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Research article

Sub-differentiating equivocal PI-RADS-3 lesions in multiparametric magnetic resonance imaging of the prostate to improve cancer detection

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ABSTRACT

Purpose: To evaluate sub-differentiation of PI-RADS-3 prostate lesions using pre-defined T2- and diffusion-weighted (DWI) MRI criteria, to aid the biopsy decision process.

Methods: 143 patients with PIRADS-3 index lesions on MRI underwent targeted transperineal-MR/US fusion biopsy. Radiologists with 2 and 7-years experience performed blinded retrospective second-reads using set criteria and assigned biopsy recommendations. Inter-reader agreement, Gleason score (GS), positive (PPV) predictive values (± 95% confidence intervals) were calculated and compared by Fisher's exact test with Bonferroni-Hom correction.

Results: 43% (61/143) patients had GS 6–10 and 21% (30/143) GS ≥ 3 + 4 cancer. For peripheral zone lesions, significant differences in any cancer detection were found for shape (0.26 ± 0.13 geographical vs. 0.69 ± 0.23 rounded; p = 0.0055) and ADC (mild 0.21 ± 0.12 vs marked 0.81 ± 0.19; p = 0.0001). For transition zone, significantly increased cancer detection was shown for location (anterior 0.63 ± 0.15 vs. mid/posterior 0.31 ± 0.14; p = 0.0048), border (pseudo-capsule 0.32 ± 0.14 vs. ill-defined 0.61 ± 0.15; p = 0.0092), and ADC (mild 0.35 ± 0.12 vs marked restriction 0.68 ± 0.17; p = 0.0057). Biopsy recommendations had 62% inter-reader agreement (89/143). Experienced reader PPVs were significantly higher for any cancer with "biopsy-recommended" 0.61 ± 0.11 vs. "no biopsy" 0.21 ± 0.10 (p = 0.0001), and for GS 7–10 cancers: 0.32 ± 0.10 vs. 0.08 ± 0.07, respectively (p = 0.0003).

Conclusion: Identification of certain objective imaging criteria as well as a subjective biopsy recommendation from an experienced radiologist can help to increase the predictive value of equivocal prostate lesions and inform the decision making process of whether or not to biopsy.

1. Introduction

Multiparametric prostate MRI (mpMRI) has become established in the diagnostic pathway of men with prostate cancer [1–3] and is now increasingly used in the pre-biopsy setting to allow selection of men with significant cancer for biopsy, while avoiding biopsy and unnecessary treatment in men without an MRI lesion [4,5].

The recently updated Prostate Imaging-Reporting and Data System (PI-RADS) guidelines are aimed at standardizing MRI acquisition and interpretation using a 5-point scoring system [6,7]. However, when MRI is being used to guide the clinical decision making process either in the context of a previous negative biopsy, or in biopsy naïve patients, this 5-point scale has to be translated into a binary decision of whether to biopsy or not. A PI-RADS score of 1–2 is considered a "negative" MRI, and has a > 90% negative predictive value (NPV) for significant disease [8,9], thus biopsy can be reasonably avoided. Conversely, a PI-RADS 4–5 lesion is of high probability and targeted biopsy is warranted. An intermediate PI-RADS 3 lesion, however, straddles this decision making process, and biopsy in this case is under debate [10–12]. The overall detection of cancer in indeterminate lesions has been shown to vary from 6.5% to 60% for any cancer and 4.1% to 21% for significant cancer [10,13–16]. This needs to be considered in the context of a "miss

Abbreviations: mpMRI, multiparametric magnetic resonance imaging; PI-RADS, Prostate Imaging-Reporting and Data System; NPV, negative predictive value; PPV, positive predictive value; US, Uultrasound; T2WI, T2-weighted imaging; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; PSA, prostate specific antigen; GS, Gleason score; PZ, peripheral zone; TZ, transition zone

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rate" of around 10% for a PIRADS score of 1–2. Importantly, detection rates have been shown to be higher in the peripheral zone [14] and as high as 40% in the context of a second-biopsy population [15], suggesting some PI-RADS 3 lesions deserve biopsy, whereas others could be safely deferred. Informing management of such lesions is particularly relevant given the reported prevalence of indeterminate of 20.5–26.3% using earlier Likert-based systems [10,16–18] is predicted to increase with a switch to using the PI-RADS-version 2 reporting system [19].

The aim of this study therefore was to evaluate if equivocal PI-RADS 3 lesions on mpMRI of the prostate can be further differentiated using pre-defined T2- and diffusion-weighted imaging (DWI) criteria, in order to aid in the biopsy decision process.

2. Materials and methods

2.1. Study population

This single-institution retrospective study was part of an evaluation of transperineal prostate biopsies with the need for informed consent for data analysis waived by the local ethics committee. From January 2013 to April 2016, 155 consecutive patients with a dominant (index) lesion considered to be equivocal on mpMRI (PI-RADS 3) underwent transperineal prostate biopsies at our tertiary center. 4 patients were excluded due to hip replacements, 8 patients were excluded as their scans were performed on a 1.5T MRI scanner. Out of the remaining 143 patients, 35 had no previous prostate biopsies, 82 had previous negative systematic transrectal ultrasound (TRUS)-guided biopsies, and 26 were due for follow-up biopsy under active surveillance for Gleason score 6 cancer. The Standards of Reporting for MRI-targeted Biopsy Studies (START) were used to describe the study population, the conduct and reporting of the MRI, and the conduct of the biopsy and the Standards of Reporting of Diagnostic Accuracy (STARD) were used to describe and discuss the results [20,21].

