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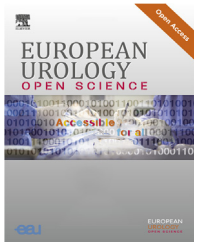

European Association of Urology

Prostate Cancer

# Targeting All Multiple Magnetic Resonance Imaging Prostate Lesions Does Not Enhance Cancer Detection: Insights from the YAU Prostate Cancer Group

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**Abstract**

***Background and objective:*** Although diagnostic efficacy of multiparametric magnetic resonance imaging (MRI) in identifying index lesions (ILs) in prostate cancer (PCa) patients is well established, challenges arise when multiple lesions (MLs) are present. Determination of an optimal biopsy strategy for these patients is crucial. This study aims to assess the risk of detecting PCa and clinically significant PCa (csPCa; International Society of Urological Pathology [ISUP] grade group $\geq$2) when targeting suspicious MRI MLs in addition to the IL.

***Methods:*** We included 1310 biopsy-naïve patients with only a single MRI lesion (SL) and 621 men with MLs. Patients underwent a subsequent targeted biopsy (TBx) of each lesion, along with a systematic biopsy (SBx). We compared TBx alone versus TBx + SBx and evaluated whether the presence of MLs increases the risk of

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PCa and csPCa using a multivariable logistic regression model (MVA), while accounting for confounders.

***Key findings and limitations:*** Overall, PCa was detected in 57.6% and 51.2% of IL-TBx for the SL and ML groups, respectively ($p \leq 0.01$). The rates of detection of csPCa with IL-TBx were 46.2% for the SL group and 36.1% for the ML group ($p < 0.01$). When combining all TBx and SBx procedures, PCa was detected in 63.8% for the SL group and 67.0% for the ML group ($p = 0.2$), while csPCa was detected in 54.1% for the SL group and 48.1% for the ML group ($p = 0.01$). SBx yielded PCa detection rates of 58.5% for the SL group and 56.7% for the ML group ($p = 0.5$) and csPCa detection rates of 42.1% for the SL group and 38.8% for the ML group ($p = 0.2$). ISUP upgrading targeting the 2° and 3° lesions was found in 14 (12.2%) and six (5.2%) cases, respectively. In the MVA, the presence of MLs was identified as an independent predictor of PCa (odds ratio [OR]: 0.6, 95% confidence interval [CI]: 0.5–0.8, $p < 0.01$) and csPCa (OR: 0.5, 95% CI: 0.4–0.6, $p < 0.01$) in TBx and combined TBx + SBx (PCa: OR: 0.6, 95% CI: 0.5–0.9, $p = 0.02$, and (csPCa: OR: 0.4, 95% CI: 0.3–0.7, $p < 0.01$), respectively.

***Conclusions and clinical implications:*** Patients with MLs have a lower risk of PCa and csPCa. In case of MLs, a TBx of the IL + a concomitant SBx allows for the diagnosis of the vast majority of PCa and csPCa cases. The added value of a second TBx on the non-IL is modest, including only a 5.6% increase in the diagnosis of csPCa.

***Patient summary:*** We studied whether targeting multiple suspicious areas on prostate magnetic resonance imaging increases cancer detection. We found that patients with multiple lesions had a lower risk of prostate cancer than those with a single lesion. Targeting the largest suspicious area along with sampling the entire prostate led to the detection of most cancer cases, with little added benefit from targeting the other smaller areas.



## 1. Introduction

The evolving landscape of prostate cancer (PCa) diagnosis has been transformed markedly by the integration of multiparametric magnetic resonance imaging (mpMRI) with a targeted biopsy (TBx) [1]. This advancement, developed over a decade of clinical research and practice, underscores the critical role of mpMRI in refining the diagnostic pathway for PCa [2]. The advent of mpMRI has facilitated accurate targeting of suspicious lesions, prompting the adoption of a TBx within modern diagnostic protocols. A TBx significantly enhanced the detection rates of clinically significant PCa (csPCa), surpassing the efficacy of conventional diagnostic approaches that rely solely on a systematic biopsy (SBx).

