Dynamic Evaluation of MRI-targeted, Systematic and Combined Biopsy for Prostate Cancer Diagnosis through 10 Years of Practice in a Single Institution

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Conflict of Interest: Pierre Mozer has patents for the targeted biopsy device and has been involved in the license of the Koelis UroStation system. All other authors have nothing to disclose

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Abstract

Purpose: To perform a dynamic evaluation of the prostate cancer (PCa) detection rate according to the biopsy strategy over 10 years of practice in a single institution that pioneered MRI-targeted fusion biopsy (MRI-TB).

Methods This stage 4 IDEAL study prospectively included all consecutive patients who underwent transrectal prostate biopsy for clinically suspected PCa between January 2010 and November 2020. Patients with positive MRI (PIRADS score ≥3) underwent both MRI-TB and systematic biopsy (SB) while those with negative MRI (PIRADS score <3) underwent SB only. The main outcome was the evolution of the detection rate of clinically relevant PCa (csPCa ; grade ≥2). The secondary outcome was the change in PCa detection rate according to the biopsy method.

Results: A total of 2942 men underwent prostate MRI and a prostate biopsy: 2322 underwent MRI-TB and 620 had SB only. The detection rate of csPCa increased 2.5-fold from 23% to 58%. The detection rate of PCa and csPCa was significantly higher in patients who underwent MRI-TB compared to those who underwent SB only (67% vs. 52 % and 40% vs. 32%, respectively (P<0.001 for both comparisons)). The number of csPCa diagnosed by MRI-TB increased linearly over the study period and represented the majority of PCa diagnoses after 2016.

Conclusion: Implementation of MRI-TB in patients with positive MRI led to improved detection of csPCa.

Key words (MeSH): Prostate neoplasm; Diagnostic; Targeted biopsy; Multiparametric magnetic resonance imaging

Introduction

The prognosis of patients with localized prostate cancer (PCa) mainly depends on the histopathological features detected in a prostate biopsy.[1] Therefore, the ability to detect patients with the highest grade of PCa is essential in order to provide counseling on the best therapeutic strategy. Before the advent of prostate multiparametric magnetic resonance imaging (MRI), PCa diagnosis was based on systematic 12-core biopsy in men with elevated serum prostate-specific antigen (PSA) or an abnormal digital rectal examination. This strategy led to false-negative biopsies, inaccurate grade diagnosis, and over-detection of clinically indolent PCa (grade 1).[2-4]

Recent advances in prostate MRI have led to better characterization of the underlying histopathology of the prostate allowing the identification of target abnormalities.[5-7] As for other cancers, the diagnostic strategy for PCa has evolved towards biopsies targeting suspicious lesions observed on MRI.[8] Recent studies have shown that the diagnostic performance of MRI-targeted biopsy (MRI-TB) was improved for high-grade lesions when compared to standard biopsies.[2, 9-11] However, these studies involved expert urologists and radiologists, and some were multicentric. Moreover, the change in detection rate over time after the implementation of an MRI-TB program has never been assessed. Therefore, the generalizability of previous findings might be questionable for any institution with less experienced practitioners.

In this study, we assessed the use of combined MRI-TB and SB versus SB only through 10 years of practice in our institution in an attempt to perform a dynamic evaluation of the PCa detection rate according to the biopsy strategy and cancer grade.

Methods

Study design

All consecutive adult males (≥18-years-old) who underwent MRI-TB and/or systematic biopsy (SB) following multiparametric MRI of the prostate for clinically suspected PCa between January 2010 and December 2020 were included prospectively in the study. The study was approved by the local IRB and ethics committee (Comité de Protection des Personnes, decision 30062004).

Patients were advised to undergo prostate MRI if they had elevated PSA or a pathological digital rectal examination. Patients were eligible for targeted biopsy when a lesion with a PIRADS or Likert score ≥3 was found on MRI. Data were collected prospectively and entered in a secure pretrial-designed database by a data manager who was not involved in patient care. This database was declared and approved by the CNIL (Commission Nationale de l'Informatique et des Libertés – 1688221v0).

The study was designed as a stage 4 or long-term study according to the IDEAL study recommendations. At this stage, established procedures are evaluated for long-term results and variations in outcomes[12].

MRI protocol

A total of 1898 MRI exams were performed in our institution before biopsy according to international guidelines[7] by an expert radiologist who had access to the clinical data. The MRI system used was a 1·5T or 3T clinical system (Siemens Healthcare) with a 32-channel phased-array torso coil. T2-weighted, contrast-enhanced and diffusion-weighted series were obtained, as described previously.[13] The remaining 586 MRI scans were performed on an outpatient basis

following a routine imaging protocol with a standardized report but without a standardized review. Data on the provenance of the MRI was missing for 458 patients (15%). The quality of multiparametric MRI was checked by the operator prior to the biopsy procedure.

Before 2015, radiologists from our institution graded suspicious prostate lesions according to the ESUR score and a 5-point Likert scoring system[5] to assess the likelihood of clinically significant PCa. After 2015, lesions were scored according to the PIRADS V2 and V2.1 score.[14-17]. All identified lesions were then labeled using an open-source DICOM viewer (Horos) and transferred to the MRI-ultrasound fusion system, Koelis Trinity® (Koelis, Meylan, France).

