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Probability of Prostate Cancer Diagnosis following Negative Systematic and Targeted MRI: Transrectal Ultrasound Fusion Biopsy: A Real-Life Observational Study

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Abstract
Introduction: The risk of occult prostate carcinoma (PCa) after negative multiparametric MRI (mpMRI)-transrectal fusion biopsy (F-Bx) is unknown. To determine the false-negative predictive value, we examined PCa detection after prior negative F-Bx. ***Methods:*** Between December 2012 and November 2016, 491 patients with suspected PCa and suspicious mpMRI findings underwent transrectal F-Bx. Patients with benign pathology (n = 191) were eligible for our follow-up (FU) survey. Patient characteristics and clinical parameters were correlated to subsequent findings of newly detected PCa. ***Results:*** Complete FU with a median of 31 (interquartile range: 17–39) months was available for 176/191 (92.2%) patients. Of those, 54 men had either surgical interventions on the prostate or re-Bxs. Newly detected PCa was evident in 14/176 (7.95%) patients stratified to ISUP ≤2 in 10 and ≥3 in 4 cases. The comparison of patients with newly detected PCa to those without cancerous findings in FU showed significant differences in prostate-specific antigen (PSA) density (0.16 vs. 0.13 ng/mL^2) and prostate volume (45 vs. 67 mL, both $p < 0.05$). Both factors are significant predictors for newly detected cancer after initial negative F-Bx. ***Conclusion:*** Only PSA density (>0.13 ng/mL^2) and small prostate volume are significant predictors for newly detected PCa after initial negative F-Bx. Despite negative mpMRI/TRUS F-Bx results, patients should be further monitored due to a risk of developing PCa over time. Notwithstanding the limitation of our study that not all patients underwent another Bx, we assume that the false-negative rate is low but existing. Our data represent a real-world scenario.

Introduction

The conventionally used method to diagnose prostate cancer (PCa) is the transrectal 12-core systematic ultrasound-guided (TRUS) biopsy (Bx). Because of limitations

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in terms of cancer visualization and characterization, up to 35% of tumors are not detected, and clinically insignificant cancers could be overrepresented during the first Bx attempt [1]. Therefore, the risk for a re-Bx after previous negative systematic Bx is 12% at 1 year and increases to 38% at 5 years [2].

To increase the detection rate of high-grade PCa compared to the conventional systematic approach (up to 24 cores in saturation protocols), current guidelines strongly (level of evidence 1a) recommend a multiparametric MRI (mpMRI) of the prostate for patients with suspected PCa [3, 4]. Suspicious lesions, usually described by "Prostate Imaging-Reporting and Data System" (PI-RADS), are significantly associated with cancerous findings in whole-mount sections after prostatectomy between 29 and 100% [5]. Based on mpMRI results, and regarding the risk of side effects (e.g., pain, infection, and bleeding), decision can be made to omit a consecutive Bx or to perform a combined Bx using systematic and mpMRI-targeted Bxs (level of evidence 2a) [6, 7]. Studies using a combined approach with targeted and systematic sampling routinely demonstrate higher yield of clinically significant cancer [8–11].

Focusing on the PROMIS trial's key findings, up to 25% of unnecessary Bx could be avoided by using mpMRI as a tool of pre-Bx risk-stratification [12]. Furthermore, the combination of suspicious MRI lesions and prostate-specific antigen (PSA) density may reduce the number of unnecessary Bxs [13]. The PROMIS trial showed a higher detection rate of 38% compared to 26% for clinically significant cancer when performing mpMRI-targeted Bx instead of systematic Bx. Follow-up (FU) of patients after initial negative mpMRI-targeted Bx was only 3% and therefore too small for a meaningful statement concerning undetected cancer [14].