A recent systematic review and meta-analysis [3] of 70 studies involving 13 330 patients evaluated the diagnostic accuracy and cancer detection rates (CDRs) of Prostate Imaging Reporting and Data System (PI-RADS) version 2.1 for prostate magnetic resonance imaging (MRI). The findings demonstrated high sensitivity (96%) but low specificity (43%) for PI-RADS scores of $\geq$3. For PI-RADS scores of $\geq$4, sensitivity was slightly lower (89%) but with higher specificity (66%). CDRs increased with PI-RADS scores, ranging from 6% for PI-RADS 1 to 84% for PI-RADS 5.

The diagnostic efficacy of mpMRI in identifying index lesions (ILs) is well established; yet, challenges arise when multiple lesions (MLs) are present, a scenario with a reported prevalence of 20–50% [4–6]. Indeed, mpMRI has limited accuracy in detecting multifocal csPCa, missing about 30% of cases outside the IL [7].

Despite the acclaim for a TBx as an optimal biopsy strategy, evidence suggests that incorporation of an SBx alongside a TBx offers a more comprehensive diagnostic evaluation, given the multifocality of PCa within the gland [8–10]. The current literature offers limited insights into the added diagnostic value of targeting secondary lesions with lower PI-RADS scores or smaller sizes on mpMRI. Thus, determination of an optimal biopsy strategy for this specific patient population remains an ongoing debate and area of investigation. Current guidelines recommend targeting all suspicious areas identified on mpMRI. However, this approach may lead to overdiagnosis and overtreatment, be time consuming, increase the risk of complications, and potentially contribute to stage and grade migration.

This study evaluates the optimal prostate TBx schemes in men with MLs visible on prostate mpMRI and determines whether targeting all suspicious areas increases the risk of PCa and csPCa in lesions other than the IL described on prostate mpMRI.

## 2. Patients and methods

Approval from the Internal Review Board was obtained from each participating institution according to their respective policies. The data from each center were

anonymized and transferred to a centralized computerized databank for an analysis. This multicenter study involved 1931 biopsy-naïve patients from ten tertiary care institutions, who underwent mpMRI followed by a TBx using mpMRI software registration and a simultaneous SBx between December 2016 and November 2020. The inclusion criteria required participants to have at least one suspicious lesion with a PI-RADS (v.2 until 2019 and v.2.1 from 2019 onward) score of ≥3. Patients with a single lesion (SL) were compared with patients with MLs at mpMRI. Patients who had received previous biopsies or treatment for PCa were excluded.

### 2.1. Multiparametric MRI protocol

Each institution performed mpMRI according to their local specific protocol (in line with the PI-RADS recommendations). Expert genitourinary radiologists reviewed all MRI scans following the European Society of Urogenital Radiology and European Society of Urological Imaging consensus guidelines for image acquisition, interpretation, and radiologists' training [11]. The IL was identified as the lesion with the highest PI-RADS assessment category and/or the largest size if MLs were present in the same category.

### 2.2. Biopsy procedures

All TBx procedures were performed by experienced urologists with >100 cases [12], using either a transrectal or a transperineal (TP) approach. The TP-TBx was conducted with a brachytherapy grid or freehand technique, employing either a fusion (TP-fusion-TBx) or a cognitive (TP-cognitive-TBx) technique under general or local anesthesia. In case of MLs at MRI, a TBx was performed for each suspicious area. A median of three (two to four) TBx samples were taken from each suspicious lesion. The median number of SBx procedures performed in all patients was 14 (10–16).

### 2.3. Covariates and outcomes

Clinically significant and clinically insignificant PCa (ciPCa) were defined as an International Society of Urological Pathology (ISUP) grade group of ≥2 and <2, respectively. The detection of PCa and csPCa was evaluated for an SL and MLs, respectively, using TBx and SBx + TBx.

### 2.4. Statistical analysis

Categorical variables were reported as frequencies, while continuous variables were presented as medians with quartiles and interquartile ranges. Differences between categorical variables were assessed using the chi-square test. For continuous variables, the *t* test or Mann-Whitney *U* test was used, as appropriate. The diagnostic findings from both an MRI TBx and an MRI SBx were analyzed to determine the presence of csPCa and ciPCa. These findings were used to create a Sankey diagram, which illustrated the flow and distribution of diagnostic outcomes across SL and ML patients. A multivariable logistic regression analysis was conducted to identify the prebiopsy predictors of PCa and csPCa, calculating the odds ratio (OR) for the SL versus MLs. The variables included in the model were age, clinical stage, prostate-specific antigen (PSA) at TBx, prostate volume, PI-RADS score of the IL, and maximum diameter of the IL.

