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Risk-adapted Omission of Systematic Cores in PI-RADS 3 Lesions Based on Prostate-specific Antigen Density, Biopsy Route, and Targeted Core Number: A Multicentre Cohort Study

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Abstract

Background: Prostate Imaging Reporting and Data System (PI-RADS) category 3 lesions represent an intermediate-risk group for which the additional diagnostic value of systematic biopsy (SBx) after multiparametric magnetic resonance imaging (mpMRI)–targeted biopsy (TBx) remains uncertain.

Objective: To quantify the absolute omission cost of a TBx-only strategy compared with overall biopsy (OBx; TBx plus SBx) and to assess whether this cost varies according to prostate-specific antigen density (PSAD), biopsy route, and targeted sampling intensity.

Design, setting, and participants: This retrospective multicentre cohort study included 902 men with exclusively PI-RADS 3 lesions on prebiopsy mpMRI who underwent index software-assisted mpMRI–ultrasound fusion biopsy at six academic and high-volume centres between January 2016 and March 2023.

Intervention: All patients underwent same-session TBx and SBx via either the transperineal (TP) or transrectal (TR) route.

Outcome measurements and statistical analysis: The primary outcome was the absolute cohort-level proportion of clinically significant prostate cancer (csPCa), defined as International Society of Urological Pathology (ISUP) grade group ≥2, detected by OBx but missed by TBx. Paired detection rates were compared using the McNemar test, and the omission cost was estimated with exact confidence intervals (CIs). An exploratory 5% margin was used to contextualise the performance of TBx alone. Factors associated with TBx failure were evaluated using multivariable Firth penalised logistic regression. A sensitivity analysis defined csPCa as ISUP grade group ≥3.

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Transrectal biopsy

Results and limitations: TBx detected csPCa in 181 of 902 men (20%), whereas OBx detected csPCa in 240 (27%). TBx alone missed 59 cases, corresponding to an absolute omission cost of 6.5% (95% CI 5.0–8.4), which exceeded the prespecified exploratory 5% benchmark. When csPCa was defined as ISUP grade group ≥3, the omission cost decreased to 2.8% (25/902; 95% CI 1.8–4.1). The lowest omission cost was observed among men undergoing TP biopsy with PSAD <0.10 ng/ml/cm^3 (0.8%, 1/126; 95% CI 0.02–4.3). Each additional targeted core was independently associated with lower odds of TBx failure (adjusted odds ratio 0.69, 95% CI 0.54–0.86). Limitations include the retrospective design, centre-level heterogeneity in mpMRI interpretation and biopsy practices, nonrandom biopsy-route selection, the use of same-session combined biopsy rather than whole-mount pathology as the reference standard, and the absence of core-by-core spatial mapping.

Conclusions: TBx alone should not be considered a universal substitute for OBx in men with PI-RADS 3 lesions when csPCa is defined as ISUP grade group ≥2. The lower omission cost observed when a stricter threshold for significant disease was applied, and in selected men with low PSAD undergoing TP biopsy, supports prospective evaluation of risk-adapted biopsy deintensification. However, these exploratory findings do not justify the routine omission of SBx.

ADVANCING PRACTICE

What does this study add?

This multicentre study focused exclusively on Prostate Imaging Reporting and Data System 3 (PI-RADS 3) lesions and quantified what would be missed if systematic cores were omitted after same-session multiparametric magnetic resonance imaging–targeted biopsy (TBx). Using International Society of Urological Pathology (ISUP) grade ≥2, TBx only missed 6.5% of clinically significant cancers detected by overall biopsy, exceeding the exploratory 5% benchmark; using the stricter ISUP grade ≥3 threshold, this omission cost decreased to 2.8%. The omission cost was lowest among men with low prostate-specific antigen density undergoing transperineal biopsy, and higher targeted sampling intensity was associated with fewer missed cancers. These findings support prospective, risk-adapted biopsy de-intensification trials, but not routine omission of systematic biopsy in all patients with PI-RADS 3.

Clinical Relevance

This is a multi-centre retrospective cohort of 902 men with PI-RADS 3 lesions who underwent software-assisted mpMRI-ultrasound fusion targeted and systematic biopsy. The authors found that targeted biopsy alone missed 59 out of 240 cases of ISUP=2 clinically significant prostate cancer, corresponding to an absolute omission cost of 6.5%. The lowest omission cost was observed in men with PSA density of <0.10 ng/ml/cm^3. Greater targeted sampling intensity was also associated with a lower probability of missed clinically significant prostate cancer. These are important factors to consider when we are planning for fusion biopsy for men with PI-RADS 3 lesions. Associate Editor: Jeremy Y.C. Teoh.

Patient Summary

We studied men whose prostate multiparametric magnetic resonance imaging (mpMRI) showed an intermediate-suspicion finding called Prostate Imaging Reporting and Data System 3. If physicians used only mpMRI–targeted biopsy samples and omitted additional systematic samples taken across the prostate, cancer that may affect treatment decisions was missed in 6.5% of men; when only higher-grade cancers were counted, this rate was 2.8%. These findings suggest that systematic samples should not be omitted for all such men, although future studies may identify lower-risk patients who can safely have fewer biopsy samples.

1. Introduction

Prostate Imaging Reporting and Data System (PI-RADS) category 3 lesions, defined in PI-RADS version 2 and retained in version 2.1 as intermediate suspicion for clinically significant prostate cancer (csPCa), remain the principal "grey zone" in multiparametric magnetic resonance imaging (mpMRI)–driven diagnosis [1,2]. Category 3 findings are fre-

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quent and drive substantial biopsy volume; however, management varies widely across practices [3,4]. Cancer yield is similarly heterogeneous, and a PI-RADS 3–focused meta-analysis highlights variable csPCa detection across biopsy strategies [5].