However, in daily clinical practice, it is not uncommon that targeted Bx reveal benign histology despite suspicious mpMRI lesions. The exact false-negative rate of mpMRI-targeted Bx (suspicious mpMRI lesions and benign Bx histology) is still unknown since studies show a high level of heterogeneity by including, for example, patients with previously diagnosed PCa under active surveillance therapy [15].

The purpose of our study was to determine the false-negative rate of mpMRI/TRUS fusion biopsy (F-Bx) during an oncological FU in form of a real-life observational study. Furthermore, we want to assess risk factors based on Bx/patient characteristics to predict cancer detection during FU.

Materials and Methods

Data Source and Study Population

After receiving ethical study approval by an institutional research committee (Ruhr-University Bochum, 17-6212), we focused on men who underwent a transrectal F-Bx in local anesthesia (n = 491) between December 2012 and November 2016 to ensure a longer FU timeframe. All Bxs were performed after rectal swab analysis and prophylactic subscription of gyrase inhibitors (e.g., ciprofloxacin) using the "Real-time Virtual Sonography technique" on a HI VISION Preirus ultrasound device (Hitachi Medical®, Tokyo, Japan). The Bx protocol consisted of 12 systematic, and 2 targeted Bx cores for every suspicious mpMRI lesion with a PI-RADS score ≥3. Fusion-guided Bxs were taken based on electromagnetic tracking (EM) through an endorectal endfire probe. MR image acquisition (Philips® Ingenia 3.0 Tesla, Germany) protocol was based on T1/T2-weighted axial, coronal, and sagittal DCE imaging without an endorectal coil. Pictures were analyzed using PI-RADS version 2 by 1 well-trained radiologist with 8 years of experience. For a better comparison in a homogeneous cohort, we converted all participants with initial PI-RADS version 1 to version 2 [16]. Men were either Bx naïve or had a re-Bx at time of our F-Bx.

Patients with inconspicuous mpMRI findings (n = 91), PCa diagnosis (n = 209), and missing FU data (n = 15) were excluded. The final study population consisted of 176 men with negative Bx results but suspicious mpMRI findings.

Baseline Characteristics

We abstracted prostate-specific variables at time of F-Bx including PSA (ng/mL), PSA density (ng/mL^2), prostate volume (mL), digital rectal examination (DRE) findings (suspicious vs. unsuspicious), history of prior Bx sessions (yes vs. no), number of prior Bx sessions (0, 1, 2, ≥3), and number of target lesions (1, 2, ≥3). For each patient, we registered the highest PI-RADS score (3, 4, or 5) and the maximum diameter (mm) of all described lesions.

Follow-Up

FU was in February 2018 with a self-created questionnaire evaluating further Bx sessions or any kind of prostate surgery (online suppl. Appendix 1; see www.karger.com/doi/10.1159/000513075). Indication for further tissue sampling was based on individual cancer risk assessments or symptoms of bladder outlet obstruction (BOO). Cancerous findings were stratified according to the "International Society of Urological Pathologists" (ISUP) classification [17]. Furthermore, median value of PSA density was used to stratify patients with new PCa findings according to ISUP classification. In addition, our survey recorded all Bx side effects according to the Clavien-Dindo classification [18].

Statistical Analyses

Continuous variables were reported as the median and interquartile range (IQR), whereas the categorical variables as frequencies and proportions. As statistical analyses, we performed Mann-Whitney U test, Fisher's exact test, and Pearson's χ^2 test to compare continuous and categorical variables. Cox regression analysis was used to calculate hazard ratios (HR) and 95% confidence intervals (CI) to predict PCa during FU. Survival estimations and cumulative hazards were generated using the Kaplan-Meier method.

All p values were two sided, with a statistical significance set at $p < 0.05$. Statistical analyses were performed using SPSS, version 25 (IBM, Chicago, IL, USA).

