Where Do Transrectal Ultrasound- and Magnetic Resonance Imaging-guided Biopsies Miss Significant Prostate Cancer?

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OBJECTIVE To identify the location of missed significant prostate cancer (sPCa) lesions by transrectal ultrasound-guided biopsy ($TRUS_{bx}$) and multiparametric magnetic resonance imaging-guided biopsy ($mpMRI_{bx}$) in men undergoing repeat biopsies.

MATERIALS AND METHODS A total of 289 men with prior negative $TRUS_{bx}$ underwent multiparametric magnetic resonance imaging. The location of any suspicious lesion was registered and scored using Prostate Imaging Reporting and Data System version 1 classification according to the likelihood of being sPCa. All patients underwent repeat transrectal ultrasound-guided biopsy ($reTRUS_{bx}$) and targeted $mpMRI_{bx}$ (image fusion) of any suspicious lesion. Biopsy results were compared and the locations of missed sPCa lesions were registered. Cancer significance was defined as (1) any core with a Gleason score of >6, (2) cancer core involvement of ≥50% and for $reTRUS_{bx}$ on patient level, and (3) the presence of ≥3 positive cores.

RESULTS Of the 289 patients, prostate cancer was detected in 128 (44%) with 88 (30%) having sPCa. Overall, 165 separate prostate cancer lesions were detected with 100 being sPCa. Of these, $mpMRI_{bx}$ and $reTRUS_{bx}$ detected 90% (90/100) and 68% (68/100), respectively. The majority of sPCa lesions (78%) missed by primary $TRUS_{bx}$ were located either anteriorly or in the apical region. Missed sPCa lesions at repeat biopsy were primarily located anteriorly (84%) for $reTRUS_{bx}$ (n = 27/32) and posterolateral midprostatic (60%) for $mpMRI_{bx}$ (n = 6/10).

CONCLUSION Both $TRUS_{bx}$ and $mpMRI_{bx}$ missed sPCa lesions in specific segments of the prostate. Missed sPCa lesions at repeat biopsy were primarily located anteriorly for $TRUS_{bx}$ and posterolateral midprostatic for $mpMRI_{bx}$. Localization of these segments may improve biopsy techniques in men undergoing repeat biopsies. UROLOGY 110: 154–160, 2017. © 2017 Elsevier Inc.

Patients with benign transrectal ultrasound-guided biopsy ($TRUS_{bx}$) for prostate cancer (PCa) detection constitute a clinical dilemma.[1] As $TRUS_{bx}$ has limited diagnostic accuracy because of poor PCa target identification, a significant number of cancers are missed[2] and the issue of possible Gleason score (GS) undergrading is evident.[3,4] Clinicians are therefore repeatedly challenged in men with negative prostate biopsies, as the indication for repeated biopsies (rebiopsy) often is driven by a rise in a nonspecific prostate-specific antigen (PSA) measure. A minimum of 10-12 systematic $TRUS_{bx}$ cores, sampling the posterior peripheral zone of the prostate, is recommended in biopsy-naive men.[5] However, the number of cores, the biopsy technique, and the sampling sites in men undergoing rebiopsies are debatable. Recommendations have been made to either increase the number of cores,[6] include sampling of the transitional zone (TZ) by directing rebiopsy cores more anteriorly[7] or moving toward saturation biopsy techniques.[8] However, these approaches often lead to an unfavorable increased detection of insignificant prostate cancers (insPCa's) potentially leading to unnecessary treatments.[7,9,10]

There is a need for an improved target identification of significant prostate cancer (sPCa) without a concurrent increase of insPCa. Prostate multiparametric magnetic resonance imaging (mpMRI) has emerged as an accurate imaging modality for this purpose.[11,12] Suspicious lesions identified on mpMRI can be targeted by selective multiparametric magnetic resonance imaging-guided biopsy ($mpMRI_{bx}$) and can improve detection of missed sPCa[13,14] at rebiopsy. However, not all cancers are visible on mpMRI and lesions may be misinterpreted.[15,16]

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Furthermore, $mpMRI_{bx}$ can be inaccurate because of lesion targeting errors and far from all institutions have the setup and experience in mpMRI diagnostics. Thus, numerous urologists still rely on systematic $TRUS_{bx}$ for rebiopsy sessions. Therefore, awareness of the location of missed sPCa foci by $TRUS_{bx}$ and $mpMRI_{bx}$ may improve rebiopsy techniques. The objective of the present study was to identify the location of sPCa lesions missed by transrectal ultrasound (TRUS) and $mpMRI_{bx}$ in men undergoing rebiopsy.

MATERIALS AND METHODS

Patients

This is a retrospective analysis of patient data from a study database approved by the Local Committee for Health Research Ethics (No.H-1-2011-066) and the Danish Data Protection Agency. All patients were prospectively enrolled from September 2011 to September 2013 and provided written informed consent. The study was registered at Clinicaltrials.gov (No.NCT01640262). Inclusion required all patients to have a history of negative $TRUS_{bx}$ findings and a clinical suspicion of missed sPCa (persistent elevated PSA, an abnormal digital rectal examination, or a previous abnormal TRUS image) that warranted a rebiopsy. The exclusion criteria were patients previously diagnosed with PCa or who had a general contraindication to mpMRI. All prior $TRUS_{bx}$ sessions included a systematic extended biopsy scheme (10-12 cores). No patient had prior mpMRIs. Parts of the patient data were included in a prior study, but no data on the location of missed sPCa were included.

mpMRI. mpMRI was performed before rebiopsy using a 3.0-T magnetic resonance imaging scanner (Philips Healthcare, Best, The Netherlands) with a pelvic–phased-array coil (Philips Healthcare) positioned over the pelvis according to the European Society of Urogenital Radiology guidelines[17] and as previously published.[18] All identified mpMRI lesions were registered and scored on a modified 18-region prostate diagram[19] by the same physician using the Prostate Imaging Reporting and Data System (PIRADS) version 1 classification.[17] Lesions were scored from 1 to 5 according to the probability of being sPCa (1, very low; 2, low; 3, intermediate; 4, high; and 5, very high). Patients with no suspicious lesions were not scored by PIRADS.

