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Prostate Cancer

Risk-based Patient Selection for Magnetic Resonance Imaging-targeted Prostate Biopsy after Negative Transrectal Ultrasound-guided Random Biopsy Avoids Unnecessary Magnetic Resonance Imaging Scans

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Abstract

Background: Multiparametric magnetic resonance imaging (mpMRI) is increasingly used in men with suspicion of prostate cancer (PCa) after negative transrectal ultrasound (TRUS)-guided random biopsy. Risk-based patient selection for mpMRI could help to avoid unnecessary mpMRIs.
Objective: To study the rate of potentially avoided mpMRIs after negative TRUS-guided random biopsy by risk-based patient selection using the Rotterdam Prostate Cancer Risk Calculator (RPCRC).
Design, setting, and participants: One hundred and twenty two consecutive men received a mpMRI scan and subsequent MRI-TRUS fusion targeted biopsy in case of suspicious lesion(s) (Prostate Imaging Reporting and Data System ≥ 3) after negative TRUS-guided random biopsy. Men were retrospectively stratified according to the RPCRC biopsy advice to compare targeted biopsy outcomes after risk-based patient selection with standard (prostate specific antigen and/or digital rectal examination-driven) patient selection.
Outcome measurements and statistical analysis: The rate of potentially avoided mpMRIs by RPCRC-based patient selection in relation to the rate of missed high-grade (Gleason $\geq$ 3+4) PCa. Receiver operating characteristic curve analysis was performed to determine the area under the curve of the RPCRC for (high-grade) PCa.
Results and limitations: Of the 60 men with a positive biopsy advice, six (10%) had low-grade PCa and 28 (47%) had high-grade PCa in targeted biopsy. Of the 62 men with a negative advice, two (3%) had low-grade PCa and three (5%) had high-grade PCa. Upfront RPCRC-based patient selection would have avoided 62 (51%) of 122 mpMRIs and two (25%) of eight low-grade PCa diagnoses, missing three (10%) of 31 high-grade PCa. The area under the curve of the RPCRC for PCa and high-grade PCa was respectively 0.76 (95% confidence interval 0.67–0.85) and 0.84 (95% confidence interval 0.76–0.93).
Conclusions: Risk-based patient selection with the RPCRC can avoid half of mpMRIs after a negative prostate specific antigen and/or digital rectal examination-driven TRUS-guided random biopsy. Further improvement in risk-based patient selection for mpMRI could be made by adjusting the RPCRC for MRI-targeted biopsy outcome prediction.
Patient summary: The suspicion of prostate cancer remains in many men after a negative ultrasound-guided prostate biopsy. These men increasingly receive an often unnecessary magnetic resonance imaging (MRI) scan. We found that patient selection for MRI based on the Rotterdam Prostate Cancer Risk Calculator biopsy advice could avoid half of the MRIs.

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1. Introduction

To date, following an abnormal prostate specific antigen (PSA) level and/or digital rectal examination (DRE), the next step in assessing the presence of prostate cancer (PCa) is a transrectal ultrasound (TRUS)-guided random biopsy. This combination of tests is known to result in approximately 60–75% benign biopsy results, questioning: (1) the actual need of the biopsy, and (2) the specificity of the biopsy [1,2]. Random TRUS-guided biopsy is especially poor at sampling the anterior, midline, and apex region of the prostate, leading to an underdiagnosis of PCa [3,4]. Although relatively expensive, multiparametric magnetic resonance imaging (mpMRI) is suggested and increasingly used instead of repeated TRUS-guided biopsy in men with a sustained suspicion of PCa after negative random biopsy [5]. Currently available data show that targeted biopsies of suspicious mpMRI lesions improve the detection of significant PCa, especially after previous negative random biopsy [6–8]. It has already been shown that applying an upfront multi-variable risk-based approach can reduce the rate of unnecessary TRUS-guided random biopsies by approximately 30% [9–12]. Therefore, we question whether upfront multi-variable risk stratification could also be used before the decision to perform mpMRI in the many men confronted with a negative random biopsy while clinical suspicion of PCa remains. The objective of this study is to assess the rate of potentially avoidable mpMRIs by comparing risk-based patient selection using the Rotterdam Prostate Cancer Risk calculator (RPCRC) with PSA/DRE-driven patient selection.