Table 1. Baseline characteristics for the whole cohort (n = 176) and stratified by secondary PCa in the FU

	Total in FU; n = 176 (100%)	No PCa in FU; n = 162 (92.05%)	PCa in FU; n = 14 (7.95%)	p value
Age, median (IQR), years	63 (58–69)	62 (58–69)	65.5 (61.8–71.25)	0.082
PSA, median (IQR), ng/mL	9.4 (6.7–13.0)	9.4 (6.7–13.0)	9.1 (6.9–12.7)	0.987
PSA density, median (IQR), ng/mL^2	0.134 (0.096–0.191)	0.132 (0.086–0.189)	0.160 (0.138–0.331)	*0.007*
Prostate vol, median (IQR), mL	65 (51.3–84.8)	67 (55–88)	45 (38.5–51.8)	*0.001*
Max PI-RADS score, %				
3	25.4	26.4	14.3	0.499
4	49.7	49.1	57.1	
5	24.9	24.5	28.6	
DRE, %				
Unsuspicious	70.4	71.0	64.3	0.558
Suspicious	29.6	29.0	35.7	
History of prior Bx sessions, %				
Yes	89.8	88.8	100	0.365
No	10.2	11.2	0	
Number of prior Bx sessions, %				
0	10.2	11.2	0	0.518
1	43.4	43.4	42.9	
2	27.1	25.7	42.9	
≥3	19.3	19.7	14.1	
Number of target lesions, %				
1	58.5	59.3	50.0	0.191
2	27.8	28.4	21.5	
≥3	13.7	12.3	28.5	
Max MRI diameter of MRI lesions, median (IQR), mm	12.5 (10–17)	13 (10–17)	12 (10–19)	0.992

PCa, prostate cancer; FU, follow-up; IQR, interquartile range; PSA, prostate-specific antigen; vol, volume; DRE, digital rectal examination; Bx, biopsy; PI-RADS, Prostate Imaging-Reporting and Data System. p values <0.05, shown in italics, are significant.

Results

Baseline Characteristics

Overall, 191 men could be included in the analysis. There were 176/191 (92.14%) men with negative Bx results but conspicuous mpMRI findings eligible for our cohort with a median age of 63 years. Of this whole cohort, 89.8% received a re-Bx, while 10.2% had their first Bx. DRE findings were unsuspicious in 70.4%. Median PSA, PSA density, and prostate volume were 9.4 ng/mL, 0.1 ng/mL^2, and 65 mL (Table 1).

Follow-Up

In a median FU of 31 (IQR: 17–39) months for the whole cohort, 54/176 (30.7%) men had different prostate interventions with tissue sampling while the other 69.3% did not have another intervention on the gland. From the 54 men, 16 patients (29.6%) had an intervention of BOO, while 38 men (70.4%) had a second Bx after our negative F-Bx. Median FU was 18 (IQR: 6–42.25) months for those 54 patients until secondary prostate intervention. That said, 38/176 (21.6%) individuals with complete FU had another Bx.

With a median FU of 36.5 (IQR: 10.3–54.3) months, 14/176 patients (7.95%), received the diagnosis of PCa by either additional Bx (n = 2) or surgical intervention for BOO (n = 12). Of those, 10 men (71.4%) were found to have PCa ISUP-1/2, while ISUP ≥ 3 was found in 4 men (28.6%). Furthermore, of the 12 individuals with BOO intervention, 8 men (66.7%) had an ISUP-1/2 and 4 patients (33.3%) an ISUP ≥ 3 in their pathology examination. Retrospectively, 14.3, 57.1, and 28.6% of those patients had a maximum PI-RADS score of 3, 4, and 5 at initial F-Bx. Lesions were allocated to ventral and dorsal parts of the prostate in 61.5 and 38.5%. The distribution to base, middle, or apex was 42.3, 30.8, and 26.9%, respectively. Compared to those patients without any cancerous findings or interventions on the gland during FU (n = 162), there was no statistically significant difference regarding the median values for age, maximum lesion di-

Table 2. Univariable Cox regression analysis examining the association of pre-Bx risk factors with the detection of PCa