Randomised trials established mpMRI-first diagnostic pathways and demonstrated that mpMRI-targeted approaches can increase csPCa detection while reducing detection of clinically insignificant prostate cancer (ciPCa) and avoiding biopsy in a subset of men [6,7]. However, these trials do not address the PI-RADS 3–specific question of whether systematic biopsy (SBx) adds meaningful value beyond targeted biopsy (TBx) in this intermediate-suspicion category. Evidence from paired-design studies and contemporary syntheses indicates that TBx and SBx are complementary, with a residual fraction of csPCa detected only when systematic cores are added; procedural factors, including targeted sampling intensity, may further influence grade assignment [8–12].

Therefore, clinical decision-making in PI-RADS 3 centres on identifying men in whom biopsy, particularly additional nontargeted cores, can be deferred with acceptably low risk. The European Association of Urology guidelines operationalise this heterogeneity by integrating mpMRI findings with prostate-specific antigen density (PSAD), and additional clinical and lesion-level modifiers have been proposed to refine risk within PI-RADS 3 [5,13–18].

We therefore evaluated men with PI-RADS 3 lesions undergoing mpMRI–ultrasound fusion TBx with concomitant SBx via transrectal (TR) and transperineal (TP) routes to estimate the absolute omission cost of a targeted-only strategy and derive a clinically actionable, risk-adapted framework for biopsy deintensification.

2. Patients and methods

2.1. Study design, setting, and population

This retrospective multicentre study included men whose prebiopsy mpMRI showed only PI-RADS 3 lesions and who underwent an index mpMRI–ultrasonography fusion biopsy session comprising overall biopsy (overall biopsy; TBx + SBx) performed in the same session via either a TP or TR route according to local practice from January 2016 to March 2023. Patients with any concomitant PI-RADS 4 or 5 lesion were excluded. Eligible cases were retrospectively contributed from six institutional databases of academic and high-volume centres, all using mpMRI diagnostic pathways. Study reporting followed the Standards of Reporting for mpMRI-targeted Biopsy Studies recommendations [19]. The study was not designed to compare centre-specific biopsy protocols; rather, it pooled data to explore whether omission of the additional systematic component might be associated with an acceptably low absolute missed csPCa rate in selected men with PI-RADS 3 lesions, thereby supporting future prospective biopsy deintensification strategies.

Prostate mpMRI was acquired locally on 1.5-T or 3-T scanners using standard sequences and was interpreted using structured reporting according to PI-RADS version 2, with PI-RADS version 2.1 applied after local adoption [1,2]. Examinations were read locally by radiologists with dedicated prostate mpMRI expertise, supported by institutional quality assurance processes aimed at consistency of PI-RADS 3 assignment.

At each site, the prebiopsy mpMRI dataset was uploaded to a commercially available software-assisted fusion biopsy platform, on which mpMRI-visible lesions were delineated for real-time mpMRI-ultrasound coregistration (rigid or elastic, according to the system used) and targeted sampling. In-bore mpMRI-guided biopsy and cognitive targeting without software fusion were not used. Because SBx was performed according to local protocols and core-level spatial mapping was unavailable, SBx cores were not required to be spatially distinct from TBx cores and could overlap with or sample tissue adjacent to the mpMRI target. Therefore, csPCa missed by TBx was defined operationally as csPCa detected in SBx but not in TBx during the same biopsy session, without implying an anatomically separate cancer focus outside the mpMRI-visible lesion. All procedures were performed by experienced urologists (>100 mpMRI fusion biopsies). Pathological assessment was performed locally by board-certified uropathologists using International Society of Urological Pathology (ISUP) grade group standards.

Eligibility for analysis required complete prebiopsy clinical data (including clinical stage, PSAD, and lesion number) and complete histopathologic reporting for both TBx and SBx, yielding 902 evaluable patients (complete case for stratified analyses, n = 887). As radical prostatectomy specimens were not available, grading comparisons were restricted to ISUP assignments.

The primary design feature was a within-patient comparison of two classifications derived from the same procedure: a TBx-only classification (based exclusively on targeted cores) versus an OBx classification (based on any core from TBx and SBx), with csPCa defined a priori as ISUP grade group $\geq$2. The patient selection process and analytic workflow are summarised in the study flowchart (Fig. 1).

2.2. Outcomes

Prespecified outcomes compared an mpMRI targeted only with the overall classification in men with PI-RADS 3 who underwent paired targeted and systematic in the same session. Analyses were performed at the patient level in those with complete ISUP for both biopsy components (n = 902); complete-case data were used for stratified analyses when applicable (n = 887). csPCa was defined a priori as ISUP grade group $\geq$2; ciPCa was defined as ISUP 1. A sensitivity analysis used a stricter threshold for csPCa, defined as ISUP $\geq$3. Under targeted only, classification was based exclusively on targeted cores; under the combined strategy, classification was based on any core from either the targeted or the systematic component. Prespecified strata were biopsy route, PSAD categories (<0.10, 0.10–0.15, 0.15–0.20, and $\geq$0.20 ng/ml/cm^3), and targeted sampling intensity (<4 versus $\geq$4 targeted cores).