When radical prostatectomy (RP) was performed, predictors of positive surgical margins (PSMs), positive nodes, and ISUP grade ≥2 at RP were also assessed using multivariable logistic regression. All tests were two tailed, with significance set at $p < 0.05$. Statistical analyses were conducted using SPSS version 23 (IBM, Armonk, NY, USA) and R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

## 3. Results

### 3.1. Patients characteristics

This study included 1310 patients in the SL group and 621 patients in the ML group. The patient characteristics are described in Table 1. PSA, PSA density, and the maximum diameter of the IL were comparable between the groups (all $p > 0.05$). A PI-RADS score of >3 for the IL was found in 64.6% of the SL group and 73.2% of the ML group ($p < 0.01$). In the ML group, 81.6% had two lesions and 18.4% had three or more lesions ($p < 0.01$).

No differences were observed in the percentage of MLs per center ($p > 0.05$).

Three distinct Sankey diagrams were generated to visually represent the diagnostic findings of csPCa and ciPCa across various lesion scenarios: an SL (Supplementary Fig. 1), two lesions (Supplementary Fig. 2), and three lesions (Supplementary Fig. 3). These diagrams illustrate the outcomes following the TBx of the IL and any secondary lesions, along with the added diagnostic impact of incorporating SBx procedures.

The additional diagnostic yields for detecting csPCa and ciPCa when an SBx was added to an SL were 4.9% and 4.5%, respectively; for MLs, the yields were 3.7% and 4.6%, respectively ($p > 0.05$).

### 3.2. ISUP and PCa TBx results

For the IL, PCa was found in 57.6% of the SL group and 51.2% of the ML group ($p < 0.01$); csPCa was found in 46.2% of the SL group and 36.1% of the ML group ($p < 0.01$). Additionally, PCa and csPCa were found in 23.0% and 13.2% for TBx 2, and in 25.4% and 12.2% for TBx 3, respectively. Second and third lesion biopsies showed an upgrading of the TBx of the IL in 29 (6.0%) and six (5.2%) cases, respectively.

### 3.3. Clinical and radiological predictors of PCa and csPCa

In the multivariable analysis, MLs versus SL predict the presence of PCa (OR: 0.6, 95% confidence interval [CI]: 0.5–0.8, $p < 0.01$) and csPCa (OR: 0.5, 95% CI: 0.4–0.6, $p < 0.01$) at the TBx.

When combining an SBx and a TBx, MLs versus SL predict the presence of PCa (OR: 0.6, 95% CI: 0.5–0.9, $p = 0.02$) and csPCa (OR: 0.4, 95% CI: 0.3–0.7, $p < 0.01$).

All the most important covariates included in the models were confirmed to be predictors of PCa and csPCa (Tables 2–5).

