Urologia Internationalis

Original Paper

Urol Int 2021;105:386–393
DOI: 10.1159/000511636

Received: May 6, 2020
Accepted: September 11, 2020
Published online: November 26, 2020

Who Can Avoid Biopsy of Magnetic Resonance Imaging-Negative Lobes without Compromising Significant Cancer Detection among Men with Unilateral Magnetic Resonance Imaging-Positive Lobes?

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Keywords
Prostate cancer · Multiparametric magnetic resonance imaging · Prostate biopsy · Statistical model

Abstract
Objectives: To assess whether biopsy of multiparametric magnetic resonance imaging (MRI)-negative lobes can be avoided without compromising significant cancer (SC) detection among men with unilateral MRI-positive lobes. ***Methods:*** From April 2013 to April 2019, 322 men with elevated prostate-specific antigen (PSA <20 ng/mL) and unilateral MRI-positive lobes underwent targeted 4-core and systematic 14-core biopsy. MRI findings were prospectively collected and evaluated according to the Prostate Imaging-Reporting and Data System (PI-RADS) version 2, and scores ≥3 were considered positive. SC was defined as Gleason score ≥3 + 4 or maximal cancer length ≥5 mm. We developed predictive models of overall cancer and SC in MRI-negative lobes and evaluated the performance of these models. ***Results:*** Detection rates of overall cancer/SC were 69%/61% for the overall cohort, 58%/48% for MRI-positive lobes, and 36%/20% for MRI-negative lobes. Age ≥75 years, PSA density ≥0.3, and PI-RADS ≥4 were independently predictive of both overall cancer and SC in MRI-negative lobes; 1 point was assigned for each risk factor, and the predictive score was defined as the sum of points (0–3) for both overall cancer and SC. Areas under the curve of the model for overall cancer/SC were 0.67/0.71. In the decision curve analysis, the model was of value above the threshold probability of 13%/6% for detecting overall cancer/SC in MRI-negative lobes. Of 40 men with score 0, overall cancer/SC was detected in the MRI-negative lobe in 4 (10%)/1 (2.5%). ***Conclusion:*** Biopsies of MRI-negative lobes may be avoided without compromising SC detection using our predictive model.

Introduction

Multiparametric (mp) magnetic resonance imaging (MRI)-based targeted biopsy (TgB) has recently been prevailing for the diagnosis of early prostate cancer. Accord-

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ing to a nationwide survey in Germany, mpMRI-based TgB has been widely accepted among urologists [1]. Major advantages of this approach over conventional systematic biopsy (SyB) include eliminating inherent sampling errors associated with random biopsy, improving high-grade cancer detection, and reducing overdiagnosis of indolent cancer [2]. The PRECISION study, which compared diagnostic performance between TgB of MRI-positive lesions and conventional SyB of 10–12 sites without prebiopsy MRI, demonstrated the superiority of TgB over SyB in terms of significant cancer (SC) detection and overdiagnosis of insignificant cancer [3].

We recently reported that SyB detected a nonnegligible proportion (16%) of SC missed by TgB in a complimentary manner [4]. Hence, it would be better to offer SyB in combination with TgB for men with MRI-positive lesions who require assessment of the whole prostate to determine the suitability of treatments such as focal therapy and nerve-sparing prostatectomy. However, because an increase in the number of biopsy cores taken is associated with increases in the overall cost [5] and total pain experienced by the patient [6], reducing the number of cores without compromising the diagnostic performance of biopsy is preferable for patients' wellbeing and medical economy.

A systematic review and meta-analysis demonstrated that SC was not detected in up to 90% of MRI-negative men [7]. Considering the multifocality of prostate cancer development [8, 9] and the high probability of SC detection in MRI-positive lesions [10–12], MRI-negative prostate lobes may harbor SC at higher risk in men with MRI-positive lesions than those without. However, limited information is available on the prevalence of SC in MRI-negative lobes among MRI-positive men. The aims of this study were to identify risk factors of SC detection in MRI-negative lobes among men with unilateral MRI-positive lobes and to define a subpopulation of men who can avoid SyB of MRI-negative lobes without compromising SC detection.