2.2.1. Primary outcome

The primary endpoint was the absolute cohort-level missed csPCa rate for the targeted-only strategy relative to the

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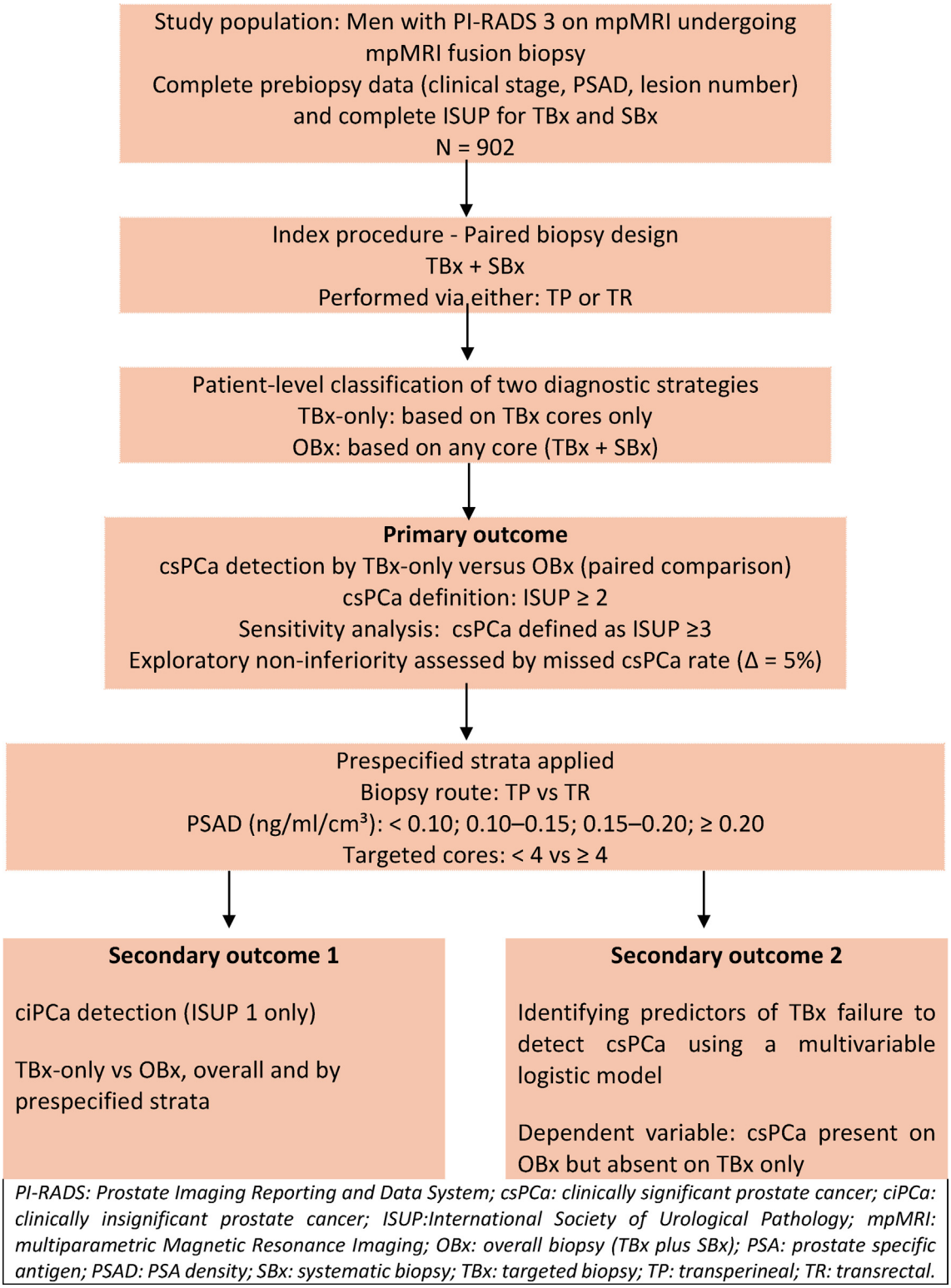

Fig. 1 – Study flowchart. PI-RADS = Prostate Imaging Reporting and Data System; csPCa = clinically significant prostate cancer; ciPCa = clinically insignificant prostate cancer; ISUP = International Society of Urological Pathology; mpMRI = multiparametric magnetic resonance imaging; OBx = overall biopsy (TBx + SBx); PSA = prostate-specific antigen; PSAD = prostate-specific antigen density; SBx = systematic biopsy; TBx = targeted biopsy; TP = transperineal; TR = transrectal.

combined strategy, defined as the proportion of men in the whole cohort in whom csPCa was detected on combined biopsy but not on TBx alone. Exploratory noninferiority analysis was performed within strata and overall. The targeted-only strategy was considered noninferior only if the upper bound of the confidence interval (CI) for the

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missed-detection rate remained below the prespecified 5% margin.

2.2.2. Secondary outcomes

Secondary outcomes were (1) detection of ISUP grade 1 cancer, defined as the proportion of men whose highest detected grade was ISUP 1 under the targeted-only versus combined strategy, overall and within prespecified strata and (2) identification of predictors of targeted-biopsy failure, defined as csPCa detected on combined biopsy but not on TBx alone, using multivariable logistic regression.

2.3. Statistical analysis

All statistical analyses were performed using R software version 4.5.1. (R Foundation for Statistical Computing, Vienna, Austria). Distributions of continuous variables were assessed using graphical methods (quantile-quantile plot), summary statistics, and normality tests (Kolmogorov-Smirnov test). Qualitative variables were summarised by counts and relative frequencies (%).