Prostate biopsy protocol

All patients underwent MRI-TB at our institution. Between January 1, 2010 and April 23, 2014, Urostation V2 was used for the computer-assisted fusion of labeled T2-weighted MRI images over real-time prostate ultrasound scans, followed by UroStation Touch until August 3, 2015, and finally, the Koelis Trinity™ system until December 2020. Once the 3D contours have been defined on the imported images and the ultrasound images, fusion of the acquired data is performed according to the elastic image fusion model. [15,16]

Each lesion with a PIRADS or Likert score of ≥3 was targeted and two to four biopsy cores from each targeted lesion were retrieved using a transrectal ultrasound probe (Koelis) and software guidance by the Koelis device. The MRI-targeted and systematic 12-core biopsies were obtained during the same session by the same practitioner. In the absence of MRI-visible prostate lesions or in addition to MRI-TB, patients underwent a 12-core SB using standard segmentation of the prostate to obtain lateral and medial cores of the base, middle, and apex of each lobe of the gland.

Prostate transrectal biopsies were obtained by surgeons and radiologists (N=28) with various levels of experience ranging from no experience to expert in MRI-TB. The novice practitioners performed the first 15 procedures under the supervision of the same expert physician.

All biopsy specimens were analyzed by a senior genitourinary pathologist with >10 years experience who classified the biopsy according to the ISUP classification using grades ranging from 1 to 5, reflecting increasing disease severity. Tumor differentiation was determined using the Gleason score and the highest Gleason score for each biopsy was recoded according to grade.[17, 18] All results are presented according to START (Standards of Reporting for MRI-TB Studies) recommendations.[19]

Definition of terms

In our study setting, clinically significant PCa (csPCa) was defined as any PCa with a grade ≥2, based on the ISUP classification. Throughout this report, SB refers to the standard 12-core biopsy procedure, MRI-TB refers to biopsy of targeted abnormalities identified on MRI, and combined biopsy refers to systematic and MRI-TB performed in the same clinical setting. Each biopsy sample is referred to as a core and a positive core is defined as the presence of PCa on histopathology findings.

Study outcomes

The primary outcome was the change in detection rate of clinically relevant PCa (grade ≥2). The secondary outcome was the evolution of PCa detection rate according to the biopsy protocol in order to identify and describe any parameters that could explain the changes in trend.

Statistical analysis

Continuous variables are described as median and interquartile range [IQR] and categorical variables are shown as frequency and percent. Continuous variables were analyzed with the Wilcoxon test. Differences between categorical variables were assessed using the Chi^2 or Fisher's exact test, where appropriate. Multinomial regression models were developed to assess the influence of key variables on the detection rate of clinically relevant PCa and non-clinically relevant PCa. The effect of age, PSA, previous biopsy results, prostate volume measured by MRI, and time period (before or after 2016) on the dependent variable was explored. Each continuous variable was tested for log-linearity and all significant variables were recoded into binary variables for multinomial analysis. The threshold for each binary was determined using the median value.

All statistical analyses were performed using open-source R statistical software v.3.4.0 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided with significance set at $P < 0.05$.

Results

Study population

Overall, 3239 patients underwent prostate biopsy in our center between January 1, 2010 and December 1, 2020. Of these patients, 297 were excluded because they had not undergone MRI before the prostate biopsy. The remaining 2942 were included in the analysis (Figure S1). The majority of the men enrolled (71%) had not undergone a previous biopsy before their enrollment (Table 1).

Of the men who were enrolled in the study, 2322 underwent targeted biopsy and 620 had SB only. A total of 1782 men underwent combined biopsy including both biopsy methods (MRI-TB + SB). The remaining 540 men underwent targeted biopsy only.

Overall PCa detection

Among the men included in this study, PCa and clinically relevant PCa were diagnosed in 1880 (64%) and 1121 (38%) cases, respectively. The detection rate of PCa and csPCa was higher in patients who underwent MRI-TB compared to those who underwent SB only (67% vs. 52% and 40% vs. 32%, respectively; $P<0.001$). Of the patients who had a positive biopsy Gleason >6 in the MRI-TB group, 826/925 (89%) had positive cores Gleason >6 on MRI-TB, meaning that most of the significant PCa were diagnosed from targeted biopsy cores.

Dynamic analysis of PCa detection

Over the 10 years of practice, the detection rate of PCa increased from 45% in 2010 to 73% in 2020. Furthermore, the detection rate of csPCa increased 2.5-fold, from 23% to 58% (Figure 1).

Between 2010 and 2020, the number of MRI-TB increased in a nonlinear fashion, starting from 122/year in 2010 to 200/year in 2020 (Figure 2a). During the same period, the number of systematic biopsies decreased 6-fold.

Interestingly, the number of csPCa diagnosed by MRI-TB increased linearly over the study period and represented the majority of PCa diagnosed after 2016. Conversely, the number of csPCa detected by SB only remained stable throughout the study period.

Finally, the overall number of patients with grade 1 PCa diagnosed by combined MRI-TB and SB decreased during the study period (76 in 2010 and 32 in 2020).