Materials and Methods

This single-institution, retrospective study was approved by the institutional review board. Written informed consent was obtained from all participants. Men with elevated prostate-specific antigen (PSA) or abnormal digital rectal examination (DRE) were recommended to undergo mpMRI, and those with abnormal MRI findings were recommended to receive prostate biopsy. Subjects in this study included men with PSA <20 ng/mL and unilateral MRI-positive lesions who underwent TgB and multicore SyB.

Between April 2013 and April 2019, all subjects underwent mpMRI in a 1.5-tesla (MAGNETOM Avanto; Siemens Medical Solutions, Erlangen, Germany, or Achieva; Philips Medical System, Best, The Netherlands) or 3-tesla (MAGNETOM Skyra; Siemens Healthcare, Erlangen, Germany) within a month before biopsy. No endorectal coils were used. MRI findings were evaluated at regular radiology-urology meetings attended by a uroradiologist and 3 or more dedicated urologists with ≥7 years' experience before biopsy. MRI findings were prospectively collected and evaluated in accordance with the Prostate Imaging-Reporting and Data System (PI-RADS) version 1 [13] until February 2016 or version 2 [14] subsequently. PI-RADS scores evaluated according to version 1 were blindly reclassified with version 2 by 2 researchers (S.I. and Y.N.). PI-RADS scores ≥3 lesions were defined as MRI-positive lesions and were subjects of TgB.

All men underwent transrectal ultrasound (TRUS)-guided transperineal 4-core TgB per MRI-positive lesion and transperineal 14-core SyB under local anesthesia as described previously [15, 16]. SC was defined as Gleason score ≥3 + 4 or maximum cancer length ≥5 mm [17].

We developed models predicting detection of overall cancer and SC in MRI-negative lobes and internally validated the performance of the predictive model. Clinical variables used included age at biopsy, PSA density (PSAD), the number of previous biopsies, PI-RADS scores, and DRE findings.

Statistical Analysis

The differences in frequency were evaluated using a χ^2 test or Fisher's exact probability test. The cutoff values of PI-RADS scores, age, and PSAD were determined using recursive partitioning analysis to best predict detection of overall cancer or SC in the MRI-negative lobe. Uni- and multivariable logistic regression analyses were used to evaluate parameters associated with overall cancer and SC detection in the MRI-negative lobe. A reduced multivariable model was developed using the stepwise backward method, in which the variable with the highest p value was eliminated from each iteration of the multivariable analysis. Models predicting detection of overall cancer and SC in an MRI-negative lobe were developed using the regression coefficients from the final multivariable model. Predictive accuracy of the models was evaluated using the area under the curve (AUC) of receiver operating characteristics (ROC) curves. Calibration plots were used for comparison between probability predicted by the models and actual outcomes. Clinical usefulness of the model was assessed using decision curve analysis (DCA). Differences were considered significant at $p < 0.05$. Statistical analyses were performed using JMP software version 13 (SAS Institute, Cary, NC, USA).

Results

Among 437 men who had MRI-positive lesions and underwent TgB and SyB, 162 were excluded due to positive MRI findings in bilateral lobes ($n = 115$). Finally, 322 men with MRI-positive lesions in unilateral lobes were eligible for analysis. Demographics of men in the cohort are summarized in Table 1. The median (range) age and

Table 1. Demographics of men with unilateral MRI-positive lobes

Variables	*N* (%)				
	total	overall cancer in MRI-negative lobes	*p* value‡	SC in MRI-negative lobes	*p* value§
Total	322 (100)	116 (100)		64 (100)	
Age,* years	69 (45–84)	70 (51–84)	0.19	70 (52–82)	0.26
PSA,* ng/mL	7.7 (1.3–19.6)	8.7 (2.9–18.7)	0.010	10.2 (2.9–18.4)	0.003
Prostate volume, mL*	30.0 (9.3–102)	26.6 (9.3–102)	<0.001	25.8 (9.3–75.6)	<0.001
PSAD,* ng/mL/mL	0.25 (0.06–2.7)	0.32 (0.06–2.3)	<0.001	0.39 (0.06–0.8)	<0.001
History of previous biopsies†					
0	302 (94)	109 (94)	0.92	59 (92)	0.55
≥1	20 (6)	7 (6)		5 (8)	
MRI†					
PI-RADS 3	59 (18)	10 (9)	0.001	5 (8)	0.034
PI-RADS 4	170 (53)	61 (52)		33 (51)	
PI-RADS 5	93 (29)	45 (39)		26 (41)	
DRE†					
Negative	299 (93)	108 (93)	0.89	59 (92)	0.81
Positive	23 (7)	8 (7)		5 (8)	
TRUS†					
Negative	128 (40)	41 (35)	0.25	23 (36)	0.5
Positive	194 (60)	75 (65)		41 (64)	
Targeted lesions,† *n*					
1	306 (95)	109 (94)	0.51	59 (92)	0.24
2	16 (5)	7 (6)		5 (8)	

PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; MRI, magnetic resonance imaging; PI-RADS, Prostate Imaging-Reporting and Data System; DRE, digital rectal examination; TRUS, transrectal ultrasound; SC, significant cancer. * Median (range). † *N* (%). ‡ Versus no cancer. § Versus no SC.

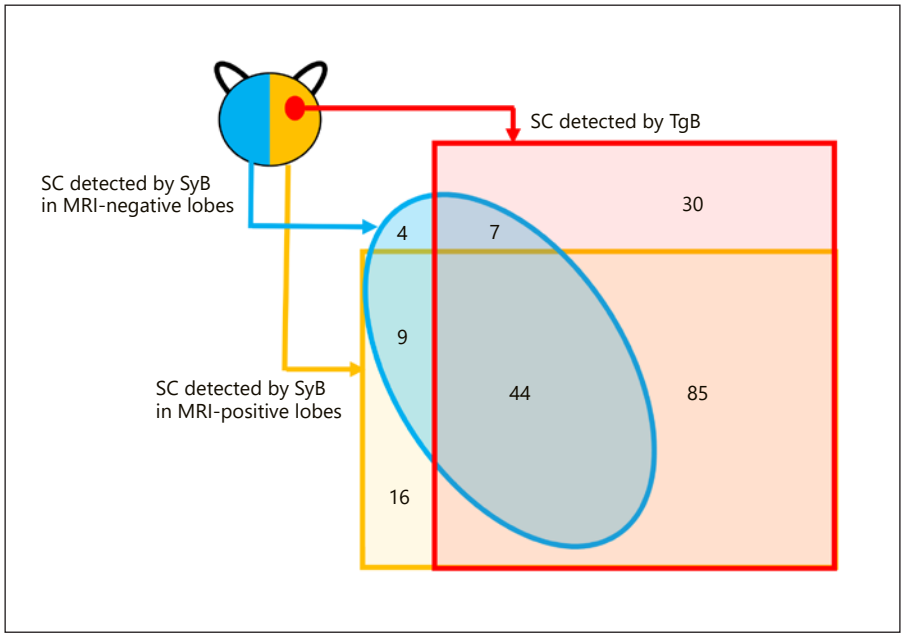


Fig. 1. Distribution of SC detected by TgB (red), SyB of MRI-positive lobes (orange), and SyB of MRI-negative lobes (blue) among 195 men diagnosed as having SC with unilateral MRI-positive lobes. TgB, targeted biopsy; SyB, systematic biopsy; SC, significant cancer; MRI, magnetic resonance imaging.

Table 2. Univariable and multivariable analysis for overall cancer and SC detection in MRI-negative lobes

Variables	Overall cancer						SC					
	univariable analysis		multivariable analysis				univariable analysis		multivariable analysis			
	OR	*p* value	OR	95% CI	regression coefficient	*p* value	OR	*p* value	OR	95% CI	regression coefficient	*p* value
Age, years												
<75	Ref	0.005	Ref	1.23–4.54	0.43	<0.001	Ref	0.035	Ref	0.95–4.0	0.33	0.076
≥75	2.41		2.37				2.09		1.94			
PSAD, ng/mL/mL												
<0.3	Ref	<0.001	Ref	1.45–3.83	0.43	0.005	Ref	<0.001	Ref	1.95–6.38	0.63	<0.001
≥0.3	2.7		2.36				3.96		3.52			
Previous biopsies, *n*												
0	Ref	0.92					Ref	0.56				
≥1	0.95						1.37					
MRI												
PI-RADS 3	Ref	<0.001	Ref	1.30–5.78	0.5	0.009	Ref	0.02	Ref	0.84–6.11	0.41	0.079
PI-RADS ≥4	2.70		2.75				3.12		2.27			
DRE												
Negative	Ref	0.90					Ref	0.082				
Positive	0.94						1.13					

MRI, magnetic resonance imaging; SC, significant cancer; PSAD, prostate-specific antigen density; PI-RADS, Prostate Imaging-Reporting and Data System; DRE, digital rectal examination; TRUS, transrectal ultrasound; ref, reference.

