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# Comparison of TRUS and combined MRI-targeted plus systematic prostate biopsy for the concordance between biopsy and radical prostatectomy pathology

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## Abstract

**Aim:** To evaluate the accuracy in histologic grading of MRI/US image fusion biopsy by comparing conventional 12-core TRUS-Bx at radical prostatectomy specimens (RP).

**Methods:** Consecutive patients diagnosed prostate cancer (127 with combination of both targeted biopsy (TBx) plus systematic biopsies (SBx) and separate patient cohort of 330 conventional TRUS-Bx without mpMRI) with a PSA level of <20 ng/mL prior to RP were included. The primary end point was the grade group concordance between biopsy and RP pathology according to biopsy technique.

**Results:** Clinically significant prostate cancer detection was 51.2% for TRUS-Bx, 49.5% for SBx, 67% for TBx and 75.7% for TBx + SBx. Upgrading and downgrading of at least one Gleason Grade Group (GGG) was recorded in 43.3%/ 6.7% patients of the TRUS-Bx and in 20.5%/ 22% of the TBX + SBx group, respectively (all $P < .001$). Concordance level was detected to be significantly higher for ISUP 1 in combined TBx + SBx method compared to conventional TRUS-Bx (61.3% vs 37.9%, $P = .014$). In ISUP 1 exclusively, significant upgrading was seen in TRUS-Bx (62.1%) when compared to TBx (41.4%) and TBx + SBx (38.7%).

**Conclusions:** MRI-targeted biopsies detected more significant PCa than TRUS-Bx but, superiority in significant cancer detection appears as a result of inadvertant selective sampling of small higher grade areas. Within an otherwise low grade cancer and does not reflect accurate GGG final surgical pathology. TBx + SBx has the greatest concordance in ISUP Grade 1 with less upgrading which is utmost important for active surveillance.

## 1 | INTRODUCTION

Twelve core transrectal ultrasound guided prostate biopsy (TRUS-Bx) is the most commonly used method for the diagnosis of prostate cancer (PCa). However, it may be hampered by several limitations such as not being targeted and not fully anatomical systematic biopsy method when we look at the magnetic resonance imaging (MRI) studies.[1-3] This method is also shown to be associated with missed diagnosis of PCa, misclassification of cancer grade and high upgrading and downgrading levels after RP.[4,5] Upgrading can in fact lead to inappropriate or under-treatment in a subgroup of patients. A more accurate diagnostic method is crucial to avoid

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misclassification, which is particularly important in appropriate decision-making for the treatment of PCa such as active surveillance or other therapies. Prior researches have shown that multiparametric MRI-targeted biopsy identifies clinically significant prostate cancers more accurately than conventional systematic biopsy in men with suspected localised prostate cancer.[6-9] Despite the improved detection of clinically significant cancers with MRI-targeted biopsies, debate persists about whether MRI-targeted biopsy better predicts final pathology at radical prostatectomy.[10,11] The MRI-targeted biopsy results in the previous studies reported that targeted biopsies have a higher rate of concordance level with the RP compared to systematic biopsy.[6-8,12-14] However, there is limited data comparing to head to head concordance, upgrading and downgrading between conventional TRUS-Bx and MRI Fusion biopsies according to ISUP grade groups. Whether MRI/US image fusion biopsy techniques better correlate with final histopathologic outcomes by reducing Gleason Score misclassifications deserves further evaluation.

In this context, we aimed to analyse the ISUP Gleason group grading concordance between prostatectomy and biopsy stratified by the approach of biopsy technique (TBx + SBx vs TRUS-Bx). Optimal agreement between biopsy and surgical Gleason Score among three biopsy schemes TBx alone vs SBx alone vs combined TBx + SBx is also investigated.

**Whats known**

MRI-targeted biopsies are reported to be able to better detect high-grade cancers than systematic biopsies and TRUS. However, several recent studies have reported a mismatch in the biopsy and radical prostatectomy Gleason Score. Despite the improved detection of clinically significant cancers with MRI-targeted biopsies, considerable disparity exists in the literature regarding MRI-targeted biopsy's ability to better detect RP pathology in biopsy-naive men over conventional TRUS biopsies.

**Whats new**

Combined TBx + SBx provides improved detection rates particularly for higher grade disease over either systematic or MRI-targeted biopsy or TRUS-Bx alone. However, superiority in significant cancer detection did not reflect accurate Gleason Grade Group in whole prostate gland at final surgical pathology due to selective sampling of higher grade areas within an otherwise low grade cancer. There is a risk of overtreatment if biopsy GGG was taken as the sole parameter for treatment decision by TBx + SBx. Conventional TRUS-Bx has superior concordance with radical prostatectomy for ISUP Grade 2,3,5 however increased upgrading should be taken into account.