The proportions of csPCa detected by TBx were compared with OBx using the McNemar test for paired dichotomous variables. The primary outcome was tested by estimating the risk difference defined as the proportion of csPCa missed by TBx and reported with 95% CI estimated using the Clopper-Pearson exact method. Comparisons of proportions of csPCa missed by TBx were performed in prespecified low-risk strata defined by biopsy route, PSAD categories, and number of targeted cores. A noninferiority exploratory analysis was conducted to evaluate whether the effectiveness of TBx in the detection of csPCa was not clinically worse than OBx in prespecified low-risk strata. Noninferiority was concluded if the upper limit of the 90% CI [20] for the risk difference was $<\Delta = 5\%$. As a sensitivity analysis, the robustness of the findings was evaluated using two-sided 95% CIs. The comparison of the frequency of ciPCa as the highest grade detected was performed using the same statistical methods.

To identify factors associated with TBx failure to detect csPCa in patients with PI-RADS 3 and to account for rare events (59 events among 887 cases), Firth penalised logistic regression was applied [21].

We fitted a multivariable Firth penalised logistic regression model with TBx failure (csPCa on OBx but missed by TBx) as the outcome and prespecified covariates (biopsy route, PSAD category, and targeted core number), reporting odds ratios (ORs) with 95% CIs. The regression model was tested using the "logistf" R package Firth bias-reduced logistic regression, version 1.26.1 [22]. Potential two-way interactions were tested by including an interaction term in the regression model.

Model discrimination was evaluated using the area under the receiver operating characteristic (AUC) based on the model-predicted probabilities, 95% CI for AUC, whereas the calibration was assessed by calibration slope and intercept. Decision curve analysis was performed to evaluate the clinical utility of a multivariable regression model for identifying patients at risk of TBx failure. In this approach, the treat-all strategy represented performing OBx in all patients with PI-RADS 3, whereas the treat-none strategy corresponded to TBx alone without SBx sampling. All two-sided statistical tests used a significance level (α) set at 0.05. In this study, an estimated significance level $p < 0.05$ denoted a statistically significant result.

Table 1 – Demographic and clinical characteristics of the patients

Characteristics	All sample (n = 902)
Age (yr)	65 (7.3)
cTNM stage, *n* (%)	
T1	768 (85)
T2	134 (15)
PSA (ng/ml)	6.5 (5, 9.8)
mpMRI-based prostate volume (ml^2)	49 (39, 66)
PSAD (ng/ml/cm^3)	0.13 (0.09, 0.20)
Biopsy approach, *n* (%)	
Transrectal	477 (53)
Transperineal	425 (47)
Lesion multiplicity per patient, *n* (%)	
Single lesion	720 (80)
Multiple lesions	182 (20)
Maximum lesion length (mm) [a]	10 (8, 13)
Number of cores on TBx	3 (3, 4)
Number of cores on SBx	10 (7, 12)
Number of cores on OBx	13 (10, 16)
Number of positive cores on TBx [b]	2 (1, 3)
Number of positive cores on SBx [b]	2 (1, 5)

cTNM = clinical Tumor Node Metastasis classification; mpMRI = multiparametric magnetic resonance imaging; OBx = overall biopsy (TBx + SBx); PSAD = prostate-specific antigen density; SD = standard deviation; SBx = systematic biopsy; TBx = targeted biopsy.
Data were summarised as mean (SD) or median (quartile 1, quartile 3) or absolute frequency (%).
[a] mean (standard deviation)
[b] absolute frequency (%)

3. Results

3.1. Description of patients with PI-RADS 3

The analysis included 902 patients with PI-RADS 3 for whom complete data on the ISUP grade for both TBx and SBx were available. Patients' characteristics before biopsy are summarised in Table 1. The cohort comprised patients with a mean age of 65 yr (SD: 7.3), with no significant differences observed in the distribution of TP and TR biopsy approaches (chi-square test, $p = 0.08$).

TBx detected csPCa in 181 patients (20%), whereas OBx identified csPCa in 240 patients (27%) in the overall cohort. Among all 902 patients who underwent the targeted and systematic, csPCa was detected in 59 patients (6.5%) with SBx alone and in 69 patients (8%) with TBx alone (Fig. 2).

Using a stricter definition of csPCa as ISUP grade $\geq$3, TBx detected significant disease in 66 of the 902 patients (7%), whereas OBx detected significant disease in 91 of the 902 patients (10%). Therefore, 25 of the 902 patients had ISUP grade $\geq$3 disease detected by SBx but not by TBx, corresponding to an absolute omission cost of 2.8% (95% CI, 1.8–4.1) for a TBx-only strategy. Conversely, 30 of the 902 patients (3%) had ISUP grade $\geq$3 disease detected by TBx but not by SBx. Therefore, the absolute omission cost of TBx-only decreased from 6.5% in the primary ISUP grade $\geq$2 analysis to 2.8% when significant disease was defined as ISUP $\geq$3.