PCa detection in patients who underwent MRI-targeted biopsy

Patients in the combined biopsy group (N= 1782) were younger, had less T2 disease (13% vs. 23%, P<0.001), more PIRADS 3 and less PIRADS 5 (P<0.001), and were less likely to have undergone previous prostate biopsy (25% vs. 41%, P<0.001) compared to those who underwent MRI-TB only (N= 540).

The detection rate of PCa and clinically relevant PCa was higher for patients who underwent targeted biopsy only compared to those who underwent combined biopsy: 74% vs. 65% and 55% vs. 35%, respectively (Table S1).

Dynamic analysis of PCa detection in patients who underwent MRI-targeted biopsy

Starting in 2012-2013, targeted biopsies alone were performed on selected patients (Figure 2b). The number of patients who received targeted biopsies alone increased gradually from 2012 to equal the number of patients who had combined biopsies in 2020. This change of practice was

associated with a reduction in detection of grade 1 PCa and a higher detection rate of csPCa in both groups.

Factors associated with the risk of having clinically significant PCa

The multinomial logistic regression model for PCa positivity showed that patients who underwent biopsy after 2016 were three times more likely to have significant PCa than those who underwent biopsy before 2016 (OR=3.23 [IQR: 2.65-3.95]; $P<0.01$) (Table S2). Patients >65-years-old and those with PSA levels >7 ng/ml also had a higher risk of being diagnosed with clinically significant PCa. Conversely, those with a previous positive or negative biopsy and those with prostate volume >40 cm^3 were less likely to have clinically significant PCa.

The multinomial logistic regression model with interaction showed that the effect of time period on PCa positivity was highly significant ($P=10^{-7}$) and that only previous prostate biopsy ($P=0.02$) and volume ($P=0.03$) had a different effect by time period.

Discussion

The present study is, to our knowledge, the first dynamic evaluation of the implementation of MRI-TB in a tertiary center, involving several practitioners with various levels of experience. Although randomized controlled trials are required to assess the effectiveness of MRI-TB against current standards, prospective "real-life" studies with long-term follow-up and dynamic analysis are the final step in the development and evaluation of surgical innovations according to IDEAL recommendations.[12] Therefore, our results should help us assess whether the positive results of previous randomized trials are generalizable to a real-life setting.

Our results indicate that the implementation of MRI-TB protocol led to the improved detection of clinically relevant PCa while decreasing the number of grade 1 PCa diagnoses over 10 years of practice. The implementation of targeted biopsy resulted in us performing more combined biopsy procedures, less SB, but also targeted biopsy alone in selected patients. In contrast to previous randomized trials including experienced practitioners and radiologists in tertiary care centers, our study includes the learning curve of the 29 operators for targeted biopsy in an academic center. This dynamic analysis reflects the institutional adoption of the technique by a tertiary center with a trained lead operator who supervised the others at the beginning of their learning while providing coordination to ensure consistency among operators' practices and decisions.

During the study period, while the number of systematic biopsies decreased 6-fold, the number of negative biopsies and grade 1 cancers detected by SB decreased significantly. Per protocol, systematic biopsies were performed in patients without a MRI-visible target. However, a previous study by our group highlighted the fact that biopsy could be avoided in selected patients without a MRI-targeted lesion.[20] Other studies reported similar results with a negative predictive

value of MRI ranging from 89.6–95.4% for clinically significant PCa.[21-23] Therefore, current European guidelines now state that in biopsy-naive patients with negative MRI (i.e., PIRADS ≤2) and low clinical suspicion of PCa, SB can be omitted.[8] In our study, this change in practice was adopted in 2016 and led to fewer systematic biopsies while decreasing the detection of the grade 1 cancer, thereby decreasing overdetection and potentially overtreatment of clinically insignificant disease. However, some shortcomings should be highlighted. First, MRI findings should be interpreted according to the risk of PCa combining clinical data, MRI findings, and perhaps, in the near future, other biomarkers.[24] Second, MRI interpretation should be standardized to avoid suboptimal care outside of expert centers, as the reproducibility of MRI between readers with various levels of experience is at best moderate[25] and may lead to significant PCa being missed. In the present study, 76% of MRIs were interpreted by the referral team, who were experts in urological imaging, and external MRIs (24%) underwent quality control (T2-weighted imaging quality, available PIRADS score, and target delineation of key images) before biopsy by the operator. Our study practice reflects the fact that MRI should be performed in accordance with PIRADS quality and interpretation guidelines, and that a review by an expert radiologist, or a new scan if the quality of the scan is not sufficient, is sometimes necessary.