## 2 | MATERIAL AND METHODS

We retrospectively reviewed completely anonymised data from nation-wide tertiary centres in Prostate Cancer Database of Turkish Urooncology Association. MRI-targeted biopsy is limited yet in this country and several centres are using conventional 12-core transrectal ultrasound-guided prostate biopsy (TRUS-Bx) protocol without mpMRI for the diagnosis of prostate cancer. Therefore, our prostate biopsy database has two different data entry: first separately from conventional TRUS-Bx without mpMRI and second MRI fusion biopsy (combined targeted and concomitant systematic biopsies) registered accordingly from collaborating centres in our database. Biopsy naive patients who were diagnosed with prostate cancer either with conventional TRUS-Bx or MRI-Targeted biopsy combined with systematic 12-core biopsy (TBx + SBx) and underwent radical prostatectomy (RP) between 2017 and 2020 were evaluated in this study. Cognitive MRI fusion biopsies were excluded. Patients who had PSA level less than 20 ng/mL were included in the study to exclude high-grade advanced PCa to ensure proportional distribution of PCa grades between biopsy methods. Patients who had complete pathological data of each Bx scheme and data of RP were investigated. The patients' age, PSA level, the highest GS and ISUP grades from each Bx scheme, RP pathology and upgrade/downgrade ratios were assessed. Patients were divided into two groups as Combined TBx + SBx and conventional TRUS-Bx method. Data were compared between these groups. Also, a sub-group analysis of the concordance of ISUP grades, upgrade, downgrade ratios between TBx alone, SBx alone and combination TBx + SBx scheme was investigated.

All TRUS-Bx biopsies were taken with a transrectal approach under local anesthesia using the 12 core approach. All mpMRI for targeted biopsies were reviewed by a specified institutional radiologist. In patients with a PI-RADS-lesion ≥ 3 (according to PI-RADS-v2 classification),[15] MRI-Targeted ultrasound fusion biopsy using different software-based platforms according to participant centre's property MIMS Symphony Dx® (MIM Software), bk3000® (BKMedical), UroNav® (Invivo Corp, Philips) was conducted. MRI image fusion-targeted biopsies were taken from each target with at least 2 or more core samples from each target lesion. In addition to targeted biopsies, systematic random biopsies were also performed using the 12-core approach.

The biopsy GS was defined as the highest Gleason score in at least one core and was reported using the ISUP Consensus Conference 2014 grading system.[16]

### 2.1 | Statistical analysis

Study data were gathered and managed using REDCap electronic data capture tools hosted at Urooncology Association Turkey.[17,18] REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies. The *t*-test, Mann-Whitney *U*-test and $\chi^2$test were used to analyse the relationship of categorical and continuous variables

between two biopsy methods and three biopsy schemes of the combined biopsy method. A $P < .05$ were considered statistically significant.

## 3 | RESULTS

Data from 457 patients who underwent RP after the diagnosis of PCa in 127 patients with combined TBx + SBx and 330 with conventional TRUS-Bx method were evaluated. Patient demographics of the study cohort stratified by biopsy approach are depicted in Table 1. Mean age and PSA values between the groups were similar. The median number of targeted biopsy cores sampled per region of interest (ROI) was 4 (range 2-7).

In the comparison of biopsy ISUP grades between TRUS-Bx and targeted biopsies, higher ISUP grades were detected by combined TBx + SBx. Significant cancer detection was 49.5% for SBx, 67% for TBx and highest 75.7% for Combination TBx + SBx. There was significant difference in missed cancer ratio between TBx and SBx (10.2% vs 24.4%) that any grade cancer detection by SBx alone was significantly lower than TBx alone.

ISUP distributions and upgrade/ downgrade ratios of the methods are also given in Figures 1 and 2 and Tables 1. Overall Biopsy and surgical pathologic ISUP Grade were concordant in 50% men of the TRUS-Bx and in 57.5% of the combined TBX + SBx group ($P = .152$). Gleason upgrading/ downgrading of at least one Gleason Grade Group (GGG) was recorded in 43.3%/ 6.7% patients of the TRUS-Bx and in 20.5%/ 22% of the TBX + SBx group, respectively (all $P < .001$).

In the evaluation of conventional TRUS-Bx method according to ISUP grades, concordance achieved in 37.9%, 70% and 56.1%, in ISUP 1, 2 and 3 grades, respectively, at RP pathology. In the TRUS-Bx group, after prostatectomy, significant upgrading of 62.1% was detected in ISUP 1 grade (Figure 3).

