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TITLE

Predictive Value of Negative 3T Multiparametric Prostate MRI on 12 Core Biopsy Results

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Disclosure of Potential Conflicts of Interest
Dr. Lepor reports co-owner of MedReviews, speaker for Allergan, investor for Serenity, consultant for Thera Coat, investor for Sonacare, consultant for Biozeus. Dr. Taneja reports consultant for Hitacha Aloka, consultant for Opko Health, royaltees for Elsevier, scientific investigator for Trod Medical, and scientific investigator for Steba Biotech. All other authors report no potential conflicts of interest.

Abstract
OBJECTIVES:
To evaluate the cancer detection rates (CDR) for men undergoing 12 core systematic prostate biopsy with negative prebiopsy mpMRI (NegMR).

MATERIALS & METHODS:

Clinical data from consecutive men undergoing prostate biopsy with prebiopsy 3T mpMRI from December 2011 to August 2014 were reviewed from an IRB approved prospective database. Prebiopsy mpMRI was read by a single radiologist and men with NegMR prior to biopsy were identified for this analysis. Clinical features, CDR, and NPV rates were summarized.

RESULTS:

Seventy five men underwent SPB with a NegMRI during the study period. For the entire cohort, men with no prior biopsy, men with prior negative biopsy, and men enrolled in active surveillance protocols, overall CDR was 18.7%, 13.8%, 8.0% and 38.1%, respectively, and detection of Gleason sum ≥ 7 (GS≥7) cancer was 1.3%, 0%, 4.0% and 0%, respectively. The NPV for all cancers was 81.3%, 86.2%, 92.0%, and 61.9%, and for GS≥7 cancer was 98.7%, 100%, 96.0% and 100%, respectively.

CONCLUSIONS:

Negative prebiopsy mpMRI confers an overall NPV of 82% on 12 core biopsy for all cancer and 98% for GS≥7. Based upon biopsy indication, these findings assist in prebiopsy risk stratification for detection of high risk disease and may provide guidance in the decision to pursue biopsy.

Introduction

Advances in prostate imaging via multi-parametric magnetic resonance imaging (mpMRI) have prompted its use prior to prostate biopsy (PB) for disease evaluation in multiple clinical scenarios. While ongoing research seeks to define optimal conditions and methodologies for applying targeted biopsy (TB), several studies have demonstrated that identification of highly suspicious lesions on mpMRI frequently results in detection of higher Gleason score on PB [1-6]. Thus, the presence of a suspicious lesion on pre-biopsy mpMRI provides a rationale for performing TB in these men [7-12].

Conversely, cancer detection rates (CDR) in men with low risk or negative mpMRI (NegMR) appear to be much lower [13,14]. Defining rates of disease detection associated with NegMR could enhance decision making capability for men considering PB. TB is not applicable in this setting given the absence of a lesion to target. However, establishing a very low risk of significant disease in men with NegMR could allow for avoiding systematic biopsy in this cohort. Therefore, this study aims to define the cancer detection rate in men with NegMR undergoing systematic 12 core biopsy (SPB) in order to inform clinical decisions for this population.

Materials and methods

Study Design and Population

Following ethics committee approval, records of men undergoing PB were identified from December 2011 to August 2014. During this period, per institutional protocol, men presenting for PB underwent pre-biopsy mpMRI. Over the study period, 256 pre-biopsy mpMRIs were negative for suspicious foci. 75/256 (29.3%) men underwent SPB. Rates of cancer detection were calculated from this group.

Multiparametric MRI Imaging Protocol

Imaging was performed on a 3T clinical system (Siemens Healthcare, Erlangen, Germany) using a pelvic phased-array coil. Examinations included multiplanar turbo spin-echo T2-weighted images (T2WI), axial turbo spin-echo T1-weighted images (T1WI), axial single-shot echo-planar diffusion-weighted imaging (DWI), and dynamic contrast enhanced (DCE) MRI using a 3D fat-suppressed spoiled gradient-echo T1-weighted sequence.