**Table 1 – Patients' characteristics**

| | All groups | SL (*n* = 1310) | ML (*n* = 621) | *p* value |
|---|---|---|---|---|
| Age (yr) | 67 (61–71) | 67.3 (62–67) | 67 (62–72) | 0.3 |
| PSA | 8.2 (5.3–17.2) | 8.7 (5.5–8.7) | 8.8 (5.7–15.9) | 0.1 |
| PSAD | 0.19 (0.1–0.5) | 0.19 (0.11–0.71) | 0.19 (0.11–0.71) | 0.5 |
| DRE | 750 (39.4) | 517 (40.2) | 233 (37.8) | 0.3 |
| Prostate volume | 44 (32–61) | 44.0 (32–61) | 44.0 (32–61) | 0.7 |
| TR | 833 (43.1) | 591 (45.1) | 242 (39) | 0.01 |
| TP | 1098 (56.9) | 719 (54.9) | 379 (61) | |
| Max diameter IL (mm) | 10 (8–15) | | | 0.01 |
| Max diameter 2° lesion | 8 (6–12) | | 8 (6–12) | – |
| Max diameter 3° lesion | 9 (6–12) | | 9 (6–12) | – |
| PI-RADS IL | | | | <0.01 |
| 3 | 629 (32.6) | 463 (35.3) | 166 (26.7) | |
| 4 | 924 (47.9) | 599 (45.7) | 325 (52.3) | |
| 5 | 378 (19.6) | 248 (18.9) | 130 (20.9) | |
| No. of lesions | | | | – |
| 1 | 1310 (67.8) | 1310 (100) | – | |
| 2 | 507 (26.3) | – | 507 (81.6) | |
| 3 | 114 (5.9) | – | 114 (18.4) | |
| ISUP target IL | | | | <0.01 |
| Negative | 859 (44.5) | 556 (42.4) | 303 (48.8) | |
| 1 | 242 (12.5) | 148 (11.3) | 94 (15.1) | |
| 2 | 396 (20.5) | 283 (21.6) | 113 (18.2) | |
| 3 | 231 (12.0) | 168 (12.8) | 63 (10.1) | |
| 4 | 143 (7.4) | 110 (8.4) | 33 (5.3) | |
| 5 | 60 (3.1) | 45 (3.4) | 15 (2.4) | |
| PCa target IL | 1072 (55.5) | 754 (57.6) | 318 (51.2) | <0.01 |
| csPCa target IL | 830 (43) | 606 (46.2) | 224 (36.1) | <0.01 |
| ISUP target 2° lesion | | | | – |
| Negative | 370 (76) | – | 370 (73.0) | |
| 1 | 50 (10.3) | | 50 (9.8) | |
| 2 | 41 (8.4) | | 41 (8.0) | |
| 3 | 18 (3.7) | | 18 (3.1) | |
| 4 | 6 (1.2) | | 6 (1.1) | |
| 5 | 2 (0.2) | | 2 (0.1) | |
| Missing | 20 (3.9) | | 20 (3.9) | |
| PCa target 2° lesion | 117 (23.0) | – | 117 (23.0) | – |
| csPCa target 2° lesion | 67 (13.2) | – | 67 (13.2) | – |
| ISUP target 3° lesion | | – | 78 (68.4) | – |
| Negative | | | 15 (13.1) | |
| 1 | | | 8 (7.0) | |
| 2 | | | 6 (5.2) | |
| 3 | | | 0 | |
| 4 | | | 0 | |
| 5 | | | 7 (6.1) | |
| Missing | | | | |
| PCa target 3° lesion | | | 29 (25.4) | – |
| csPCa target 3° lesion | | | 14 (12.2) | – |
| ISUP upgrading targeting 2° lesion | | | 29 (6.0) | – |
| ISUP upgrading targeting 3° lesion | | | 6 (5.2) | – |
| ISUP SBx | | | | 0.3 |
| Negative | 813 (42.1) | 544 (41.5) | 269 (43.3) | |
| 1 | 325 (1.8) | 214 (16.3) | 111 (17.9) | |
| 2 | 416 (21.5) | 280 (21.4) | 136 (21.9) | |
| 3 | 189 (9.8) | 131 (10.0) | 58 (9.3) | |
| 4 | 124 (6.4) | 93 (7.1) | 31 (5.0) | |
| 5 | 64 (3.3) | 48 (3.7) | 16 (2.6) | |
| PCa SBx | 1118 (57.9) | 766 (58.5) | 352 (56.7) | 0.5 |
| csPCa SBx | 793 (41.1) | 552 (42.1) | 241 (38.8) | 0.2 |
| ISUP SBx + TBx | | | | 0.2 |
| Negative | 657 (34.0) | 432 (33.0) | 225 (36.2) | |
| 1 | 266 (13.8) | 169 (12.9) | 97 (15.6) | |
| 2 | 477 (24.7) | 327 (25.0) | 150 (24.2) | |
| 3 | 273 (14.1) | 191 (14.6) | 82 (13.2) | |
| 4 | 178 (9.2) | 132 (10.1) | 46 (7.4) | |
| 5 | 80 (4.1) | 59 (4.5) | 21 (3.4) | |
| PCa SBx and TBx | 1274 (66) | 396 (63.8) | 878 (67.0) | 0.2 |
| csPCa SBx and TBx | 1008 (52.2) | 709 (54.1) | 299 (48.1) | 0.01 |

csPCa = clinically significant prostate cancer; DRE = digital rectal examination; IL = index lesion; ISUP = International Society of Urological Pathology; Max = maximum; ML = multiple lesions; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; PSAD = PSA density; SBx = systematic biopsy; SL = single lesion; TBx = targeted biopsy; TP = transperineal approach; TR = transrectal approach.