	HR	95% CI	*p* value
Age, ref. below median 63, years	2.448	0.817–7.336	0.110
PSA, ref. below median 9.4, ng/mL	1.097	0.384–3.137	0.863
PSA density, ref. below median (<0.13),* ng/mL	3.619	1.005–13.003	*0.049*
Max MRI diameter of MRI lesions, ref. below median 12.5, mm	1.194	0.339–3.578	0.751
Prostate vol, ref. below median 65, mL	0.95	0.061–1.249	0.095
DRE, ref.: unsuspicious	2.030	0.067–6.115	0.211

Bx, biopsy; PCa, prostate cancer; HR, hazard ratio; CI, confidence interval; PSA, prostate-specific antigen; vol, volume; DRE, digital rectal examination; ref., reference; AIC, Akaike information criterion. *p* value <0.05, shown in italics, is significant. * Using backward selection according to AIC, this variable was the most informative variable of all variables presented.

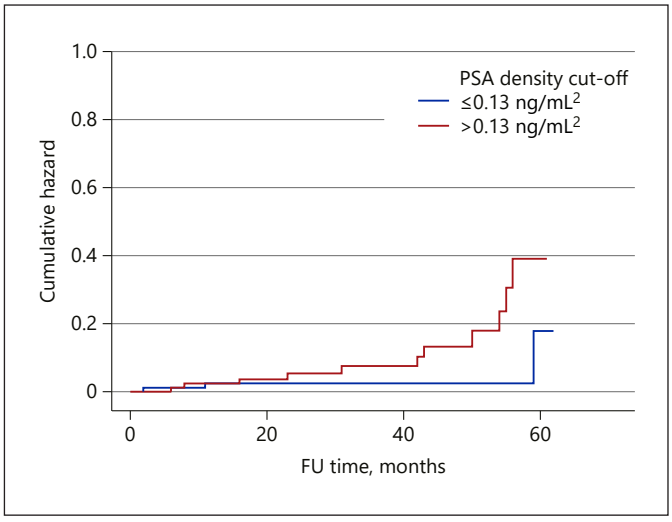

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Fig. 1. Cumulative hazard function for prostate cancer detection according to PSA density ($n = 175$; log rank, $p = 0.035$). PSA, prostate-specific antigen; FU, follow-up.

ameter, and PSA. Nevertheless, there was a significant difference in PSA density (0.132 vs. 0.160 ng/mL^2; $p = 0.007$) and prostate volume (67 vs. 45 mL; $p = 0.001$) (Table 1). Furthermore, univariable Cox regression analysis shows that PSA density (HR:3.619; 95% CI:1.005–13.003; $p = 0.049$) and prostate volume (HR:0.961; 95% CI:0.929–0.994; $p = 0.020$) are significant predictors for PCa (Table 2). Moreover, multivariate Cox regression analysis with all prostate-specific variables from Table 1 displays the impact of PSA density on PCa detection (HR:3.779; 95% CI:1.038–13.767; $p = 0.044$). In case of a PSA density >0.13 ng/mL^2, ISUP-1/2 cancer was present in 8 (72.7%) patients, whereas 3 (27.3%) men showed ISUP-3. Cumulative hazard function revealed significant different PCa detection rates during FU when using PSA density of <0.13 ng/mL^2 (Fig. 1).

Furthermore, clinical complications were part of our survey. According to the questionnaires, 50% did not report any problems within 5 days after F-Bx (CDC0). The most frequent minor complications were hematuria (34.86%), hematospermia (29.55%), or dysuria (8.52%) (all CDC1). Only 2/176 patients (1.14%) experienced prostatitis with consecutive sepsis (CDC3a).

Discussion

We followed up all patients with a self-created questionnaire who received an F-Bx between December 2012 and November 2016 at our institution. The current study evaluates a homogenous cohort after negative F-Bx. In comparison to the majority of published data, the current work did not include patients with previously diagnosed PCa under active surveillance or patients with ≤PI-RADS 2 lesions [15, 19, 20].

