consideration. Importantly, the Likert 5 lesion with an initial negative biopsy represented the index lesion in 75% of our patients who ultimately underwent radical prostatectomy.

Interpretation of TRUS-guided core biopsy specimens by pathologists is the mainstay of preoperative PCa diagnosis, with an increasing contribution of mpMRI in patients being evaluated before biopsy. In this setting, imaging localizes suspicious lesions while pathology confirms the diagnosis of cancer and characterizes the tumor (i.e., Gleason score, number of positive cores and the percentage of core length involved by tumor). Generally, however, radiologists and pathologists function as members of distinct disciplines, with no direct linkage between their workflows or reporting systems under the current architecture of diagnostic medicine[19]. Several studies have demonstrated the value of integrating imaging and pathology findings in other oncologic settings such as breast cancer diagnosis, where such correlation was shown to detect misdiagnosis and to prompt repeat biopsy in instances of unexplained discrepancy between imaging and pathologic findings[20, 21]. Our results suggest that the same principles apply to patients with suspected PCa who undergo mpMRI and MRI-TRUS fusion biopsy.

Except for the number of targeted cores, none of the potential predictors evaluated – including PSA, PSA density, lesion size, lesion location, prostate volume, biopsy operator experience and number of targeted cores – were associated with an increased false-negative rate. It is unclear if this was related to our relatively small sample size and these findings will require validation in studies with larger cohorts.

Our study has limitations. First, a large proportion (50%; 20/40) of the lesions was not re-sampled; therefore, the prevalence of PCa described herein represents a best case estimate as it assumes that patients who were not re-biopsied or did not undergo surgery did not have clinically significant PCa. On the other hand, if this assumption is not accurate, the prevalence of clinically significant cancer would only increase and therefore strengthen our conclusions. Secondly, the retrospective, observational nature of this study with a relatively small sample size is best considered as a presentation of our preliminary experience.

Moreover, we did not assess which of the different steps involved in the MRI-TRUS fusion biopsy workflow was implicated in the cases shown to represent false-negative targeted biopsies. While the expected performance heterogeneity in a group with several radiologists and biopsy-operators may be a limitation, it is a better representation of clinical practice than single-radiologist, single-urolologist investigations. Finally, although the Likert scale has been previously validated as a predictor of PCa[13], the extent to which our results are applicable to those centers using different scoring systems is unknown. The imaging features used for this subjective grading do share, though, a similar rationale as other scoring systems such as the revised version of PI-RADS[22].

5. Conclusions

Our preliminary experience suggests that a negative round of targeted MRI-TRUS fusion biopsy does not exclude clinically significant PCa in patients with highly suspicious mpMRI findings. Therefore, a post-biopsy imaging-pathology reconciliation is critical and patients with discordant findings should be carefully reviewed and entered into a formal repeat biopsy/follow-up management algorithm. Future studies should investigate the role of early repeat targeted biopsy, the differences across various MRI-TRUS fusion biopsy systems, the implications of different strategies such as direct, in-bore MRI-guided approach in selected patients and the potential clinical utility of epigenetic tests.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

1. A negative targeted biopsy does not exclude significant PCa in men with highly suspicious mpMRI.
2. A post-targeted prostate biopsy imaging-pathology reconciliation is crucial.
3. Men with imaging-pathology discordant findings should follow a strict surveillance algorithm.

Figure 1. Eligibility criteria and patient cohort

Figure 2. Clinically significant prostate cancer missed by a first round of targeted MRI-TRUS fusion biopsies

in a 67-year-old man with elevated PSA (8 ng/mL) and 3 previous negative systematic 12-core biopsies. MRI for biopsy planning revealed a highly suspicious lesion prospectively assigned a Likert 5 score in the midline and left paramedian anterior gland with homogeneous low signal intensity on T2-weighted images (*dashed line* in **A**), significantly restricted diffusion (**B**) with low values on the apparent diffusion coefficient map and abnormal contrast kinetics (not shown). Biopsy map generated during the initial targeted biopsy revealed 3 cores (*green* in **C**) that seemed to have properly sampled the suspicious area (*yellow* in **C**) however no cancer was found. Review of biopsy session data revealed inadequate automated segmentation of the prostate boundaries by the fusion biopsy software (**D**; yellow line represents the automated segmentation used by the system and green line represents the actual, manually *post hoc* edited prostate boundaries after the imaging-pathology discrepancy was identified). A repeat targeted biopsy was performed and revealed 3 out of 3 positive cores with Gleason 4+3 disease (**E**). Whole mount radical prostatectomy specimen confirmed site-concordant Gleason 4+3 tumor (*dashed line* in **F**)

Table 1
Potential predictors of increased risk for false-negative targeted biopsies

Parameter	Targeted biopsy result (per lesion)		Statistical analysis	
	False-Negative	True-Positive	Univariate*	Multivariate**
PSA (ng/mL)	4	12/112	p=0.41 OR: 0.96 [0.88-1.05]	NA
	4-10	60/112		
	10	40/112		
PSA density (ng/mL-g)	0.1	35/112	p=0.61 OR: 0.42 [0.01-12.21]	NA
	0.1-0.2	44/112		
	0.2	33/112		
Lesion size (mm)	10	31/112	p=0.16 OR: 0.94 [0.86-1.03]	NA
	>10	81/112		
Lesion location	Anterior	47/112	p=0.74 OR: 1.21 [0.41-3.55]	NA
	Posterior	65/112		
Prostate Volume (cc)	30	16/112	p=0.28 OR: 1.01 [0.99-1.03]	NA
	30-60	45/112		
	60	51/112		
Biopsy operator experience	More	102/112	p=0.24 OR: 2.35 [0.57-9.68]	NA
	Less	10/112		
Number of targeted cores	2	53/112	p<0.01 OR: 0.25 [0.10-0.64]	p<0.01 OR: 0.25 [0.10-0.64]
	>2	59/112		

Numbers within brackets: 95% interval confidence

* Univariate logistic regression

** Multivariate logistic regression with stepwise selection

NA, not applicable