Biopsies. All patients underwent both systematic repeat transrectal ultrasound-guided biopsy ($reTRUS_{bx}$) and $mpMRI_{bx}$ in the same biopsy session. Ten systematic $reTRUS_{bx}$ cores from 10 prostatic regions (6 lateral and 4 medial from the base, middle, and apex from both left and right sides) were obtained by the operator blinded to any mpMRI findings and marked separately. Suspicious lesions seen on TRUS were sampled using the core for the corresponding region. The operator then subsequently reviewed the patients' mpMRI data on a dedicated workstation in the biopsy room and additional $mpMRI_{bx}$ (1-2cores per lesion) were targeted toward any PIRADS 2-5 lesion using mpMRI-TRUS image fusion either cognitive-based (n = 83) or software-based (n = 206, HI-RVS system; Hitachi, Tokyo, Japan). All prostate biopsies were performed in the axial plane using the end-fire technique by the same operator.

Histopathology and Cancer Significance

For each PCa-positive biopsy core, the location according to the scheme, the biopsy technique, the GS[20] on both patient and lesion levels, and the extent of cancer core involvement (%) were determined by the same genitourinary pathologist. Histopathologic findings were used to define sPCa as (1) any biopsy core with a GS of >6; (2) a maximum cancerous core length of ≥50%; and for $reTRUS_{bx}$ only on a patient level, (3) the presence of ≥3 PCa-positive cores.

Biopsy Comparison

Any sPCa detected by either $reTRUS_{bx}$ or $mpMRI_{bx}$ was considered to be the result of a prior false-negative $TRUS_{bx}$. Biopsy results (pathologically proven cancer location, the GS, and the tumor length) from $reTRUS_{bx}$ and $mpMRI_{bx}$ were compared according to the 18-region prostate scheme. PCa-positive lesions detected solitarily by 1 biopsy technique ($reTRUS_{bx}$ or $mpMRI_{bx}$) were interpreted as missed lesions with the other method. Only PCa-positive $mpMRI_{bx}$ from intermediate- and high-risk lesions (PIRADS score of 3-5) were included in the analysis as a true-positive mpMRI. However, because of the study design, $mpMRI_{bx}$ were also obtained from PIRADS score 2 (low risk) lesions. Thus, any PCa-positive $mpMRI_{bx}$ from these lesions was interpreted as a false-negative mpMRI and an $mpMRI_{bx}$ missed lesion when a recommended biopsy threshold of PIRADS ≥3 was used. As our $TRUS_{bx}$ core length obtained 18-mm tissues samples of the posterior part of the prostate (peripheral zone), the anterior region was defined as a vertical line 18 mm from the prostatic posterior surface independent of prostate size. Consequently, all $reTRUS_{bx}$ PCa-positive lesions were defined as part of the prostate's posterior region according to the scheme.

The diagnostic yields of any PCa and sPCa were compared and stratified by biopsy technique. As the $TRUS_{bx}$ cores were systematically dispersed throughout the prostate targeting 1 core per region, a patient with a GS 6 tumor on $reTRUS_{bx}$ was defined as having sPCa if more than 2 biopsy cores were positive for PCa. However, the number of $mpMRI_{bx}$ positive cores did not influence the definition of sPCa, as more than 1 core often were targeted toward the same prostatic region or lesion.

Suspicious lesions on mpMRI were confirmed to be PCa by positive targeted $mpMRI_{bx}$. Suspicious lesions that involved more than 1 prostatic region and were directly connected on mpMRI were defined as the same lesion and positive if $mpMRI_{bx}$ proved PCa from at least one of the involved regions. Similarly, PCa-positive adjacent regions (medial-lateral and base-mid-apex) on $reTRUS_{bx}$ were defined as the same lesion.

Benign $mpMRI_{bx}$ of a suspicious lesion could be the result of either mpMRI misinterpretation or targeting error because of image-fusion misregistration. A benign $mpMRI_{bx}$ of an mpMRI suspicious lesion that was rectified as a false-negative result by a positive $reTRUS_{bx}$ core from the targeted region was defined as a missed lesion by $mpMRI_{bx}$.

Statistics

Patient characteristics were described by descriptive statistics. Continuous variables (age, PSA, PSA density, prior biopsy sessions, and TRUS volume) were stratified by biopsy outcome and compared using the Mann-Whitney *U* test. The locations of the PCa-positive regions were specified on the 18-region prostate scheme in number and percentage. A McNemar test was used to compare PCa detection rates between $mpMRI_{bx}$ and $TRUS_{bx}$. Cancer significance was compared stratified by biopsy technique ($TRUS_{bx}$ vs $mpMRI_{bx}$ and cognitive-based vs software-based $mpMRI_{bx}$) using chi-squared analyses and the Fisher exact test. A P value of $<.05$ was considered statistically significant. Statistical analyses were