Finally, one of the most important questions is whether we can perform targeted biopsy alone without missing clinically significant PCa, and if so, in which patients. It is tempting to conclude that targeted MRI biopsy alone could be considered as a valid alternative since it allows the detection of the majority of clinically significant cancers, avoids 12-core biopsies, and leads to 10% fewer diagnoses of clinically insignificant cancers. However, in our cohort, only highly selected patients underwent targeted biopsy alone, based on the experience of the operator, and according to several parameters: age and comorbidity of the patient, the nature of the target

(PIRADS), the results of previous biopsies, and the curative treatments available. Ultimately, the decision to omit systematic biopsy was made by the treating specialist. We reported that the detection rate of clinically relevant PCa was 55% (N= 296) among patients who had targeted biopsy alone while it was only 33% (N=589) in those who underwent combined biopsy. We also found that once we began selecting patients for targeted biopsy alone based on previously mentioned criteria, there was a progressive and linear reduction in the detection of grade 1 PCa and a higher rate of detection of csPCa in patients who underwent targeted biopsy alone, but also in those who underwent combined biopsy. Other studies have reported the superior diagnostic performance of targeted biopsy at detecting clinically relevant PCa without showing whether routine biopsy can be omitted.[2, 26-28] Adhoot et al. reported increased cancer detection with combined biopsy and a non-negligible risk of missing grade 2 and grade 3 PCa (5.8% and 1.9%, respectively). Moreover, they also reported that MRI-TB alone would have led to 30.9% of any upgrading and 8.7% risk of upgrading to a clinically significant grade when compared to whole-mount histopathological analysis after radical prostatectomy. Therefore, targeted biopsy alone should not be chosen for all patients and our study helps to define the pre-biopsy criteria to select the best candidates for MRI-TB only. Young patients who have already undergone a series of prostate biopsies and are candidates for MRI-TB because of a PIRADS 5 target, and who could benefit from radical curative treatment, are very unlikely to benefit from a new series of systematic biopsies. In contrast, older patients with a PIRADS 3 target on MRI will likely benefit from SB and MRI-TB because the result could change the therapeutic strategy.

Our study has several strengths, including the prospective and consecutive inclusion of patients and the analysis of 10 years of practice in a single center with operators with different levels of experience. Therefore, our results should be generalizable to any institution, provided

that an experienced operator oversees the implementation of this biopsy protocol. However, our study also has several limitations. According to IDEAL recommendations, this is a stage 4 study, which is a long-term study designed as a prospective registry of consecutive patients. Although this is the standard methodology for assessing long-term effects, these studies have inherent limitations in their design. The absence of randomization and retrospective analysis are associated with bias. In addition, changes in practice and guidelines due to scientific developments led to variations in selection criteria. This selection bias prevents us from drawing conclusions from the analysis of overall detection rates for the whole study population, but the dynamic analysis is informative about how these practice changes have impacted PCa detection rates.

Conclusion

Implementation of a MRI-TB protocol in patients with a positive MRI (PIRADS score ≥3) led to the improved detection of csPCa while decreasing the number of grade 1 PCa diagnoses. This long-term follow-up patient-based study including operators with different levels of experience should encourage institutions with less experienced practitioners to initiate a program of targeted MRI biopsy.

Statements and Declarations

Conflict of Interest: Pierre Mozer has patents for the targeted biopsy device and has been involved in the license of the Koelis UroStation system.

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Author's Contribution

Louis Lenfant: Project development, Statistical analysis, analysis and interpretation of data Manuscript writing
Raphaele Renard-Penna: Data Collection, critical revision of the manuscript for important intellectual content
Yann de Rycke: Statistical analysis,
Morgan Rouprêt: critical revision of the manuscript for important intellectual content
Aurelien Beaugerie: Data Collection
Eva Comperat: Data Collection
Emmanuel Chartier-Kastler: Data Collection, critical revision of the manuscript for important intellectual content
Pierre C. Mozer: Project development, Data Collection, supervision

Research involving human participants, their data or biological material: Yes

This study was approved by our institution IRB and we certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards

Availability of data and material (data transparency): Yes

Code availability (software application or custom code): Not Applicable

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Figure legends

Figure 1. Detection of prostate cancer over time

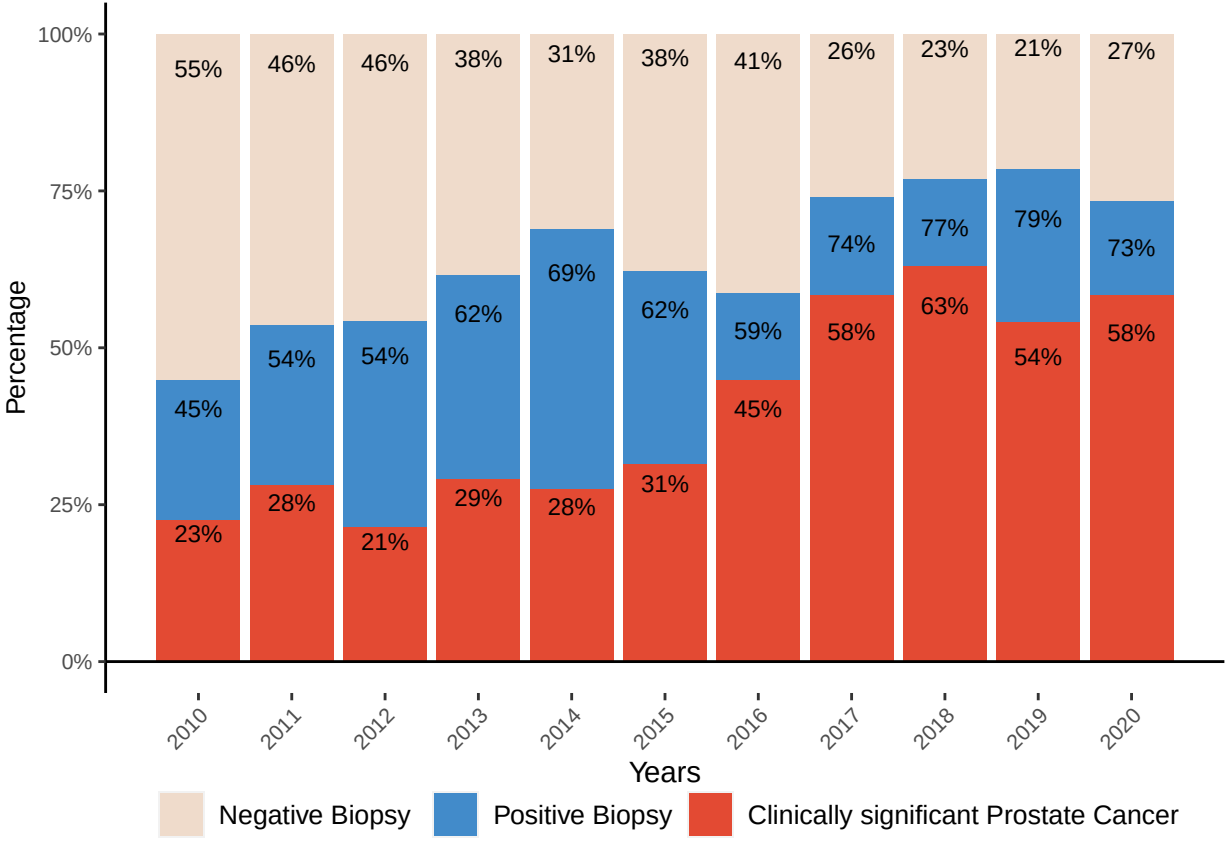
Over the 10 years of practice, the detection rate of PCa increased from 45% in 2010 to 73% in 2020. Furthermore, the detection rate of clinically significant PCa increased 2.5-fold, from 23% to 58%

Figure 2a. Prostate biopsy result stratified by biopsy approach (systematic only, or MRI-targeted)

Between 2010 and 2020, the number of MRI-TB increased in a nonlinear fashion, starting from 122/year in 2010 to 200/year in 2020. During the same period, the number of systematic biopsies decreased 6-fold. Interestingly, the number of clinically significant PCa diagnosed by MRI-targeted biopsy increased linearly over the study period and represented the majority of PCa diagnosed after 2016. Conversely, the number of clinically significant PCa detected by systematic biopsy only remained stable throughout the study period

Figure 2b. Biopsy results stratified by biopsy approach (combined, or MRI-targeted only)