2. Material and methods

2.1. Study population

From September 2013 until May 2015 a total of 122 men were referred from 12 different peripheral institutions to our tertiary referral center for a mpMRI scan after one or more previous negative random TRUS-guided biopsies. These men had a sustained suspicion of PCa according to the referring urologist, based on PSA (kinetics). The indication for the primary TRUS-guided biopsy in all referring centers was a PSA $\geq$ 3.0 ng/ml and/or an abnormal DRE, in accordance with the European Association of Urology guidelines [5]. The biopsy scheme for the primary TRUS-guided biopsy consisted of sextant lateral biopsies with a minimum of two additional medial cores in all referring centers. The referring urologist ordered the performance of the mpMRI and targeted biopsy with or without additional random biopsy in our expert center. Treatment and follow-up after the mpMRI and targeted biopsy took place in the referring institutions. Data of the mpMRI and targeted biopsy were included in our prospective, institutional review board approved database. Men analyzed in this study have not been included in previous reports.

2.2. mpMRI protocol

The mpMRI protocol consisted of T2-weighted imaging, diffusion-weighted imaging with apparent diffusion coefficient reconstructions, and dynamic contrast enhanced imaging according to the European Society of Urogenital Radiology guidelines [13]. MRIs were performed on a 3-T system (Discovery MR750, General Electric Healthcare) using a 32-channel pelvic phased-array coil. The images were analyzed by a single expert radiologist with more than 4 yr of experience in prostate mpMRI at the start of this study. Individual lesions, as well as the whole prostate, were scored on the Prostate Imaging Reporting and Data System (PI-RADS) 5-point likelihood scale for significant PCa [13]. Individual lesions with a PI-RADS score $\geq$ 3 were classified as suspicious. Suspicious lesions were delineated on the T2-weighted imaging, based on the areas with the lowest b-values on the apparent diffusion coefficient-maps.

2.3. Targeted biopsy with the MRI-US fusion technique

MRI-targeted biopsy was performed using the MRI-US fusion technique. The MRI-US fusion was performed with the UroStation (Koelis). The UroStation implements elastic registration to fuse the MRI and three-dimensional TRUS images and allows guiding and the recording of biopsy core locations on the images [14]. All suspicious MRI lesions (PI-RADS $\geq$ 3) were targeted with two to four cores, depending on the lesion size. All biopsy procedures were performed by two experienced operators (urologists in training) who had managed approximately 50 cases at the beginning of this study. In a subset of men additional random biopsies were taken on the order of the referring urologist. The random biopsy outcomes of these men were not analyzed within this study.

2.4. Pathological examination of the targeted biopsy cores

All targeted biopsy cores were examined by one expert uro-pathologist. Gleason score (GS) 3+3 PCa was defined as low-grade, while GS $\geq$ 3+4 PCa was classified as high-grade. The primary negative TRUS-guided biopsy specimens performed in the referring institutions were not centrally reviewed.

2.5. Retrospective assessment of the RPCRC biopsy advice

The RPCRC is a prediction model based on data of 3624 initially screened and 2896 repeatedly screened men in the European Randomized study of Screening for Prostate Cancer Rotterdam [9]. In the screening arm of the European Randomized study of Screening for Prostate Cancer Rotterdam a sextant TRUS-guided biopsy was performed in men with a PSA $\geq$ 4.0 ng/ml and/or abnormal DRE, and later on in men with a PSA $\geq$ 3.0 ng/ml [15]. The RPCRC uses PSA, DRE, TRUS (hypoechoic lesions), and TRUS-measured prostate volume as prebiopsy variables and takes a previously performed negative biopsy into account. The RPCRC calculates the risk of finding PCa and the risk of finding high-grade (GS $\geq$ 3+4) and/or locally advanced (T-stage $\geq$ T2C) PCa in random biopsy. The RPCRC is available on the internet (www.prostatecancer-riskcalculator.com) and as an app for iOS/Android. The established PCa risk cut-off values to advise a TRUS-guided random biopsy are a risk of any PCa $\geq$ 20% and/or a risk of high-grade and/or locally advanced PCa $>$ 3% [9]. To assess whether these established PCa risk thresholds could also be used to select men for mpMRI, the RPCRC PCa risks and biopsy advice were retrospectively determined in all men using the preMRI clinical variables.

2.6. Statistical analysis

Statistically significant differences in patient characteristics after risk-stratification were assessed using the Mann-Whitney U test for continuous data and the chi-square test for categorical data. The rate of (high-grade) PCa in targeted biopsy was compared between the RPCRC-positive and RPCRC-negative group. The diagnostic accuracy of the RPCRC for any-grade and high-grade PCa in targeted biopsy was quantified using receiver operating characteristic curve analysis. Calibration of the RPCRC for any-grade and high-grade PCa in targeted biopsy was explored graphically by the construction of validation plots. Statistical tests were 2-sided with the criterion of significance set at