**Table 2 – Univariable and multivariable predictors of PCa at TBx**

| Parameter | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *p* value | OR | 95% CI | *p* value |
| ML vs SL | 0.8 | 0.6–1.1 | 0.08 | 0.6 | 0.5–0.8 | <0.01 |
| Age | 1.0 | 1.0–1.1 | <0.01 | 1.0 | 1.0–1.1 | <0.01 |
| cT ≥2 vs cT <2 | 5.4 | 4.5–6.4 | <0.01 | 2.2 | 1.7–2.7 | <0.01 |
| PSA at biopsy | 1.1 | 1.1–1.1 | <0.01 | 1.1 | 1.1–1.1 | <0.01 |
| PSAD | 26.8 | 19–37 | <0.01 | | | |
| Prostate volume | 0.9 | 0.9–0.9 | <0.01 | 0.3 | 0.3–0.4 | <0.01 |
| PI-RADS (higher) | | | <0.01 | | | <0.01 |
| 3 | 1 | Ref | – | 1 | Ref | – |
| 4 | 3.5 | 2.9–4.2 | <0.01 | 3.4 | 2.8–4.8 | <0.01 |
| 5 | 11.9 | 9.1–15.5 | <0.01 | 9.6 | 5.4–15.2 | <0.01 |
| Max diameter lesion | 1.1 | 1.1–1.1 | <0.01 | 1.1 | 1.1–1.1 | <0.01 |

CI = confidence interval; Max = maximum; ML = multiple lesions; OR = odds ratio; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; PSAD = PSA density; Ref = reference; SL = single lesion; TBx = targeted biopsy.

**Table 3 – Univariable and multivariable predictors of csPCa at TBx**

| Parameter | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *p* value | OR | 95% CI | *p* value |
| ML vs SL | 0.7 | 0.6–0.8 | <0.01 | 0.5 | 0.4–0.6 | <0.01 |
| Age | 1.0 | 1.0–1.1 | <0.01 | 1.0 | 1.0–1.1 | <0.01 |
| cT ≥2 vs cT <2 | 5.5 | 4.6–6.5 | <0.01 | 2.9 | 2.4–3.8 | <0.01 |
| PSA at biopsy | 1.0 | 1.0–1.1 | <0.01 | 1.1 | 1.1–1.1 | <0.01 |
| PSAD | 14.7 | 11–19 | <0.01 | | | |
| Prostate volume | 0.9 | 0.9–0.9 | <0.01 | 0.3 | 0.3–0.4 | <0.01 |
| PI-RADS (higher) | | | <0.01 | | | <0.01 |
| 3 | 1 | Ref | – | 1 | Ref | – |
| 4 | 3.8 | 3.1–4.7 | <0.01 | 3.6 | 2.7–4.8 | <0.01 |
| 5 | 10.3 | 8.0–13.2 | <0.01 | 6.1 | 4.4–10.9 | <0.01 |
| Max diameter lesion | 1.1 | 1.1–1.1 | <0.01 | 1.1 | 1.1–1.1 | <0.01 |

CI = confidence interval; csPCa = clinically significant prostate cancer; Max = maximum; ML = multiple lesions; OR = odds ratio; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; PSAD = PSA density; Ref = reference; SL = single lesion; TBx = targeted biopsy.

**Table 4 – Univariable and multivariable predictors of PCa at SBx and TBx**

| Parameter | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *p* value | OR | 95% CI | *p* value |
| ML vs SL | 0.9 | 0.7–1.1 | 0.2 | 0.6 | 0.5–0.9 | 0.02 |
| Age | 1.0 | 1.0–1.1 | <0.01 | 1.0 | 1.0–1.1 | <0.01 |
| cT ≥2 vs cT<2 | 7.1 | 5.7–8.8 | <0.01 | 2.2 | 1.6–2.8 | <0.01 |
| PSA at biopsy | 1.0 | 1.0–1.1 | <0.01 | 1.1 | 1.1–1.1 | <0.01 |
| PSAD | 20.9 | 19–32 | <0.01 | | | |
| Prostate volume | 0.9 | 0.9–0.9 | <0.01 | 0.3 | 0.3–0.4 | <0.01 |
| PI-RADS (higher) | | | <0.01 | | | <0.01 |
| 3 | 1 | Ref | – | 1 | Ref | – |
| 4 | 4.0 | 3.3–4.8 | <0.01 | 3.5 | 2.7–4.5 | <0.01 |
| 5 | 12 | 9–15 | <0.01 | 6.1 | 4.4–16.6 | <0.01 |
| Max diameter lesion | 1.1 | 1.1–1.1 | <0.01 | 1.1 | 0.9–1.0 | 0.5 |

CI = confidence interval; Max = maximum; ML = multiple lesions; OR = odds ratio; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; PSAD = PSA density; Ref = reference; SBx = systematic biopsy; SL = single lesion; TBx = targeted biopsy.