Starting in 2012-2013, targeted biopsies alone were performed on selected patients. This change of practice was associated with a reduction in detection of grade 1 PCa and a higher detection rate of clinically significant PCa in both groups.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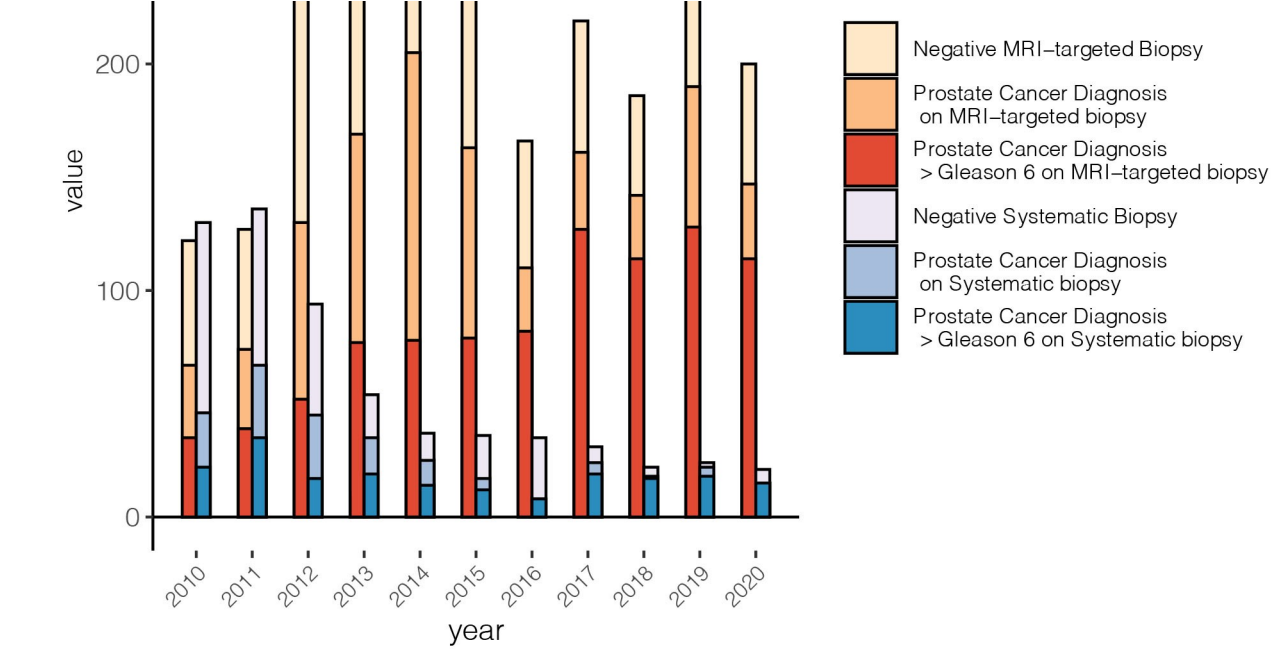
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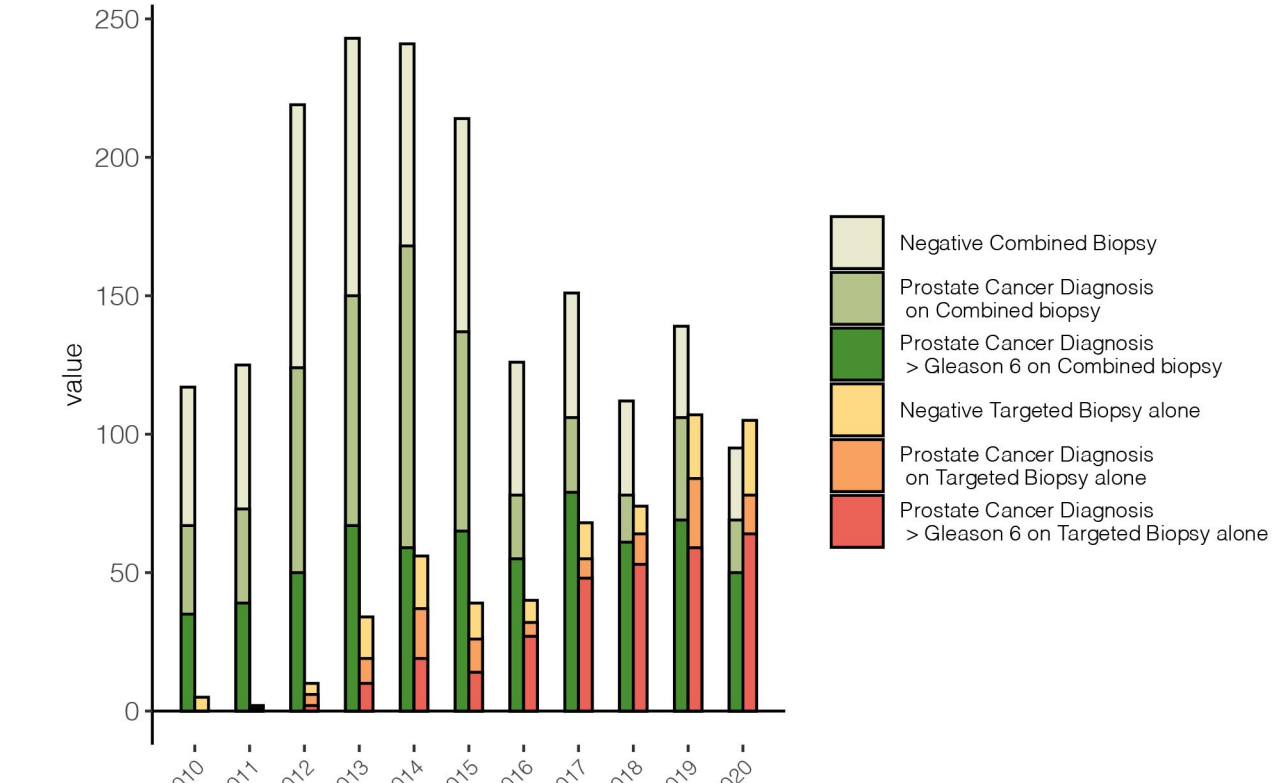
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Prostate Cancer Diagnosis on Targeted Biopsy alone
Prostate Cancer Diagnosis > Gleason 6 on Targeted Biopsy alone

Supplementary materials

Figure S1 : Flowchart of the study population

Of the 2942 men who were enrolled in the study, 2322 underwent targeted biopsy and 620 had systematic biopsy only. A total of 1782 men underwent combined biopsy including both biopsy methods (targeted + systematic biopsy). The remaining 540 men underwent targeted biopsy only