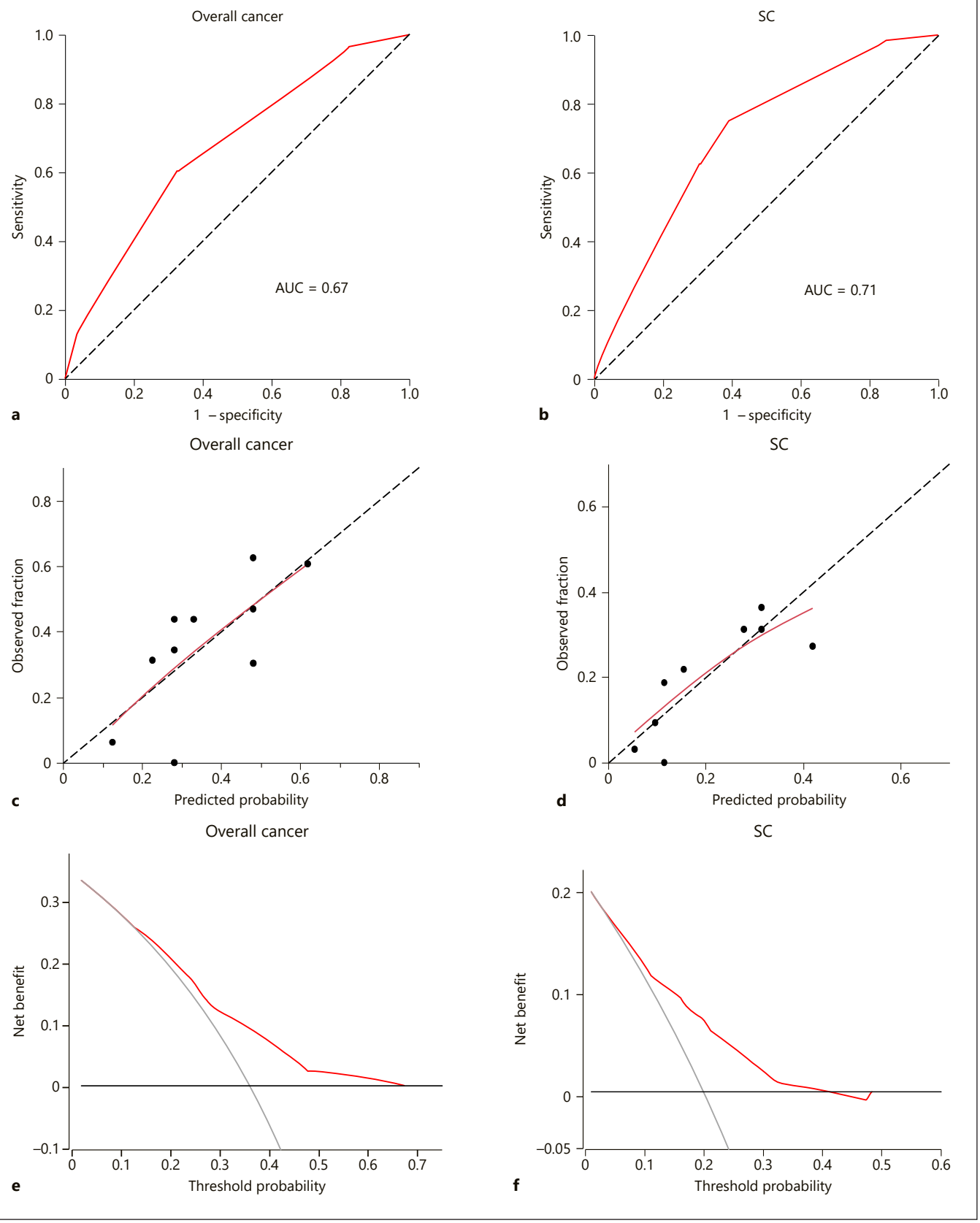
PSA levels were 69 (45–84) years and 7.7 (1.3–19.6) ng/mL, respectively. DRE was positive in 23 men (7%), and 302 (94%) had no previous history of biopsy. TgB was performed for 2 lesions in 16 (5%).