Multiparametric MRI Imaging Interpretation and mSR Demarcation

A single fellowship-trained radiologist with dedicated expertise in prostate imaging evaluated all examinations based upon previously published methodology for the interpretation and reporting of prostate MRI [14-17]. Examinations with no mSR received a score of 1 and were included in evaluation.

Biopsy Protocol

Biopsies were performed in left lateral decubitus position using BK Profocus™ ultrasound system (BK Medical, Peabody, MA, USA) or Noblus ultrasound systems (Hitachi Aloka Medical America, Wallingford, CT, USA), endfire probe, reusable biopsy gun, 18G needles and local anesthesia with 1% lidocaine infiltration.

The biopsy process was initiated with a 360° reference scan of two dimensional (2D) US images. Segmentation of 2D US generated a 3D virtual US map. A 12 point SB template generated by the Artemis™ software was overlaid on the virtual 3D map. The device was then set to “biopsy” mode, which enabled US probe tracking and provided projected biopsy needle trajectories.

Study Design and Statistical Analysis

Analysis of data was completed using SPSS® software (version 15.0). Comparisons of categorical variables were performed using $\chi 2$ or Fisher exact test and continuous variables were evaluated with a two-tailed T-test and/or Mann-Whitney test. Negative predictive value (NPV) was calculated as the number of negative biopsies divided by the sum of negative biopsies and positive biopsies.

RESULTS:

Study Population

Table 1 provides clinical characteristics for each group. Among the 75 men with NegMR, 29 (38.7%) had no prior biopsy, 25 (33.3%) had a prior negative biopsy and 21 (28.0%) were on active surveillance with a prior diagnosis of Gleason score 3+3 cancer. There were no significant differences in the clinical parameters amongst these groups.

Biopsy Outcomes

Table 2 provides biopsy results. Overall, cancer was detected in 14 (18.7%) men. One (1.3%) had Gleason score 3+4 cancer, and the remaining 13 (17.3%) had Gleason score 6 (GS6) cancer. Of the cancers detected, 8/14 (57%) were in men on active surveillance, accounting for 38% (8/21) of men in this group. This frequency in AS patients was significantly higher than in the other patient groups ($p = 0.003$). The single Gleason core 7 tumor was in a patient with a prior negative biopsy. No Gleason score ≥ 3+4 (GS≥7) tumor was detected in men without a prior biopsy or on active surveillance. Four men (13.8%) without prior biopsy and 1 man (4.0%) with a prior negative biopsy had GS6 cancer.

Overall, the NPV for detecting any cancer, and for detecting GS≥7 cancer, on SB for men with a NegMR was 81.3% and 98.7%, respectively. These NPV were 86.2% and 100% for men without prior biopsy, 92.0% and 96% for men with a prior negative biopsy, and 61.9% and 100% for men on active surveillance.

Discussion

The efficacy of contemporary prostate cancer screening and diagnosis practices is subject to the limited sensitivity and specificity of current clinical tools, which primarily reply on serum PSA, and TRUS-guided biopsy. With the emergence of prostate mpMRI and subsequent development of platforms for MRI-targeted biopsy, the clinical utility of mpMRI in identifying areas of suspicion for prostate cancer has been the subject of substantial investigation over the last decade [18-21]. A major advantage of this approach is the ability to identify and target areas which are likely to demonstrate cancer in order to overcome the inherent sampling error associated with random biopsy. Additionally, MRI-targeted biopsy appears to offer an advantage over systematic biopsy in terms of improving the accuracy of high grade cancer detection and decreasing low volume, low-grade cancer detection [22-23].

Since high suspicion findings on mpMRI often represent clincially significant cancer, the absence of findings on mpMRI will likely play a role in guiding decison making in multiple clinical scenarios. The potential benefits of a high negative predictive value for significant cancer extend to men presenting

for first biopsy as well as those with prior negative biopsies. A negative mpMRI in these men has the potential to lower suspicion for aggressive prostate cancer and allow avoidance of biopsy. Additionally, for men with low-risk cancer identified on prior biopsy, a negative MRI may rule out occult disease and thus improve selection criteria for active surveillance.