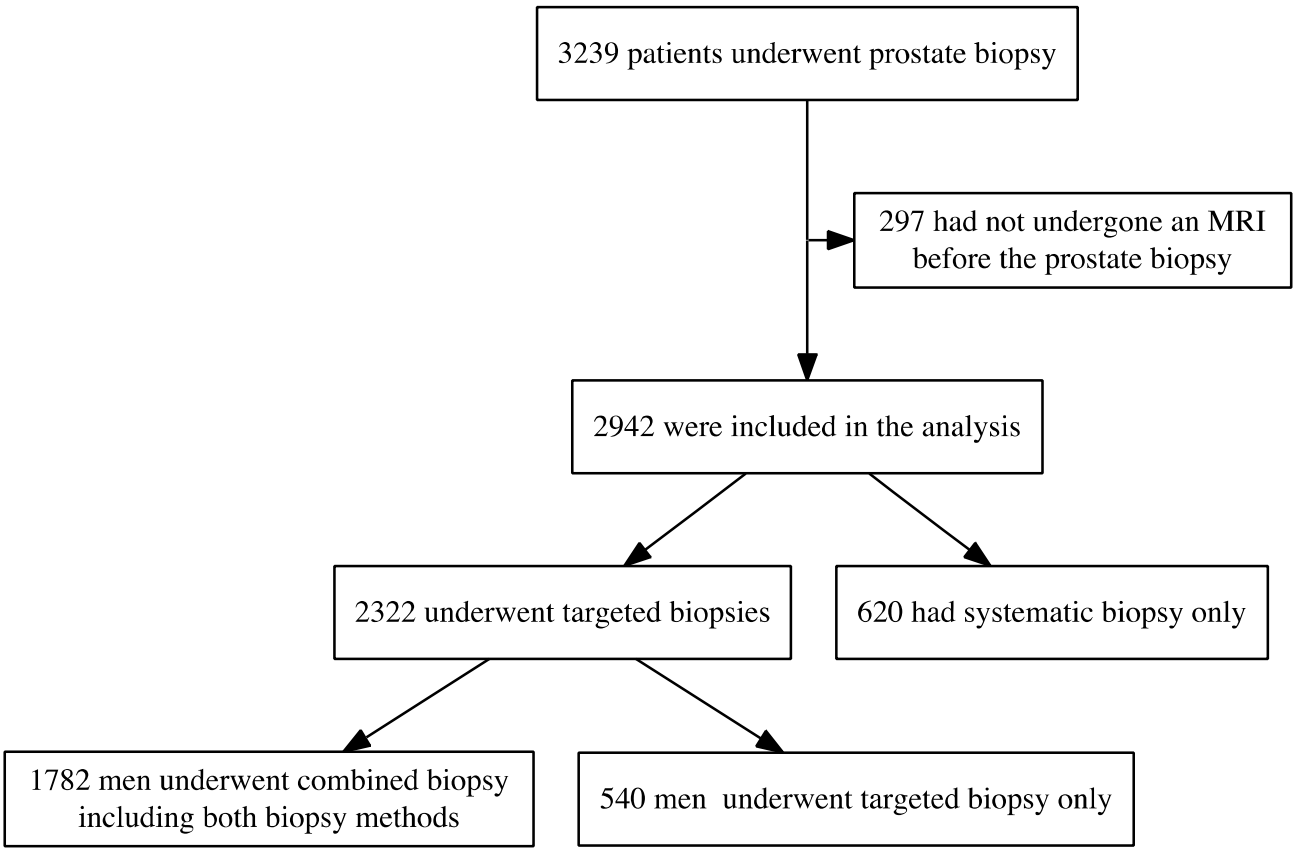

Table S1. Demographics and biopsy results among patients who underwent combined biopsies (e.g., MRI-targeted biopsy and systematic biopsy) and those who underwent MRI-targeted biopsy alone.

Characteristic	**Overall**, N = 2,322[1]	**Combined biopsy,** N = 1,782[1]	**Targeted biopsy alone**, N = 540[1]	p-value[2]
Age -years	66 (61, 71)	65 (61, 71)	67 (62, 73)	**<0.001**
Missing	10	9	1	
Prostate-specific antigen — ng/ml	7 (5, 10)	7 (5, 10)	8 (5, 12)	**<0.001**
Missing	22	17	5	
Tumor stage — no. (%)				**<0.001**
T1c	1,738 (84%)	1,381 (87%)	357 (77%)	
T2	320 (16%)	214 (13%)	106 (23%)	
Missing	264	187	77	
Previous biopsy result — no. (%)				**<0.001**
Positive	249 (11%)	177 (10%)	72 (13%)	
Negative	401 (18%)	252 (15%)	149 (28%)	
No Previous biopsy	1,627 (71%)	1,308 (75%)	319 (59%)	
Prostate volume on MRI — cm3	41 (30, 60)	40 (30, 60)	43 (30, 61)	0.10
PI-RADS Score — no. (%)				**<0.001**
1	1 (0.1%)	1 (0.2%)	0 (0%)	
2	5 (0.6%)	2 (0.4%)	3 (0.9%)	
3	54 (6.5%)	40 (8.2%)	14 (4.1%)	
4	454 (55%)	296 (61%)	158 (46%)	
5	317 (38%)	148 (30%)	169 (49%)	
Missing	1,491	1,295	196	
No. of cores on MRI-targeted biopsy	3.00 (2.00, 4.00)	3.00 (2.00, 3.00)	5.00 (4.00, 6.00)	**<0.001**
No. of cores on systematic biopsy	12 (12, 12)	12 (12, 12)	NA (NA, NA)	
No. of patient diagnosed with prostate cancer on systematic biopsy	1,049 (45%)	1,049 (59%)	0 (0%)	**<0.001**
No. of patient diagnosed with clinically relevant prostate cancer on systematic biopsy	524 (23%)	524 (29%)	0 (0%)	**<0.001**
No. of patient diagnosed with prostate cancer on targeted biopsy	1,316 (57%)	914 (51%)	402 (74%)	**<0.001**
No. of patient diagnosed with clinically relevant prostate cancer on targeted biopsy	826 (36%)	530 (30%)	296 (55%)	**<0.001**
Overall positive biopsy	1,558 (67%)	1,156 (65%)	402 (74%)	**<0.001**
Overall positive biopsy ≥ Gleason 6	925 (40%)	629 (35%)	296 (55%)	**<0.001**
Cancer Grade group				**<0.001**
Grade Group NA	818 (35%)	665 (37%)	153 (28%)	
Grade Group 1	619 (27%)	528 (30%)	91 (17%)	
Grade Group 2	418 (18%)	300 (17%)	118 (22%)	
Grade Group 3	229 (9.9%)	147 (8.2%)	82 (15%)	
Grade Group 4	180 (7.8%)	107 (6.0%)	73 (14%)	
Grade Group 5	58 (2.5%)	35 (2.0%)	23 (4.3%)	