To assess the robustness of our findings, we conducted additional analyses using ISUP grade of ≥3 as the outcome in the logistic regression for TBx and TBx + SBx. The results were consistent with those obtained using the definition of ISUP ≥2 (see Supplementary Tables 3 and 4).

### 3.4. *Treatments and concordance with final pathology*

Supplementary Table 1 summarizes the RP specimen data for 750 patients. The ML group had fewer PSMs than the SL group (18.5% vs 27.2%, $p = 0.01$).

The presence of MLs was also tested as a predictor of PSMs, positive nodes, and ISUP grade ≥2 at RP in an multivariable logistic regression model. Among these models, only PSMs were predicted by MLs versus an SL (OR: 0.5, 95% CI: 0.3–0.7, $p < 0.01$; Supplementary Table 2).

## 4. Discussion

In the present study, we investigated whether targeting of MLs increases the risk of finding PCa and csPCa at TBx and TBx + SBx. Interestingly, we found that patients with an SL have a higher risk of aggressive disease and PSMs if RP was performed. The added value of targeting a secondary lesion is minimal, contributing to improved tumor characterization in no more than 5.6% of cases.

**Table 5 – Univariable and multivariable predictors of csPCa at SBx and TBx**

| Parameter | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *p* value | OR | 95% CI | *p* value |
| ML vs SL | 0.8 | 0.6–0.9 | 0.02 | 0.4 | 0.3–0.7 | <0.01 |
| Age | 1.0 | 1.0–1.1 | <0.01 | 1.0 | 1.0–1.1 | <0.01 |
| cT ≥2 vs cT <2 | 6.4 | 5.3–7.6 | <0.01 | 3.0 | 2.4–3.8 | <0.01 |
| PSA at biopsy | 1.1 | 1.1–1.1 | <0.01 | 1.1 | 1.1–1.1 | <0.01 |
| PSAD | 22.9 | 16–31 | <0.01 | | | |
| Prostate volume | 0.9 | 0.9–0.9 | <0.01 | 0.3 | 0.3–0.4 | <0.01 |
| PI-RADS (higher) | | | <0.01 | | | <0.01 |
| 3 | 1 | Ref | – | 1 | Ref | – |
| 4 | 3.3 | 2.8–4.0 | <0.01 | 3.5 | 2.7–4.5 | <0.01 |
| 5 | 14 | 10–19 | <0.01 | 6.1 | 4.4–8.5 | <0.01 |
| Max diameter lesion | 1.1 | 1.1–1.1 | <0.01 | 1.1 | 0.9–1.0 | 0.2 |

CI = confidence interval; csPCa = clinically significant prostate cancer; Max = maximum; ML = multiple lesions; OR = odds ratio; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; PSAD = PSA density; Ref = reference; SBx = systematic biopsy; SL = single lesion; TBx = targeted biopsy.

Specifically, our study highlights several key considerations. First, the primary diagnostic focus should remain on the IL, typically the lesion with the highest PI-RADS score or the largest volume/size [13]. The modest increase in csPCa detection from targeting a non-IL suggests that a routine TBx of these secondary lesions may not be necessary in most cases. A treatment strategy based on a TBx of the IL and an SBx appears adequate, as the concordance with the final pathology is comparable with that of cases with an SL. This finding is consistent with the findings of previous studies that questioned the need to biopsy all mpMRI-visible lesions. For instance, Stabile et al [14] demonstrated that of the addition of a TBx of secondary lesions did not improve csPCa detection rates significantly when SBx and IL-TBx procedures were already performed. Thus, determination of the optimal number of cores for a TBx requires balancing the need to minimize sampling errors with ensuring comprehensive PCa detection, tailored to each patient's individual characteristics and the prostate [15]. Currently, there is no evidence that the presence of MRI MLs is a predictive factor for PSMs [16]. However, the role of a contralateral SBx to the IL seems reasonable for correct surgical planning, whether for nerve-sparing surgery or focal therapy preoperatively.

