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Prostate Cancer

Prospective Randomized Trial Comparing Magnetic Resonance Imaging (MRI)-guided In-bore Biopsy to MRI-ultrasound Fusion and Transrectal Ultrasound-guided Prostate Biopsy in Patients with Prior Negative Biopsies

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Abstract

Background: A significant proportion of prostate cancers (PCas) are missed by conventional transrectal ultrasound-guided biopsy (TRUS-GB). It remains unclear whether the combined approach using targeted magnetic resonance imaging (MRI)-ultrasound fusion–guided biopsy (FUS-GB) and systematic TRUS-GB is superior to targeted MRI-guided in-bore biopsy (IB-GB) for PCa detection.
Objective: To compare PCa detection between IB-GB alone and FUS-GB + TRUS-GB in patients with at least one negative TRUS-GB and prostate-specific antigen $\geq$4 ng/ml.
Design, setting, and participants: Patients were prospectively randomized after multiparametric prostate MRI to IB-GB (arm A) or FUS-GB + TRUS-GB (arm B) from November 2011 to July 2014.
Outcome measurements and statistical analysis: The study was powered at 80% to demonstrate an overall PCa detection rate of $\geq$60% in arm B compared to 40% in arm A. Secondary endpoints were the distribution of highest Gleason scores, the rate of detection of significant PCa (Gleason $\geq$7), the number of biopsy cores to detect one (significant) PCa, the positivity rate for biopsy cores, and tumor involvement per biopsy core.
Results and limitations: The study was halted after interim analysis because the primary endpoint was not met. The trial enrolled 267 patients, of whom 210 were analyzed (106 randomized to arm A and 104 to arm B). PCa detection was 37% in arm A and 39% in arm B (95% confidence interval for difference, –16% to 11%; $p = 0.7$). Detection rates for significant PCa (29% vs 32%; $p = 0.7$) and the highest percentage tumor involvement per biopsy core (48% vs 42%; $p = 0.4$) were similar between the arms. The mean number of cores was 5.6 versus 17 ($p < 0.001$). A limitation is the limited number of patients because of early cessation of accrual.
Conclusions: This trial failed to identify an important improvement in detection rate for the combined biopsy approach over MRI-targeted biopsy alone. A prospective comparison between MRI-targeted biopsy alone and systematic TRUS-GB is justified.

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Patient summary: Our randomized study showed similar prostate cancer detection rates between targeted prostate biopsy guided by magnetic resonance imaging and the combination of targeted biopsy and systematic transrectal ultrasound-guided prostate biopsy. An important improvement in detection rates using the combined biopsy approach can be excluded.
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1. Introduction

The rate of prostate cancer (PCa) detection for a first systematic transrectal ultrasound-guided biopsy (TRUS-GB) is typically 30–50% [1,2]. However, a substantial proportion of men with initially negative TRUS-GB still harbor PCa and present with persistently increasing prostate-specific antigen (PSA) values. These patients pose a diagnostic dilemma. Repeated prostate biopsies using ultrasound-based techniques show PCa detection rates of 11–47% [3]. Nevertheless, clinically significant PCa can be missed even after several repeat TRUS-GBs. This applies especially to patients with anteriorly located tumors, which are frequently underdiagnosed by TRUS-GB [4,5]. Therefore, contemporary guidelines recommend the use of multiparametric MRI (mpMRI) of the prostate and MRI-guided targeted biopsy if a suspicion of PCa persists in spite of prior negative prostate biopsies [6]. In recent years, two different MRI-guided biopsy techniques have been established: direct MRI-guided biopsy, which is performed in-bore (IB-GB); and MRI-ultrasound fusion–guided biopsy (FUS-GB), which combines MRI-guided targeted biopsy and systematic TRUS-GB within one biopsy session [7–9]. In the re-biopsy setting, PCa detection rates of 9.5–59% have been reported for MRI-guided biopsy approaches [3]. However, direct comparisons of novel biopsy approaches are still pending. Owing to the rapid increase in the use of MRI-guided biopsy, the question of whether MRI-guided biopsy yields comparable PCa detection rates is of utmost importance.