During early FU, the procedure is associated with low risk of major complications (CDC3) and therefore a safe method [21]. During later FU, almost 8% of men with initial negative F-Bx will receive the diagnosis of PCa. According to our results, PSA density (HR: 3.619) and prostate volume (HR: 0.961) are significant predictors for newly detected PCa. Similar to the multivariable Cox regression analysis of Panebianco et al. [22], our analyses show that a high PSA density is associated with a subsequent PCa diagnosis. In contrast to their study with previous negative mpMRI findings, all patients in our study had suspicious lesions according to the PI-RADS proto-

col [22]. Men with newly detected PCa had smaller prostate volume compared to patients without PCa in FU (45 vs. 67 mL). Those results are in concordance with published literature, especially in patients with PSA around 9.0 ng/mL [23]. In our cohort, 21.6% had another Bx in a median FU of 18 months. Despite a similar FU period like Ploussard et al. [2] (19 months), the re-Bx rate was lower in our study (21.6 vs. 31%). The difference between both studies is that in contrast to our mpMRI-based-F-Bx, Ploussard et al. [2] performed systematic Bx alone. Furthermore, we included men with BOO surgery for a higher chance of histopathology results. But, similar to our study, the same factors for newly detected PCa were found to be of high predictive value (high PSA density and low prostate volume) [2]. Hong et al. [20] could show a PCa detection rate of 41.2% in their FU which consists of re-MRI and F-Bx, in contrast to our study without a standardized FU schedule. That shows, how important an appropriate FU for patients with a negative Bx but suspicious MRI findings is [20].

Reasons for negative F-Bx results and following secondary cancer diagnosis in initial suspicious mpMRI findings are manifold and may be caused by false-positive mpMRI results and/or by a false-negative Bx. According to Gordetsky et al. [24], especially, lesions in the central and anterior parts of the prostate were found to imitate as transitional tumors due to low T2 signals based on PI-RADS scoring in version 2. Our results show 61% suspicious ventral lesions in men with negative F-Bx but later PCa diagnosis. Moreover, as stated by the authors, those regions could be misinterpreted by radiologists [24]. The success of a F-Bx is directly correlated to the radiologist's experience and skill for identifying suspicious lesions in mpMRI and minimizing false-positive results. Prostate deformity, triggered by different bladder fillings, patient positions, or respiratory activity at the time of mpMRI and TRUS, has an impact on image registration. Thus, we gave special attention to analyze the anatomical prostate boundaries at the procedures beginning to minimalize the deviations in prostate imaging [25]. For better examinations, mpMRI and F-Bx were performed after voiding.

Furthermore, a well-trained radiologist can help to avoid unnecessary Bxs and indicate Bxs with a high chance of PCa detection [26]. In a study by Sonn et al. [26], 9 radiologists with different levels of experience had a variation in PI-RADS distribution and cancer detection. For example, an average of 13% of clinically significant cancer was found in PI-RADS 2 lesions. Usually, patients with PI-RADS score <3 do not undergo F-Bx as proposed in the PROMIS trial [12]. Besides, the variability of high and low volume centers/radiologists for the difference in numbers for PI-RADS lesions is shown in the PRECISION trial [14]. To minimize the interobserver variability, 1 well-trained radiologist took part in our study.