Second, in a small subset of cases, the highest-grade or most csPCa cases may not always correspond to the largest or most suspicious lesion on mpMRI. While the concept of the IL in multifocal PCa has widely been accepted as the primary determinant of disease prognosis [17], our findings underscore the need for a better understanding of the relationship between mpMRI findings and pathological outcomes, and it may prompt a re-evaluation of how MLs are evaluated with imaging and managed during and after biopsy. While mpMRI detects 45% of all PCa and 65% of csPCa cases successfully, its sensitivity decreases notably in patients with MLs [5]. Specifically, mpMRI missed at least one PCa focus in 45% of men with MLs, compared with 34% overall [5]. Smaller, low-grade, multifocal, and nonindex tumors were more likely to be missed [5]. These considerations may explain the results from Patel et al [6], which showed that the presence of MLs on mpMRI was not associated with increased detection of csPCa (multiple regions of interest OR: 1.05, 95% CI: 0.60–1.84, $p = 0.857$). However, the study included a relatively small subset of patients, with only 145 (38% of the study population) having at least two lesions.

Third, a correct assessment of the IL becomes important as an indicator of higher-risk disease. Therefore, accurate MRI assessment of the IL is critical for guiding surgical planning and minimizing the risk of a single PSM or multiple PSMs. Thus, predictive models for assessing side-specific extraprostatic extension in the era of MRI TBx [18] should also consider this important variable. Additionally, the appropriateness of focal therapy targeting only the main tumor area may be reasonable in cases of MLs, if an adequate SBx is performed [18]. The presence of contralateral or multifocal disease can influence treatment decisions substantially, especially for patients being considered for focal therapy, in whom only a portion of the prostate is treated. This also has implications for the surgical approach RP, particularly regarding the extent of nerve-sparing techniques. MLs, especially when identified through an SBx, are often associated with more aggressive cancer characteristics, such as extracapsular extension and seminal vesicle invasion, both of which can affect postoperative outcomes and subsequent treatment plans.

An SBx is vital for detecting cancer beyond the primary lesion or the IL identified by MRI [19]. The amount of cancer identified in these biopsy cores may serve as an indicator of tumor volume outside the primary lesion, which has been linked to an increased risk of lymph node involvement and biochemical recurrence after surgery. Clinicians can enhance preoperative planning by understanding the complete extent of csPCa through both an MRI TBx and an MRI SBx. A key factor in prostate MRI is to ensure optimal image quality. Prostate MRI scans should consistently be acquired at the highest possible standard, ideally achieving a Prostate Imaging Quality (PI-QUAL) version 2 score of 3. Additionally, the results of these scans should be interpreted exclusively by specialized genitourinary radiologists with extensive expertise in prostate MRI evaluation [20].

This study is not without limitations. The retrospective nature of this analysis may introduce a selection bias, and the modest increase in csPCa detection with an ML TBx could be influenced by patient-specific factors that were not fully accounted for in our study. Additionally, the results may be affected by the definitions used for the IL, csPCa, and ciPCa, which could vary across different clinical

contexts. TP access was more frequently used in the ML group. However, as shown by recent prospective studies and meta-analyses [21], no significant differences exist in the detection rates between the various biopsy methods. We could not correct the yield of the additional targeted cores to the second lesion for the yield that any systematic core would also have regarding PCa detection. We could not explore the molecular and genetic characteristics of the ILs and nonindex lesions to determine whether there are specific subgroups of patients who might benefit from more extensive biopsy protocols or treatments. We could not exclude the possibility that SL versus ML status affects the nerve-sparing strategy, as more aggressive surgery in ML cases appears to result in less surgical margin positivity. We accounted for the additional lesions missed by MRI TBx and detected them through random sampling at a "per-patient" level rather than at a "per-lesion" level. Additionally, further evaluation with site-specific positive margins and longer follow-up after RP was not available. This is particularly important in cases where a non-IL may harbor aggressive disease that could be missed if only the IL is targeted during a TBx. Finally, no data on complications and pain during the procedure were collected.

## 5. Conclusions

Patients with MLs are at a lower risk of PCa and csPCa. The diagnostic benefit of targeting a non-IL is limited, supporting a biopsy strategy focused on the IL with an SBx, and potentially omitting an additional TBx of an SL in most cases. Surgical strategies should prioritize the correct IL identification to minimize the PSM risk.

***Author contributions***: Fabio Zattoni 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.

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## Appendix A. Supplementary material

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