[1]Median (IQR); n (%)

[2]Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Table S2. Multinomial logistic regression of PCa positivity without interaction

	Non-significant PCa	**Significant PCa**
Age >65 years	1.52 [1.24, 1.86] ***	2.41 [1.98, 2.93] ***
PSA >7 ng/mL	1.00 [0.81, 1.23]	2.37 [1.94, 2.89] ***
Previous positive biopsy	1.34 [1.00, 1.81] *	0.49 [0.35, 0.70] ***
Previous negative biopsy	0.59 [0.45, 0.77] ***	0.52 [0.41, 0.67] ***
Prostate volume >40 cm^3	0.46 [0.37, 0.56] ***	0.25 [0.20, 0.30] ***
Time period >2016	0.81 [0.64, 1.00] *	3.23 [2.65, 3.95] ***

Results shown are median [IQR]. **P*=0.1 ***P*<0.05 ****P*<0.01

PCa: prostate cancer; PSA: prostate-specific antigen.

Table 1. Baseline Characteristics of the study population

Characteristic	Overall, N = 2,942[1]	MRI-targeted Biopsy, N = 2,322[1]	Systematic Biopsy Only, N = 620[1]	p-value[2]
Age -years	66 (61,71)	66 (61, 71)	65 (59, 70)	**0.050**
Missing	12	10	2	
Prostate-specific antigen — ng/ml	7 (5, 11)	7 (5, 10)	8 (5, 13)	**0.002**
Missing	43	22	21	
Tumor stage — no. (%)				**<0.001**
T1c	2,119 (83%)	1,738 (84%)	381 (77%)	
T2	434 (17%)	320 (16%)	114 (23%)	
Missing	389	264	125	
Previous biopsy result — no. (%)				0.060
Positive	312 (11%)	249 (11%)	63 (11%)	
Negative	525 (18%)	401 (18%)	124 (22%)	
No Previous biopsy	2,008 (71%)	1,627 (71%)	381 (67%)	
Missing	97	45	52	
MRI done at the host center (%)				0.077
Yes	1,898 (76%)	1,484 (77%)	414 (74%)	
No	586 (24%)	437 (23%)	149 (26%)	
Missing	458	401	57	
Prostate volume on MRI — cm3	41 (30, 60)	41 (30, 60)	40 (25, 60)	**0.027**
PI-RADS Score — no. (%)				0.4
1	1 (0.1%)	1 (0.1%)	0 (0%)	
2	5 (0.6%)	5 (0.6%)	0 (0%)	
3	56 (6.7%)	54 (6.5%)	2 (22%)	
4	457 (54%)	454 (55%)	3 (33%)	
5	321 (38%)	317 (38%)	4 (44%)	
Missing	2,102	1,491	611	
No. of cores on systematic biopsy	12 (12,12)	12.0 (12,12)	12 (12,12)	**<0.001**
No. of cores on MRI-targeted biopsy	3 (2, 4)	3 (2, 4)	NA (NA, NA)	
No. of positive cores on systematic biopsy	3 (2, 5)	3 (2, 4)	4.0 (2, 6)	**<0.001**
No. of positive cores on MRI-targeted biopsy	2 (1, 3)	2 (1, 3)	NA (NA, NA)	
Positive cores > Gleason 6 on systematic biopsy	720 (24%)	524 (23%)	196 (32%)	**<0.001**
Positive cores > Gleason 6 on MRI-targeted biopsy	826 (28%)	826 (36%)	0 (0%)	**<0.001**
Overall positive biopsy	1,880 (64%)	1,558 (67%)	322 (52%)	**<0.001**
Overall positive biopsy ≥ Gleason 6	1,121 (38%)	925 (40%)	196 (32%)	**<0.001**
Overall higher grade group				**<0.001**
Grade Group 1	723 (25%)	619 (27%)	104 (17%)	
Grade Group 2	470 (16%)	418 (18%)	52 (8.4%)	
Grade Group 3	280 (9.5%)	229 (9.9%)	51 (8.2%)	
Grade Group 4	233 (7.9%)	180 (7.8%)	53 (8.5%)	
Grade Group 5	98 (3.3%)	58 (2.5%)	40 (6.5%)	

[1]Median (IQR); n (%)

[2]Kruskal-Wallis rank sum test; Pearson's Chi-squared test