In light of these potential benefits, several reports in the literature have attempted to validate the utility of a negative prostate mpMRI [Table 3]. Villers et al. compared radical prostatectomy specimen histopathology results to DCE-MRI findings in 24 men with suspicious areas detected by pre-biopsy MRI. They reported a NPV of 85% for foci greater than 0.2 cm^3 and a NPV of 95% for foci greater than 0.5 cm^3 [24].

Clinical outcomes of biopsy results in men with negative mpMRI have also been reported. Squillaci et al. described cancer detection rates amongst 65 men with suspicious areas of the prostate detected by TRUS which were further evaluated by mpMRI with proton MR spectroscopy (MRSI) [25]. This study reported a NPV for overall cancer detection of T2W-MRI alone, MRSI alone, and combined MRI/MRSI as 77%, 78%, and 74%, respectively. Manenti et al. also reported PB results of 39 men undergoing mpMRI with MRSI, with similar NPV of T2W-MRI, MRSI, and combined MRI/MRSI of 77%, 74%, and 74%, respectively [26].

More recently, Girometti et al. reported a NPV of 100% for a series of 8 men with prior negative biopsy using DWI in addition to T2W- and MRSI prior to biopsy [27]. When analyzed on a per-region (rather than per-patient) basis, with each prostate divided into 8 standardized regions, T2W, DWI, and MRSI demonstrated NPVs of 97%, 96%, and 94%, respectively.

In a recent prospective trial of 226 men undergoing 3T mpMRI prior to primary biopsy, Pokorny et al reported negative biopsies in 56/81 (69%) men with normal mpMRI [3]. However, this group included men with Prostate Imaging Reporting and Data Systems (PI-RADS) scores of both 1 and 2. Among the 25 men with normal mpMRI and prostate cancer on biopsy, 20/25 (80%) had low-risk disease (low volume Gleason score 3+3 tumor or very low volume Gleason score 3+4 tumor), such that the NPV for intermediate/high risk disease was 94%. Itatani et al. also recently described 5-year follow-up outcomes of men with initial negative mpMRI. The authors reported the NPV of negative mpMRI for cancer on initial TRUS-guided biopsy of 87%, with only 15% and 10% of men found to have cancer and clinically significant cancer, respectively, on biopsy or radical prostatectomy within the five-year period following MRI [28]. Filson et al. reported outcomes of 12-core biopsy among 244 men with negative mpMRI, observing a negative predictive value of only 54%, with 38 men (16%) found to have Gleason score ≥ 7 cancer on biopsy [29]. However, 116/244 (48%) men in this cohort had a history of prior positive biopsy.

The results of our study agree with the more comprehensive results of Pokorny, et al. and Villers et al. Negative mpMRI was highly predictive of the absence of cancer on systematic biopsy, and only one man (1.3%) had Gleason 3+4 cancer on biopsy. Additionally, this study further details clinical outcomes of PB by biopsy history. For men with negative mpMRI and no history of previous prostate cancer, the NPV for cancer and GS≥7 cancer were 91.7% and 97.9%, respectively. Among men on active surveillance, none were diagnosed with GS≥7 cancer after negative mpMRI. These findings strengthen previously reported outcomes and lend further support to the utility of mpMRI in predicting negative biopsy among men with clinical suspicion for PCa and predicting a low likelihood of Gleason upgrade among men on active surveillance.