In the current study, an EM-based F-Bx system was used, which allows the examiner to move the endorectal endfire probe with multiple degrees of freedom. The system is limited by potential operator errors due to free-hand probe guidance at time of Bx, which may lead to missing target lesions [27]. To minimize these factors, devices with semi-robotic guidance can overcome the limitations of EM systems. Westhoff et al. [28] compared an EM-based fusion device and an elastic fusion semi-robotic system and demonstrated a higher mismatch potential for the EM system. The rate of missing small lesions (5 mm) was significantly higher for the EM system (44.4%) compared to the semi-robotic system (11.1%) [28]. Another factor influencing PCa detection is the learning curve associated with F-Bx. One study compared the performance of performing target and systematic Bxs between senior urologists and urology residents. This study found out that experienced urologists yield a higher PCa detection rate than beginners (49 vs. 23%) [29]. At out institution, F-Bx are always carried out under guidance of experienced colleagues to bring beginners as quickly as possible to a high level of expertise. Even though all our biopsies had high mpMRI PI-RADS scores [3–5], as was later recommended by the consensus statement of Rosenkrantz et al. [30] in 2016, there is still a risk of missing cancer. In this case we also recommend continuing clinical and laboratory controls or possibly re-Bxs. If those factors are minimized, the transrectal F-Bx method may be limited by the prostate volume and the area of the region of interest. Halstuch et al. [31] showed that there is a needle tip deflection of 1.77 (IQR: 1.35–2.47) mm for the transrectal way, which can lead to mistargeting of small suspicious PI-RADS lesions especially in the ventral/anterior area of the gland. But the maximum mpMRI lesion size in both groups of our cohort was not significantly different ($p = 0.992$). Other authors, like Sonn et al. [26], hypothesized that the perineal Bx method has an advantage for those ventral/anterior regions, due to the higher yield of clinically significant cancer of about 70% in the anterior stroma. Nevertheless, a targeted transrectal Bx should reach anterior lesions, irrespective of the needle approach. After all, 40% of the positive mpMRI lesions in our cohort of men with later findings of secondary PCa were peripheral and therefore did not explain the false-negative F-Bx of missing the anterior re-

gion. Furthermore, we cannot describe the exact area of newly detected PCa due to histology extraction method.

Finally, the sepsis rate of our study was lower than already published. Reasons could be the risk-adapted pathway of rectal swabs for immunocompromised patients (e.g., diabetes) and men who have taken an antibiotic within the last 6 months. Those patients received their antibiotic according to the testing [21].

Some limitations of this study should be addressed. This is a retrospective and single-center study. Based on this study design, the small cohort has meaningful results. Furthermore, we do not know the precise newly detected PCa location according to 14.3% of PCa results, which came from TUR material. We are not able to give any information if a potentially performed mpMRI has already shown the tumor or not. That said, the tumor could be either newly detected PCa or been overlooked at the time of F-Bx. Furthermore, 122 men without further indication for re-Bx based on individual risk evaluation did not undergo any tissue sampling of the prostate in the FU. It could be assumed that some cases of occult PCa are not diagnosed. However, even in the case of re-Bx, occult cancer foci can be missed, and only a whole-mount analysis could reveal the true burden of cancer. Due to ethical reasons, this was not part of our study protocol. The present study is limited by all the drawbacks inherent to a retrospective cohort but represents a real-world scenario with a FU according to national and international guideline recommendations. Furthermore, we cannot provide detailed information about indication and/or imaging prior re-Bx of the 2 men with tumor. Last, the effect of the examiners learning curve and experience could have an impact on the PCa detection rate.

Conclusions

Men with PI-RADS 3 or 4 should be observed clinically with DRE, PSA monitoring, TRUS imaging, and re-mpMRI [32]. Our results suggest a PSA density threshold of >0.13 ng/mL^2 to indicate a re-Bx, especially in the case of PI-RADS 5 lesions, to exclude a personal operator error. Based on our data, patients with suspicious mpMRI but negative Bx should be monitored as there is still a low but existing risk of occult PCa.

Statement of Ethics

Ethical study approval by an institutional research committee, Ruhr-University Bochum, 17-6212.

Conflict of Interest Statement

The authors have nothing to declare.

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There was no extra founding.

Author Contributions

M. Brock, N. von Landenberg, and J. Noldus: protocol/project development. J. Hanske, S. Berg, and J. Wald: data collection or management. N. von Landenberg, M. Brock, and F. Roghmann: data analysis. N. von Landenberg and M. Brock: manuscript writing/editing.