The present prospective randomized study compares PCa detection rates between IB-GB (up to six cores) and FUS-GB combined with systematic 12-core TRUS-GB (up to 18 cores) in patients with at least one negative TRUS-GB and persistent suspicion of PCa.

2. Patients and methods

2.1. Study design

The detailed design of this prospective study (ClinicalTrials.gov NCT02220517) has been published previously [10]. A Consolidated Standards of Reporting Trials flow chart for the study is shown in Fig. 1. From November 2011 to July 2014, 275 consecutive patients referred to our institution by office urologists were assessed for eligibility. Patients were randomly allocated at a ratio of 1:1 to IB-GB (arm A) or FUS-GB plus systematic 12-core TRUS-GB (arm B) if mpMRI was suspicious for PCa. Overall, 210 out of 224 randomized patients (94%) were analyzed.

2.2. Study population

Patients were eligible to participate in the study if they had at least one negative TRUS-GB and persistent serum PSA levels $\geq$4 ng/ml. Exclusion criteria were known PCa, a contraindication to MRI or biopsy, and prior MRI-guided biopsy. The study was approved by our institutional review board, and written informed consent was obtained from all patients.

2.3. Study endpoints

The primary endpoint was the overall PCa detection rate. Secondary endpoints included (1) the distribution of the highest Gleason scores; (2) the detection rate for significant tumors, defined as cancers with Gleason score $\geq$7; (3) the positivity rate for biopsy cores; (4) the number of biopsy cores needed to detect one PCa or one significant PCa; (5) the percentage tumor involvement per biopsy core; and (6) for arm B, comparison of FUS-GB and systematic 12-core TRUS-GB.

2.4. Imaging

Patients underwent mpMRI performed at 3 T (Magnetom Trio; Siemens Healthcare, Erlangen, Germany) with a six-channel phased-array body coil. The imaging protocol included T1- and T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), and dynamic contrast-enhanced imaging (DCE-MRI) [11,12]. Up to three intraprostatic lesions per patient were scored on a 5-point Likert scale for each MRI sequence (T2WI, DWI, DCE-MRI). The single scores were summed up to a score of 3–15 points. After April 2012, once the Prostate Imaging Reporting and Data System (PI-RADS) classification had been published, a protocol amendment was submitted and the scoring followed the PI-RADS classification. PI-RADS single scores (PS_{single}) and PI-RADS sum scores (PS_{sum}) were assessed for each intraprostatic lesion [13]. Scoring was performed by three radiologists (M.Q., D.B., L.S.) who had 2–4 yr of experience in prostate MRI at the start of the study.

2.5. Randomization

Patients were randomly assigned in a 1:1 ratio to arm A or to arm B if they had at least one intraprostatic lesion with a total score $\geq$10 (up to April 2012) or a PS_{sum} $\geq$10 (after April 2012). A computer-generated list of random numbers was used for allocation of patients. This list was password-protected in a computer database. Patients were allocated by an independent research nurse to ensure that the randomization group could not be predicted.

2.6. Interventions

2.6.1. MR in-bore guided biopsy (arm A)

For IB-GB, patients were placed in a prone position and a needle guide fixed to a portable biopsy device (DynaTRIM; Invivo, Gainesville, FL, USA) was introduced rectally [12]. Lesions were reidentified by direct visual correlation using the initial mpMRI (marks on T2WI and DWI). The MRI patient table was moved out of the bore for needle placement. Needle-in control scans were performed in two different planes (axial and coronal/sagittal half-Fourier acquisition single-shot turbo spin-echo sequences). Two targeted cores were taken from each lesion using an MRI-compatible, 18G, fully automatic biopsy gun (Invivo). Biopsies were carried out by two radiologists (M.Q., L.S.) who had performed more than 50 procedures at the start of the study.

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