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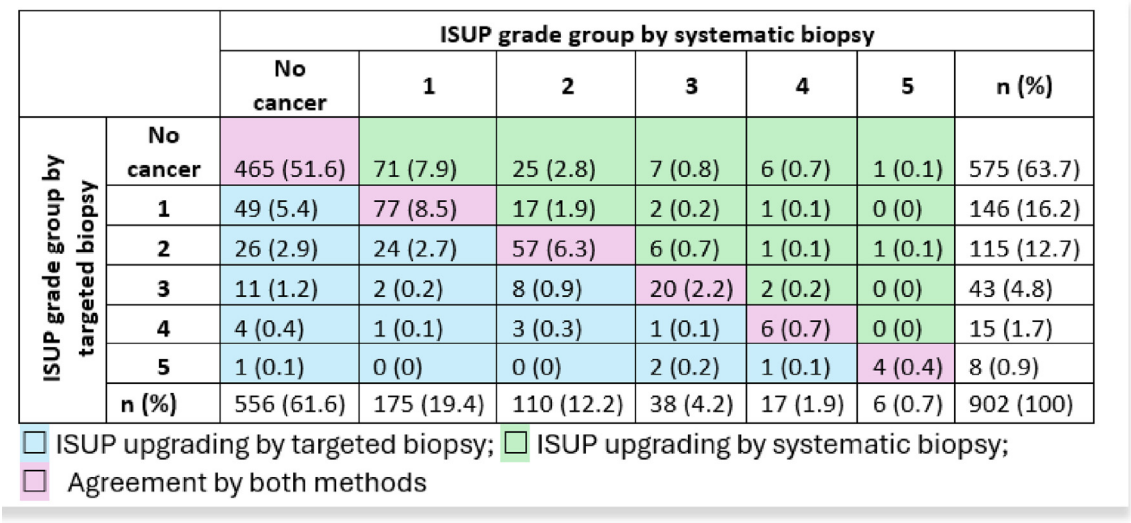

Fig. 2 – Distributions of cases by ISUP grade by targeted and systematic biopsy. The blue-shaded cells denoted the number (percentage) of men who exhibited a higher ISUP grade on TBx, whereas the green-shaded cells indicated those who were found to have a higher ISUP grade on SBx. SBx = systematic biopsy; TBx = targeted biopsy; ISUP = International Society of Urological Pathology.

3.2. *Exploratory noninferiority analysis for TBx only versus OBx for detecting csPCa in prespecified low-risk strata*

The results indicated a significant difference ($p < 0.001$) in the detection rate of csPCa between the TBx and OBx methods in all samples of patients with PI-RADS 3. Specifically, 59 cases (6.5%) were identified using the OBx approach but were not detected by TBx alone. Results were similar across PSAD-level subgroups and the number of targeted cores (Supplementary Tables 1 and 2).

After stratification by biopsy route and PSAD levels, the McNemar exact test revealed no statistically significant difference ($p > 0.99$) in csPCa detection rate between the TBx and OBx methods in patients with the TP route and PSAD <0.10 ng/ml (Table 2). The upper limit of the CI for the missed csPCa detection rate was below the prespecified margin of 5%. TBx met the criterion for noninferiority for csPCa detection in patients with the TP route and PSAD <0.10 ng/ml.

3.3. *Exploratory analysis for TBx only versus OBx for detecting ciPCa in prespecified low-risk strata*

Although TBx showed a lower csPCa detection rate compared with OBx (20% vs 27%), it was also associated with a lower ciPCa detection rate (16% vs 22%). After stratification by biopsy route, PSAD levels and number of targeted cores, TBx alone was significantly associated with a reduction in ciPCa detection rate compared with OBx in all strata (Supplementary Table 3) except for patients with TP route and

Table 2 – Detection of csPCa according to biopsy route and PSAD levels among men with PI-RADS 3

Biopsy route	PSAD subgroup (ng/ml/cm^3)	*n*	csPCa detected by TBx only [a] *n* (%)	csPCa detected by OBx, [b] *n* (%)	Missed csPCa detection rate [c] (%)	90% CI	95% CI
Transperineal	overall	425	60 (14)	81 (19)	4.9	(3.3–7)	(3.1–7.5)
	<0.10	126	10 (7.9)	11 (8.7)	0.8	(0.04–3.7) [d]	(0.02–4.3) [d]
	0.10–0.15	132	16 (12)	24 (18)	6.1	(3.1–11)	(2.7–12)
	0.15–0.20	72	15 (21)	20 (28)	6.9	(2.8–14)	(2.3–16)
	≥0.20	95	19 (20)	26 (27)	7.4	(3.5–13)	(3.0–15)
Transrectal	overall	477	121 (25)	159 (33)	8.0	(6–10)	(5.7–11)
	<0.10	126	20 (16)	31 (25)	8.7	(5.0–14)	(4.4–15)
	0.10–0.15	134	29 (22)	39 (29)	7.5	(4.1–12)	(3.6–13)
	0.15–0.20	87	23 (26)	29 (33)	6.9	(3.1–13)	(2.6–14)
	≥0.20	130	49 (38)	60 (46)	8.5	(4.8–14)	(4.3–15)

csPCa = clinically significant prostate cancer; TBx = targeted biopsy; OBx = overall biopsy (TBx + SBx); CI = confidence interval; PSAD = prostate-specific antigen density.

[a] csPCa was found on targeted cores irrespective of systematic results.

[b] The combined biopsy was considered positive if csPCa was detected on any core.

[c] Missed csPCa detection rate of targeted relative to the combined biopsy method was defined as the proportion of patients in whom csPCa was detected by combined biopsy but not by TBx.

[d] Noninferiority criterion: upper limit of the confidence interval for missed csPCa detection rate was below the pre-specified margin of $\Delta = 5\%$.

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PSAD between 0.10 and 0.15 ng/ml (Supplementary Table 4).