Of the 322 men, any cancer and SC were detected in 222 (69%) and 195 men (61%), respectively; detection rates of overall cancer/SC were 58% (188/322)/48% (154/322) for MRI-positive lobes but 36% (116/322)/20% (64/322) for MRI-negative lobes. Detection rates of overall cancer and SC in MRI-negative lobes were significantly lower than those in MRI-positive lobes (both $p < 0.001$). Distribution of SC detected by TgB, SyB of the MRI-positive lobe, and SyB of the MRI-negative lobe is shown in Figure 1. Of the 195 men with SC, SC was detected only from the MRI-negative lobe in 4 men (2.1%). When only TgB was performed without SyB in our study population, SC detection was missed in 29 men (15%).

Multivariable analysis revealed that age ≥75 years (OR 2.37, $p < 0.001$), PSAD ≥ 0.3 (OR 2.36, $p = 0.005$), and PI-RADS ≥ 4 (OR 2.75, $p = 0.009$) were significantly and independently associated with overall cancer detection in MRI-negative lobes. Although 2 of them did not reach statistical significance, age ≥75 years (OR 1.95, $p = 0.076$), PSAD ≥ 0.3 (OR 3.52, $p < 0.001$), and PI-RADS ≥ 4 (OR 2.27, $p = 0.079$) were independently associated with SC detection in MRI-negative lobes (Table 2).

Based on the results of the multivariable analysis, we developed a scoring model predicting overall cancer and SC in MRI-negative lobes as follows: predicting score = 1 (if age ≥75 years) + 1 (if PSAD ≥ 0.3) + 1 (if PI-RADS ≥ 4) for both overall cancer and SC. The median predicting score was 1 (range 0–3, mean 1.4). AUCs of the scoring model were 0.67 for overall cancer and 0.71 for SC (Fig. 2a, b). Calibration plots of the scoring model demonstrated good agreement between predicted probability and actual observation for both overall cancer and SC (Fig. 2c, d). DCA showed that the predicting model was of value above the threshold probability of 13 and 6% for detecting overall cancer and SC in MRI-negative lobes, respectively (Fig. 2e, f).

Among 40 men with score 0, detection rates of overall cancer and SC in MRI-negative lobes were 10% (4/40) and 2.5% (1/40), respectively, which were significantly lower than those of men with score ≥1 with respective detection rates of 40% (112/282, $p < 0.001$) and 22% (63/282, $p = 0.003$). When combining men of 75 years or older with score 1 and those with score 0, the respective



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detection rates were 13% (6/47) and 4.3% (2/47), which were significantly lower than those of their counterparts (40% [110/275], $p < 0.001$ and 23% [62/275], $p = 0.004$, respectively).

Discussion

In the present study, we focused on MRI-negative lobes in men with unilateral MRI-positive lobes and developed a predictive model of overall cancer and SC in an MRI-negative lobe, consisting of 3 risk factors: age ≥75 years, PSAD ≥ 0.3, and PI-RADS ≥ 4. Internal validation of the model exhibited AUCs of 0.67 and 0.71 for overall cancer and SC, respectively, and DCA demonstrated clinical benefits of this model for deciding the indication for SyB in the MRI-negative lobe. Among men without any risk factors, the detection rate of SC was 2.5% in MRI-negative lobes. These results indicated that biopsy of an MRI-negative lobe can be avoided without overlooking SC in a select subpopulation. Although external validation is mandatory, the predictive model proposed may help men with unilateral MRI-positive lobes decide whether or not to receive a biopsy of the MRI-negative lobe.

The present study found that the detection rates of overall cancer and SC in MRI-negative lobes were 36 and 20%, respectively. The prevalence of prostate cancer, particularly SC, in MRI-negative lobes of unilaterally MRI-positive men appeared to be higher compared with that in MRI-negative men. This is conceivable when considering the high probability of SC detection in MRI-positive lesions [10–12] and the multifocal development of prostate cancer [8, 9]. According to a recently published meta-analysis, the prevalence of overall cancer ranged from 14.3 to 35.3% (median 29.4%) and that of SC (defined as Gleason score ≥7) was 12.1% in MRI-negative men (PI-RADS/Likert score <3) [7]. Thompson et al. [18] reported that the prevalence of SC (defined as Gleason score ≥7 with >5% grade 4) was 8% among 79 MRI-negative men (PI-RADS < 3).