References

1 Cooperberg MR, Broering JM, Kantoff PW, Carroll PR. Contemporary trends in low risk prostate cancer: risk assessment and treatment. J Urol. 2007;178(3 Pt 2):S14–9.
2 Ploussard G, Nicolaiew N, Marchand C, Terry S, Allory Y, Vacherot F, et al. Risk of repeat biopsy and prostate cancer detection after an initial extended negative biopsy: longitudinal follow-up from a prospective trial. BJU Int. 2013;111(6):988–96.
3 Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft Deutsche Krebshilfe, AWMF): Interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms, Langversion 5.1, 2019, AWMF Registernummer: 043/022OL. Available from: http://www.leitlinienprogramm-onkologie.de/leitlinien/prostatakarzinom/. abgerufen am 2020 Oct 10.
4 EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2020. ISBN 978-94-92671-07-3.
5 Junker D, Quentin M, Nagele U, Edlinger M, Richenberg J, Schaefer G, et al. Evaluation of the PI-RADS scoring system for mpMRI of the prostate: a whole-mount step-section analysis. World J Urol. 2015;33(7):1023–30.
6 Borghesi M, Ahmed H, Nam R, Schaeffer E, Schiavina R, Taneja S, et al. Complications after systematic, random, and image-guided prostate biopsy. Eur Urol. 2017;71(3):353–65.
7 Loeb S, van den Heuvel S, Zhu X, Bangma CH, Schröder FH, Roobol MJ. Infectious complications and hospital admissions after prostate biopsy in a European randomized trial. Eur Urol. 2012;61(6):1110–4.
8 Tang Y, Liu Z, Tang L, Zhang R, Lu Y, Liang J, et al. Significance of MRI/transrectal ultrasound fusion three-dimensional model-guided, targeted biopsy based on transrectal ultrasound-guided systematic biopsy in prostate cancer detection: a systematic review and meta-analysis. Urol Int. 2018;100(1):57–65.
9 Ahdoot M, Wilbur AR, Reese SE, Lebastchi AH, Mehralivand S, Gomella PT, et al. MRI-targeted, systematic, and combined biopsy for prostate cancer diagnosis. N Engl J Med. 2020;382(10):917–28.