For ISUP 1 grade, TBx + SBx and TBx showed significantly higher concordance over SBx at RP (Figure 2). Concordance level was significantly higher for ISUP 1 in combined TBx + SBx method compared to conventional TRUS-Bx (61.3% vs 37.9%, $P = .014$). In patients with biopsy ISUP 1 exclusively, significant upgrading was seen in TRUS-Bx (62.1%) and SBx (55.5%) when compared to TBx (41.4%) and TBx + SBx (38.7%). Upgrading rates for ISUP 2 were similar in SBx, TBx and TBx + SBx. However, for ISUP, 2 downgrading rates were significantly higher in TBx and TBx + SBx when compared to SBx alone. For ISUP Grade 2, SBx and TRUS-Bx showed similar upgrading and downgrading rates. In ISUP 2, all biopsy methods showed similar upgrading but downgrading was higher in TBx and TBx + SBx probably due to over sampling tersiyer 4 pattern in biopsy. Combined TBx + SBx showed significant downgrading in 47.8% and 54.6% for ISUP 3 and 4, respectively. For ISUP 3, 4 and 5 groups TBx, SBx and TBx + SBx showed similar concordances. No upgrading was detected in SBx group for ISUP 3, 4 but downgrading was higher in SBx group when compared to TBx and TBx + SBx. For ISUP grade 2, TRUS-Bx showed the highest concordance among all biopsy methods (70%) with less downgrading (Figure 3). For ISUP 2 and 3, TRUS-Bx showed superior but not significant concordance than combined TBx + SBx method (70% vs 64.7% $P = .509$ and 56.1% vs 43.5%, $P = .332$). For ISUP 3 and 4, TRUS-Bx showed higher upgrading and less downgrading when compared to TBx + SBx.

**TABLE 1** Patients' characteristics and pathological findings of Combined MRI-TBx + SBx method and Conventional TRUS-Bx method

| Variables | | Combined MRI-TBx + SBx method (n = 127) | | | Conventional TRUS-Bx method (n = 330) | *P* |
|---|---|---|---|---|---|---|
| Age (year) | | 63.6 ± 6.4 (43-77) | | | 62.7 ± 6.8 (42-77) | .224 |
| PSA (ng/dL) | | 8.1 ± 4.9 (1-31.6) | | | 8.5 ± 4 (1.8-19.9) | .327 |
| Bx schemes | | SBx | TBx | Combined TBx + SBx | TRUS-Bx | – |
| Biopsy ISUP Grades | Missed | 31 (24.4) | 13 (10.2) | 0 (0) | 0 (0) | – |
| | 1 | 33 (26) | 29 (22.8) | 31 (24.4) | 161 (48.8) | <.001[a] |
| | 2 | 36 (28.3) | 48 (37.8) | 51 (40.2) | 100 (30.3) | |
| | 3 | 15 (11.8) | 19 (15) | 23 (18.1) | 41 (12.4) | |
| | 4 | 5 (3.9) | 9 (7.1) | 11 (8.7) | 17 (5.2) | |
| | 5 | 7 (5.5) | 9 (7.1) | 11 (8.7) | 11 (3.3) | |
| RP GS | | 7 ± 0.8 (6-10) | | | 7 ± 0.8 (6-9) | .623 |
| RP ISUP Grades | 1 | 27 (21.3) | | | 67 (20.3) | .966 |
| | 2 | 61 (48) | | | 159 (48.2) | |
| | 3 | 24 (18.9) | | | 57 (17.3) | |
| | 4 | 7 (5.5) | | | 22 (6.7) | |
| | 5 | 8 (6.3) | | | 25 (7.6) | |
| Upgrading rate | | 26 (20.5) | | | 143 (43.3) | <.001 |

[a] $\chi^2$ test was performed between highest ISUP grades of Combined TBx + SBx scheme and Conventional TRUS-Bx.