3.4. Factors associated with TBx failure to detect csPCa in patients with PI-RADS 3

In multivariable Firth logistic regression, the number of targeted cores remained an independent predictor for csPCa missed by TBx, each additional targeted core being associated with lower odds of TBx failure (adjusted OR = 0.69; 95% CI, 0.54–0.86). A significant interaction was observed between the biopsy route and the PSAD levels (p for interaction = 0.01), indicating that the association between biopsy route and the odds of csPCa missed by TBx varied according to the PSAD levels (Table 3). Specifically, the TP route was associated with lower odds of csPCa missed by TBx (adjusted OR = 0.13; 95% CI, 0.01–0.56) in patients with PSAD <0.10 ng/ml, whereas no such association was observed in patients with PSAD level >0.10 ng/ml (adjusted OR = 0.92; 95% CI, 0.49–1.68).

The tested multivariable logistic model showed an adequate fit to the data with moderately significant discriminative ability (Table 3).

Predicted probability of TBx failure according to the number of targeted cores was depicted in Fig. 3. Using a predicted model probability threshold of 0.05 for the risk of csPCa missed by TBx, 543 patients (61%) were classified as high-risk and selected for additional SBx. At a threshold probability of 0.05, the model avoided ~11 unnecessary systematic biopsies per 100 patients with PI-RADS 3 lesions compared with the strategy of performing OBx in all patients, without an increase in missed csPCa cases. Decision curve analysis indicated that selective addition of SBx based on model-predicted risks provided a superior net benefit compared with the OBx strategy (Fig. 4).

Table 3 – Results of multivariable model[a] based on Firth penalised logistic regression (n = 887) for TBx failure risk

Clinical characteristics	Levels	Events, n (%)	Adjusted OR (95% CI)
Clinical TNM stage	T1	53 (7.0)	1 (Reference)
	T2	6 (4.7)	0.64 (0.25–1.41)
Biopsy route[b]	Transrectal	38 (8.0)	1 (Reference)
	Transperineal	21 (5.1)	0.13 (0.01–0.56)[c]
PSAD (ng/ml/cm^3)	<0.10	12 (4.9)	1 (Reference)
	≥0.10	47 (7.3)	0.78 (0.39–1.68)
Number of targeted cores	Continuous		0.69 (0.54–0.86)

AUC = Area Under the Curve; CI = confidence interval; mpMRI = multiparametric magnetic resonance imaging; OR = odds ratio; PSAD = prostate-specific antigen density; TNM = Tumor, Node, Metastasis staging system; TBx = targeted biopsy.

[a] Outcome of the model: mpMRI-TBx failure for csPCa defined as csPCa missed by TBx and detected by OBx; Odds ratios (ORs) were estimated from multivariable penalized logistic regression (Firth) and represented adjusted associations. All reported associations were adjusted for age. ORs represented main effects while interaction effects were evaluated separately; Model's performance: AUC = 0.67; 95% CI, 0.61–0.73; Likelihood ratio test: statistics χ^2 = 22.99, df = 6, p = 0.0008; calibration intercept = 0.13; calibration slope = 1.08.

[b] p value for interaction term Biopsy route × PSAD levels = 0.01. The p-value for the interaction term was obtained from a global test for interaction, specifically an likelihood ratio test based on the difference in penalized log-likelihoods.

[c] Significant result: $p < 0.05$.

4. Discussion

In this large multicentre PI-RADS 3 cohort, TBx alone missed 59 cases of csPCa identified when the systematic component was added. Expressed at the cohort level, this absolute omission cost was 6.5% (59/902), exceeding the prespecified 5% exploratory benchmark, and it corresponded to 24.6% (59/240) of all csPCa detected by the combined approach. In the sensitivity analysis using ISUP grade ≥3 as the threshold for significant disease, the omission cost of TBx alone decreased to 2.8% (25/902). The probability of TBx failure was not uniform: omission cost was lowest in men with low PSAD undergoing TP biopsy, and a higher number of targeted cores was independently associated with lower failure.

These findings should be interpreted in the context of the well-recognised heterogeneity of PI-RADS 3 lesions despite standardised mpMRI reporting [1,2]. Practice variation remains substantial [4], and pooled PI-RADS 3 data suggest wide variation in csPCa prevalence, with the combined approach generally providing the highest detection [5]. Our data add a pragmatic estimate of the residual risk associated with omitting the systematic component in this intermediate-suspicion category.

Our findings are consistent with paired-biopsy evidence indicating that targeted and systematic sampling remain complementary rather than interchangeable in mpMRI-based diagnostic pathways [8,12,23]. A plausible explanation is imperfect spatial concordance between the mpMRI-defined target and the highest-grade focus. In PI-RADS 3 cohorts, csPCa may be identified by targeted cores alone, by template cores alone, or immediately outside the region of interest, consistent with residual diagnostic uncertainty and the "penumbra" concept [24–26].

Risk stratification within PI-RADS 3 requires more than the mpMRI category alone. A risk-adapted framework integrating mpMRI findings with PSAD has been proposed, and recent data suggest that PSAD thresholds are not uniform but may vary according to prostate volume [27,28]. Across PI-RADS 3 cohorts, PSAD has emerged as the most consistent clinical discriminator, whereas selected lesion-level mpMRI features, including Apparent Diffusion Coefficient (ADC) and lesion size, may provide further refinement in specific settings [16,17,29]. Our findings extend this literature by showing that the omission cost of a targeted-only strategy depends not only on baseline risk but also on procedural factors, particularly biopsy route and targeted sampling intensity.