10 Siddiqui MM, Rais-Bahrami S, Turkbey B, George AK, Rothwax J, Shakir N, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. JAMA. 2015; 313(4):390–7.
11 Drost FH, Osses DF, Nieboer D, Steyerberg EW, Bangma CH, Roobol MJ, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. Cochrane Database Syst Rev. 2019; 4(4):Cd012663.
12 Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet. 2017;389(10071):815–22.
13 Záleský M, Stejskal J, Adamcova V, Hrbáček J, Minarik I, Pavlicko A, et al. Use of prostate specific antigen density combined with multiparametric magnetic resonance imaging improves triage for prostate biopsy. Urol Int. 2019;103(1):33–40.
14 Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med. 2018; 378(19):1767–77.
15 Bloom JB, Hale GR, Gold SA, Rayn KN, Smith C, Mehralivand S, et al. Predicting gleason group progression for men on prostate cancer active surveillance: role of a negative confirmatory magnetic resonance imaging-ultrasound fusion biopsy. J Urol. 2019;201(1):84–90.
16 Rothke M, Blondin D, Schlemmer HP, Franiel T. [PI-RADS classification: structured reporting for MRI of the prostate]. Rofo. 2013; 185(3):253–61.
17 Egevad L, Delahunt B, Srigley JR, Samaratunga H. International Society of Urological Pathology (ISUP) grading of prostate cancer: an ISUP consensus on contemporary grading. APMIS. 2016;124(6):433–5.
18 Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009; 250(2):187–96.
19 Boesen L, Nørgaard N, Løgager V, Thomsen HS. Clinical outcome following low suspicion multiparametric prostate magnetic resonance imaging or benign magnetic resonance imaging guided biopsy to detect prostate cancer. J Urol. 2017;198(2):310–5.
20 Hong CW, Walton-Diaz A, Rais-Bahrami S, Hoang AN, Türkbey B, Stamatakis L, et al. Imaging and pathology findings after an initial negative MRI-US fusion-guided and 12-core extended sextant prostate biopsy session. Diagn Interv Radiol. 2014;20(3):234–8.
21 Berger AP, Gozzi C, Steiner H, Frauscher F, Varkarakis J, Rogatsch H, et al. Complication rate of transrectal ultrasound guided prostate biopsy: a comparison among 3 protocols with 6, 10 and 15 cores. J Urol. 2004;171(4):1478–1.
22 Panebianco V, Barchetti G, Simone G, Del Monte M, Ciardi A, Grompone MD, et al. Negative multiparametric magnetic resonance imaging for prostate cancer: what's next? Eur Urol. 2018;74(1):48–54.
23 Al-Azab R, Toi A, Lockwood G, Kulkarni GS, Fleshner N. Prostate volume is strongest predictor of cancer diagnosis at transrectal ultrasound-guided prostate biopsy with prostate-specific antigen values between 2.0 and 9.0 ng/mL. Urology. 2007;69(1):103–7.
24 Gordetsky JB, Ullman D, Schultz L, Porter KK, Del Carmen Rodriguez Pena M, Calderone CE, et al. Histologic findings associated with false-positive multiparametric magnetic resonance imaging performed for prostate cancer detection. Hum Pathol. 2019;83:159–65.
25 Cash H, Günzel K, Maxeiner A, Stephan C, Fischer T, Durmus T, et al. Prostate cancer detection on transrectal ultrasonography-guided random biopsy despite negative real-time magnetic resonance imaging/ultrasonography fusion-guided targeted biopsy: reasons for targeted biopsy failure. BJU Int. 2016; 118(1):35–43.
26 Sonn GA, Fan RE, Ghanouni P, Wang NN, Brooks JD, Loening AM, et al. Prostate magnetic resonance imaging interpretation varies substantially across radiologists. Eur Urol Focus. 2019;5(4):592–9.
27 Franz T, von Hardenberg J, Blana A, Cash H, Baumunk D, Salomon G, et al. [MRI/TRUS fusion-guided prostate biopsy: value in the context of focal therapy]. Urologe A. 2017; 56(2):208–16.
28 Westhoff N, Siegel FP, Hausmann D, Polednik M, von Hardenberg J, Michel MS, et al. Precision of MRI/ultrasound-fusion biopsy in prostate cancer diagnosis: an ex vivo comparison of alternative biopsy techniques on prostate phantoms. World J Urol. 2017;35(7): 1015–22.
29 Westhoff N, Haumann H, Kriegmair MC, von Hardenberg J, Budjan J, Porubsky S, et al. Association of training level and outcome of software-based image fusion-guided targeted prostate biopsies. World J Urol. 2019;37(10): 2119–27.
30 Rosenkrantz AB, Verma S, Choyke P, Eberhardt SC, Eggener SE, Gaitonde K, et al. Prostate magnetic resonance imaging and magnetic resonance imaging targeted biopsy in patients with a prior negative biopsy: a consensus statement by AUA and SAR. J Urol. 2016;196(6):1613–8.
31 Halstuch D, Baniel J, Lifshitz D, Sela S, Ber Y, Margel D. Assessment of needle tip deflection during transrectal guided prostate biopsy: implications for targeted biopsies. J Endourol. 2018;32(3):252–6.
32 Ullrich T, Arsov C, Quentin M, Laqua N, Klingebiel M, Martin O, et al. Analysis of PI-RADS 4 cases: management recommendations for negatively biopsied patients. Eur J Radiol. 2019;113:1–6.