2.2. Magnetic resonance imaging

All patients underwent MRI on a 3-T scanner (HDx, GE Healthcare) using a 16–32 channel phased-array body coil. The MRI protocol included axial T1-weighted fast spin-echo (FSE) images of the pelvis and high-resolution T2-weighted fast recovery FSE images of the prostate in axial, sagittal, and coronal planes. T1-weighted imaging parameters were as follows: TR/TE, 561/11; flip angle, 70°; FOV, 24 × 24 cm; resolution 1.1 × 1.0. T2-weighted imaging parameters were as follows: TR/TE, 4273/102; FOV, 22 × 22 cm; resolution 0.8 × 0.7; 1.5 signal averages. Axial DWI was performed using a dual spin-echo planar imaging pulse sequence (TR/TE, 3775/70; FOV, 28 × 28 cm; resolution 2.2 × 2.2). A parallel imaging with array spatial sensitivity encoding technique was used with an acceleration factor of 2 to reduce image distortion, with 6 signal averages. The slice thickness for the axial T2-weighted and DWI sequences was 3 mm with 0-mm gap. Isotropic DW images were automatically obtained by combining images with three perpendicular diffusion axes, and b values of 150, 750, 1400 and 2000 s/mm^2 were acquired; apparent diffusion coefficient (ADC) maps were automatically calculated.

2.3. Image analysis

All mpMRI images were prospectively read at our center by one of two subspecialist body radiologists experienced in reading prostate MRI. T2WI and DWI sequences were prospectively evaluated using a Likert scale of tumor probability, based on the Prostate Imaging Reporting and Data System (PI-RADS v1) structured scoring criteria developed by the European Society of Urogenital Radiology (ESUR) [22] and a final score was defined by combining all scores for T2WI and DWI sequences as recommended in PI-RADS version 2 [23]. Equivocal "Likert 3" was taken to be equivalent to PI-RADS 3 and only the equivocal lesions were further analysed for this study. Two radiologists with 2 years (approximately 200 cases read) and 7 years (over 2000 cases) years of experience performed a blinded retrospective second-read of each. In each case the readers were provided with the location of the lesion originally reported according to the PI-RADS sector map, in order to ensure the same lesion was re-assessed. Objective imaging criteria derived from PI-RADS descriptors were used to assess each lesion, along with topographical information such as anterior location of transition zone lesions or radial/parallel orientation of peripheral zone lesions [24–26]; Table 1. The location of transition zone lesions was identified according to the sector map as originally reported and therefore inter-reader agreement was not assessed for this criterion. Finally, readers were asked to give a subjective binary recommendation whether or not to biopsy.

Table 1
Imaging criteria used for reevaluation of PIRADS 3 lesions depending on location in peripheral and transition zone.

Feature	Peripheral zone lesions	Transition zone lesions
Location	Radial vs. Parallel to capsule	Mid/posterior vs. Anterior
Shape	Wedge vs. Round	Round vs. Irregular
Border	Ill vs. Well-defined	Pseudocapsule vs. Ill-defined
Signal intensity	Low vs. > Bladder wall	Low vs. > Bladder wall
Homogeneity	Heterogenous vs. Homogeneous	Heterogenous vs. Homogeneous
DWI	Normal/Iso vs. High Intensity	Normal/Iso vs. High Intensity
ADC	Normal/Mild vs. Low	Normal/Mild vs. Low

2.4. Biopsy

The Biopsee™ transperineal MRI/TRUS fusion biopsy system version 1 or 2 (Medcom, Darmstadt, Germany) was used for all biopsies. All patients had 18–24 systematic biopsies taken according to the Ginsburg protocol, using a spring-loaded biopsy gun with an 18 gauge needle [27]. 2 target biopsy cores were taken from each lesion before the systematic biopsies. In the systematic biopsy, 2 biopsy cores were sampled from each of 12 sectors, starting with the anterior sectors. All procedures were undertaken by 1 of 2 urologists with several years' experience of transperineal biopsy using the Biopsee™ MRI/TRUS fusion biopsy system.

2.5. Histopathology

All biopsies were reported by a specialist uropathologist and were reviewed a second time, by another uropathologist, prior to discussion at a multidisciplinary team meeting. Biopsies were reviewed according to the ISUP 2005 recommendations [28]. The final Gleason score (GS) was used as data for this study, with GS ≥ 3 + 4 being considered as significant cancer.

2.6. Statistics

Inter-reader agreement and Kappa value with 95% Confidence Interval (CI) were calculated for each criterion. Gleason score 7–10 cancer detection rate, all cancer detection rate, and positive predictive values were calculated for each criterion, including targeted and systematic biopsy cores in the area that the index lesion was located in. For example: if an index lesion was called in the right anterior, the results for the targeted cores and the systematic cores in the right anterior were used for analysis. Fisher's exact test in combination with Bonferroni-Holm correction and a p-value target alpha level of 0.05 was used to test for statistically significant difference of cancer proportions. The GraphPad QuickCalcs calculator software (GraphPad Software Inc. La Jolla, CA, USA) was used to calculate the respective p-values.