Our subgroup findings extend this literature by linking PSAD-based risk to a biopsy technique–specific miss rate; TBx-only performed best when TP access was used and PSAD was low, with an observed csPCa miss rate of 0.8% in PSAD <0.10. These data support a cautious, risk-adapted hypothesis that SBx might be safely omitted in carefully selected patients with PI-RADS 3, but they also underscore that such omission is not defensible as a blanket policy given the overall noninferiority failure. In the GÖTEBORG-2 trial, the csPCa detected only by SBx were all ISUP 2, suggesting that the incremental SBx yield in mpMRI-based pathways may often represent intermediate-risk disease

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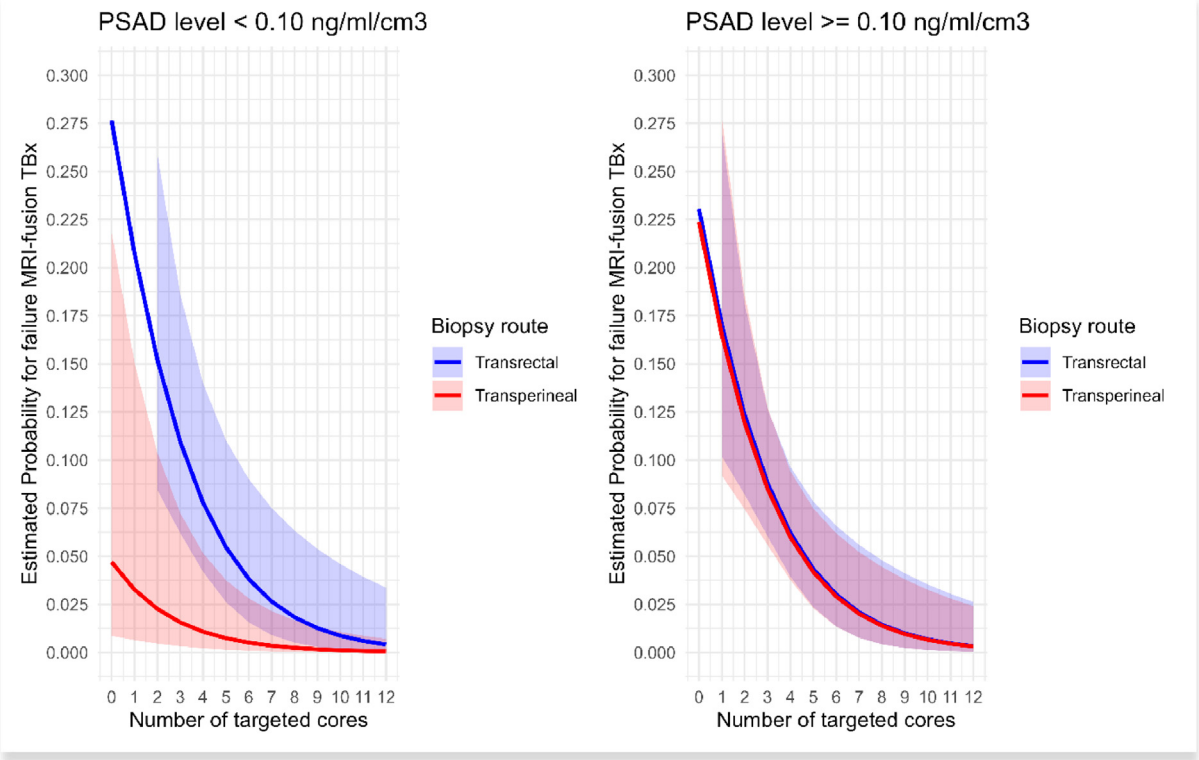

Fig. 3 – Plot of model-estimated probabilities of TBx failure by number of targeted cores, stratified by PSAD levels (<0.10 ng/ml/cm^3 vs ≥0.10 ng/ml/cm^3) and biopsy route, with all covariates held constant. Lines represented predicted probabilities derived from the Firth logistic model, and the shaded area represented corresponding confidence intervals. MRI = magnetic resonance imaging; PSAD = prostate-specific antigen density; TBx = targeted biopsy.

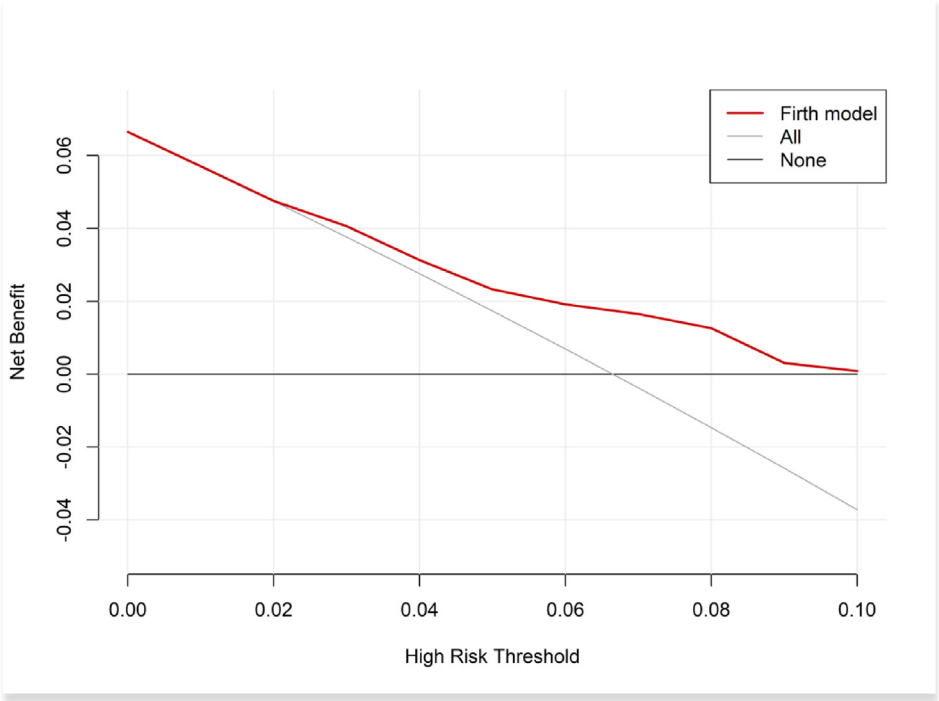

Fig. 4 – Decision curve analysis assessing the clinical utility of the multivariable model to predict TBx failure in patients with PI-RADS 3 lesions. PI-RADS = Prostate Imaging Reporting and Data System; TBx = targeted biopsy.