The present study, demonstrating nonnegligible proportion (20%) of SC detection in the MRI-negative lobe, would support a substantial role of biopsy of the MRI-negative lobe among unilaterally MRI-positive men. Healthy young men with unilateral MRI-positive lobes, who need rigorous assessment of the whole gland for anticipated curative treatments, may consider whether or not to receive SyB of MRI-negative lobes according to their risk of SC detection. The present model may be used for decision-making by these men. On the other hand, SyB of the MRI-negative lobe compensated for a negligible proportion (2.1%) of the diagnosis of SC in the present study. This result suggests that SyB of the MRI-negative lobe can be safely avoided without compromising the diagnosis of SC among men with unilateral MRI-positive lobes.

Our predictive model consisted of 3 risk factors: age ≥75 years, PSAD ≥ 0.3, and PI-RADS ≥ 4. Inclusion of these risk factors was reasonable based on the published literature. According to a population-based cohort study, more high-risk cancers were detected with increasing age [19]. Higher PSAD [20, 21] and PI-RADS ≥ 4 [22] have also been reported to be associated with higher SC detection rates. Although accuracy of our predictive model for SC was moderate with an AUC of 0.71, DCA demonstrated its clinical benefits for deciding the indication for SyB in the MRI-negative lobe. Despite a small proportion (12%, 40/322), men without any risk factor may avoid SyB of the MRI-negative lobe without compromising SC detection, contributing to reducing medical cost and patients' discomfort.

The present study has several limitations. First, performance of the predictive model has not been evaluated with external validation, which is mandatory to confirm the clinical utility of a predictive model. Second, all MRI results were prospectively reviewed by a uroradiologist and several dedicated urologists at meetings. Although a strength of the present study, it may not be a realistic representation in the real world and may influence the generalizability of this study. In addition, we did not assess the accuracy of biopsy pathology using prostatectomy specimens.

Fig. 2. The receiver operator characteristic curves of the predictive model for overall cancer (**a**) and SC (**b**). Calibration plots of the predictive model for overall cancer (**c**) and SC (**d**). The *y* axis represents the actual observed rates of cancer detected in MRI-negative lobes, and the *x* axis represents the predicted probability estimated using the model. Decision curve analysis of the predictive model for overall cancer (**e**) and SC (**f**). The decision curve was created by plotting the net benefit on the *y* axis against the varying threshold probability on the *x* axis. A black line represents the net benefit when carrying out no biopsies (parallel to the *x* axis at a net benefit of zero). A gray line represents the net benefit when carrying out biopsies on all men. A red line represents the net benefit when carrying out biopsies on men based on the predictive model. SC, significant cancer; MRI, magnetic resonance imaging; AUC, area under the curve.

Conclusions

A predictive model for overall cancer and SC in an MRI-negative lobe, consisting of age ≥75 years, PSAD ≥ 0.3, and PI-RADS ≥ 4, may help men with unilateral MRI-positive lobes decide whether or not to undergo biopsy of the MRI-negative lobe. Biopsy of the MRI-negative lobe may be avoided without overlooking SC among men without any risk factors.

Acknowledgements

This research was supported by the Clinical Research Fund of the Tokyo Metropolitan Government.

Statement of Ethics

This study was approved by the institutional review board (#2144), and written informed consent was obtained from all participants.

Conflict of Interest Statement

No potential conflicts of interest are disclosed.

Author Contributions

Y. Nakanishi: data acquisition, data analysis, drafting the manuscript, statistical analysis, and obtaining funding. M. Ito: concept and design, data acquisition, critical revision, and statistical analysis. M. Kataoka: data acquisition and obtaining funding. S. Ikuta: data acquisition and data analysis. K. Sakamoto and H. Suzuki: data acquisition. K. Takemura: data acquisition and critical revision. K. Tobisu: supervision. F. Koga: concept and design, data analysis, drafting the manuscript, critical revision, obtaining funding, and supervision.

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