The primary limitation of this study is that not all men with negative MRI at our institution underwent biopsy. As a result, there exists the potential for selection bias as men included in the study may represent those with elevated clinical suspicion, despite NegMRI, due to other risk factors. However, it is conceivable that men with lower clinical suspicion, who may not have been biopsied and included in our study, are even less likely to harbor significant disease. Additionally, the accuracy of biopsy is limited by the lack of confirmation with whole mount pathology from radical prostatectomy. Our ability to assess the true NPV of MRI for PCa is inherently limited by the sensitivity of systematic biopsy to detect prostate cancer. Prior studies have directly compared pre-operative mpMRI to histological outcomes of men undergoing radical prostatectomy, reporting significant cancers missed by MRI in 5-28% of patients [13, 32-34]. While these findings were not reported in men specifically with negative MRI, but rather in men with significant cancer detected on biopsy who underwent definitive treatment, the results indicate that there is a real, but small, rate of higher risk disease that is difficult to detect by MRI, potentially related to low tumor volume. These small, yet significant, foci would also be difficult to detect on systematic biopsy as well, and remain a topic of further investigation. Nevertheless, the strong association between negative mpMRI and negative SPB provides evidence to suggest that cancers not seen on MRI are unlikely to be detected on subsequent SPB, and thus may be of limited clinical utility in men with negative mpMRI. Future studies may define a need for surveillance of men with clinical suspicion for prostate cancer and a negative mpMRI, potentially through the addition of biomarkers or additional surveillance imaging. Finally, CDR with Artemis-directed SPB has not been fully defined.

Conclusions

In this prospective series of men with NegMR undergoing SPB, the detection of Gleason score >6 prostate cancer was low. The rates of cancer detection in the setting of NegMR vary by biopsy history, though show that mpMRI has a high NPV in men with no prior prostate cancer diagnosis, and that NegMR predicts a low likelihood of identifying Gleason score >6 cancer in men on active surveillance. Together, these results suggest that biopsy may be of little clinical utility in men with negative mpMRI.

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	Entire Cohort (75)	**Biopsy Naïve (29, 38.7%)**	**Prior Negative Biopsy (25, 33.3%)**	**Active Surveillance (21,28.0%)**	**p**
Age (yrs)	62 [57.0-68.0]	61 [53.8-66.0]	64 [57.3-68.8]	63 [57.0-68.0]	0.378
PSA (ng/mL)	4.7 [3.00-6.50]	3.7 [2.93-4.85]	5.3 [4.23-8.40]	5.4 [1.70-6.50]	0.119
Prostate Volume (MRI, median, cc)	54.5 [39.00 – 74.00]	41.7 [33.75- 63.00]	60.1 [42.30-90.75]	56.0 [36.50-70.70]	0.175

	Entire Cohort	**Biopsy Naïve**	**Prior Negative Biopsy**	**Active Surveillance**	**p**
Overall Cancer Detection Rate on 12 core	14/75 (18.7%)	4/29 (13.8%)	2/25 (8.0%)	8/21 (38.1%)	0.003
Detection of GS6	13/75 (17.3%)	4/29 (13.8%)	1/25 (4.0%)	8/21 (38.1%)	-
Detection of GS≥7	1/75 (1.3%)	0	1/25 (4.0%)	0	-
Negative Predictive Value (All CaP)	81.3%	86.2%	92.0%	61.9%	
Negative Predictive Value (GS≥7)	98.7%	100%	96.0%	100%	

Authors	No. total subjects	Biopsy indication	Biopsy method among negative MRI men	MRI field strength/ receiver coil	Axial MR sequences	No. men with no suspicious region	Per patient NPV
Girometti et al. (2012)	26	Previous negative biopsy	Extended 8-24 core TRUSGB	3.0 T PPA coil	T2WI/DWI/MRS	8 (31%)	100%
Perdonà et al. (2013)	106	Elevated PSA (4.0 - 10.0 ng/mL)	Extended 12-16 core TRUSGB	1.5 T ER Coil	T2WI/DCE/MRS	67 (63%)	91%
Pepe et al. (2013)	78	Previous negative biopsy	Transperineal saturation	3.0 T PPA coil	T2WI/DWI/ DCE/MRS	46 (59%)	81%
Pokorny et al. (2014)	226	No previous biopsy	12-core TRUSGB	3.0 T PPA coil	T2WI/DWI/DCE	81 (36%)*	69%
Itatani et al. (2014)	621	Elevated PSA or outside referral	10-14 core TRUSGB	1.5 T PPA coil	T2WI/DWI/DCE	193 (31%)*	87%
Filson et al. (2015)	1044	Mixed	12-core TRUSGB	3.0 T	NR	244	54%
Wysock et al.	824	Mixed	12-core TRUSGB	3.0 T PPA coil	T2WI/DWI/DCE	75	81%