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rather than uniquely capturing very high-grade tumours [30]. Reassuringly, multicentre radical prostatectomy correlative data suggest that TBx overgrading has a low absolute impact on overtreatment [31]. When SBx is deferred, external follow-up cohorts indicate that subsequent assessment after an initially negative TBx can still detect csPCa, and repeat mpMRI at ~12–24 mo appears reasonable, with limited value for earlier reimaging [32,33].

Two procedural implications emerge from our findings. First, obtaining ≥4 targeted cores was associated with lower TBx failure, consistent with the risk of undersampling heterogeneous PI-RADS 3 lesions and with prior data showing that sampling strategy and registration method may influence grade concordance [34]. Second, the biopsy route may matter, although this should be interpreted cautiously. In our multivariable model, TP access was associated with lower TBx failure only in men with PSAD <0.10 ng/ml/cm^3, whereas csPCa detection remained higher in the TR cohort, likely reflecting case mix and centre-level differences in the added nontargeted component rather than route alone. This interpretation is consistent with contemporary comparative studies suggesting that the TP approach is at least diagnostically equivalent to, and possibly safer than, the TR route, particularly with respect to infectious complications [35–38].

A regional "penumbra" concept provides an anatomical rationale for sampling immediately around the mpMRI target, as most csPCa detected outside the region of interest lies within ~10 mm of the target boundary [25]. Consistent with this rationale, structured perilesional sampling has in selected settings achieved csPCa detection broadly comparable to full systematic sampling while reducing core burden and ISUP grade 1 detection [39–41]. However, its value appears context dependent: prospective and multicentre data suggest that perilesional cores may add little on top of combined targeted plus SBx, may reduce csPCa detection when substituted for systematic sampling in some settings, and can still miss contralateral disease [42–44]. The recent prospective MIRAGE study further suggests that, once a targeted plus perilesional strategy is applied, distant sampling adds minimal diagnostic benefit overall and that in PI-RADS 3 lesions perilesional sampling yields relatively more ISUP grade 1 cancers than additional ISUP 2 cancers [45]. Together, these data support prospective evaluation of regional reduced-core strategies.

Finally, the predictive model showed only moderate discrimination and should be viewed as hypothesis generating. The study was retrospective and multicentre, with centre-level heterogeneity in mpMRI interpretation, biopsy route, and sampling practice. Selection bias cannot be excluded because the databases included only men with isolated PI-RADS 3 lesions who proceeded to biopsy, and centre-specific biopsy uptake could not be determined. Differences in local biopsy thresholds may therefore limit the generalisability of our findings. The additional nontargeted component was not delivered according to a single harmonised template, and standardised core-by-core spatial mapping relative to the mpMRI target was unavailable; consequently, potential overlap between targeted and nontargeted cores could not be quantified, particularly in diffuse bilateral PI-RADS 3 abnormalities, and lesion-location effects could not be analysed reliably. Combined biopsy within the same session, rather than whole-mount pathology, served as the reference standard, so "missed" csPCa refers to cancer detected by the added nontargeted component rather than disease absence on exhaustive pathology. In addition, the 5% margin was applied as an exploratory benchmark in an observational dataset rather than within a prospectively designed noninferiority framework. Accordingly, the subgroup findings require independent prospective external validation before they can inform biopsy deintensification strategies.

5. Conclusions

In this PI-RADS 3 cohort, TBx alone should not be considered a universal substitute for OBx when csPCa is defined as ISUP grade ≥2. The absolute omission cost of a targeted-only strategy exceeded the exploratory benchmark in the primary analysis but decreased when significant disease was defined more strictly as ISUP grade ≥3. This distinction is clinically relevant because management of ISUP grade 2 disease varies according to patient and disease context. The omission cost of TBx alone was not uniform and appeared lower in men with low PSAD undergoing TP biopsy, particularly when targeted sampling intensity was higher. These subgroup findings are hypothesis generating and require prospective external validation before being used to guide biopsy deintensification strategies.

Author contributions: Mihaela Iancu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Buhas, Iancu, Ploussard.
Acquisition of data: Buhas, Mjaess, Diamand, Peyrottes, Uleri, Baboudjian, Borz, Crisan, Baudewyns, Jabbour, Jeglinschi, Ploussard.
Analysis and interpretation of data: Buhas, Mjaess, Diamand, Peyrottes, Uleri, Brown, Abou Chakra, Borz, Baudewyns, Jabbour, Jeglinschi, Iancu, Ploussard.
Drafting of the manuscript: Buhas, Iancu.
Critical revision of the manuscript for important intellectual content: Buhas, Mjaess, Diamand, Peyrottes, Uleri, Brown, Abou Chakra, Iancu, Ploussard.
Statistical analysis: Iancu.
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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2026.07.003.

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