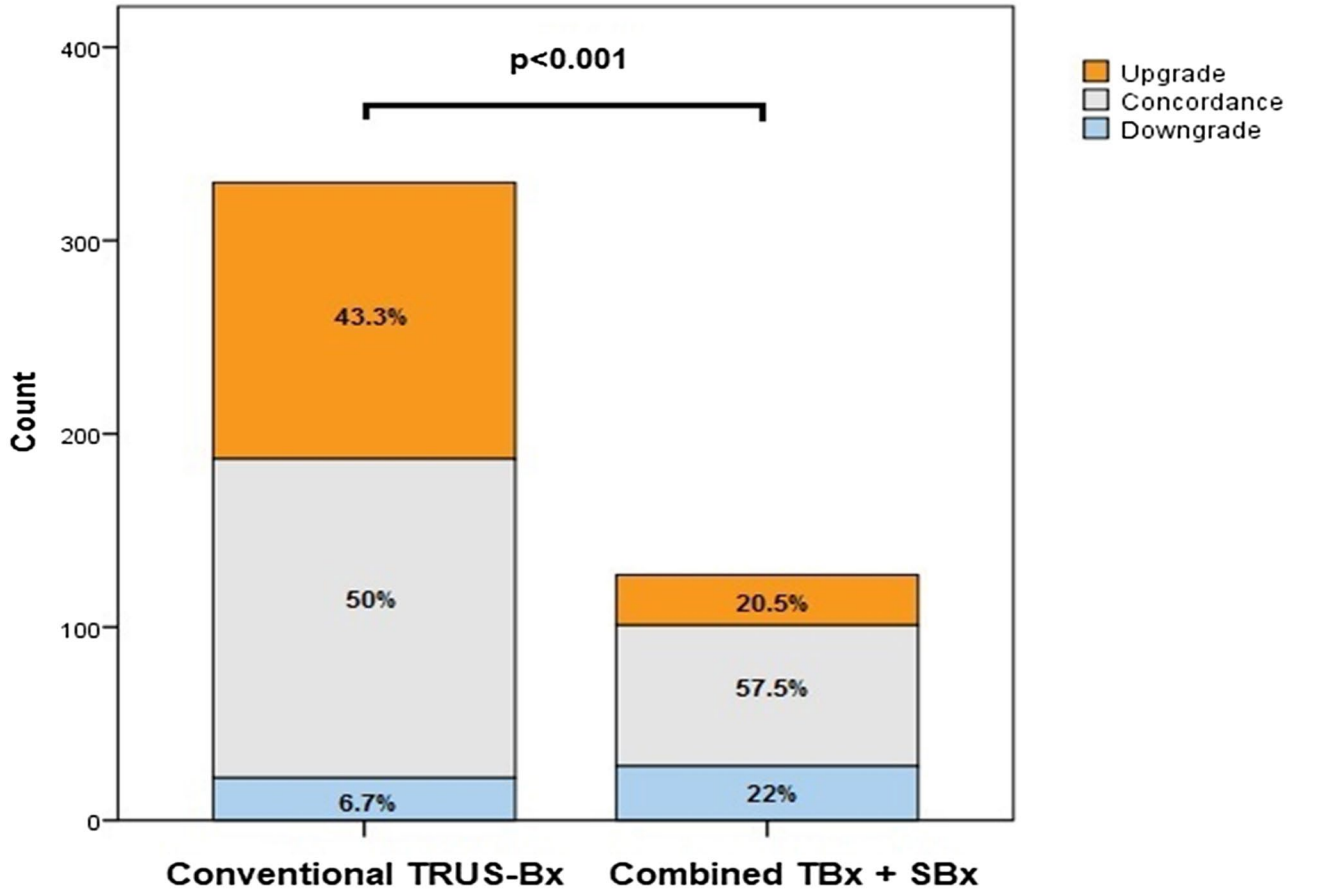


**FIGURE 1** Concordance, upgrade and downgrade ratios between Combined TBx + SBx and Conventional TRUS-Bx method

Conventional TRUS-Bx showed the worst concordance with 17.6% at ISUP Grade 4 with an upgrading rate of 47.1%, which might be a reflection of inadequate sampling.

## 4 | DISCUSSION

The Gleason grading system has been shown to be the most important determinant of tumour aggressiveness, disease outcome and mortality from prostate cancer.[19] Gleason Score discordance can confound optimal treatment allocation of patients diagnosed with prostate cancer and place them at risk of worse oncological outcomes. MRI-targeted biopsies, which utilise previously taken MRI images of suspected cancer and fuse them with real-time ultrasound images, are reported to be able to detect high-grade cancers better than systematic biopsies and TRUS.[6-9,20,21] However, several recent studies have reported a mismatch in the biopsy and radical prostatectomy Gleason Score.[10,11,22] Despite the improved detection of clinically significant cancers with MRI-targeted biopsies, considerable disparity exists in the literature regarding MRI-targeted biopsy's ability to better detect RP pathology in biopsy-naive men over conventional TRUS biopsies.[10,11,22] We performed this study in order to investigate if targeted prostate biopsy has a performance superior to untargeted biopsy in determining the optimal agreement between biopsy and surgical Gleason Score. Our findings suggest that in the overall patient cohort, combined TBx + SBx provides improved detection rates particularly for higher grade disease over either systematic or MRI-targeted biopsy or TRUS-Bx alone. However, superiority in significant cancer detection did not reflect accurate Gleason Grade Group in the whole prostate gland at final surgical pathology due to selective sampling of higher grade areas within an otherwise low grade cancer. MRI-targeted biopsy was better in the prediction of the result of final histopathological analysis for ISUP 1 and ISUP 4 than systematic biopsies or TRUS-Bx. Our analysis of biopsy techniques according to ISUP Grade groups showed increased downgrading in MRI fusion biopsy and increased upgrading in TRUS-Bx.

In this cohort of patients, combined TBx + SBx biopsy provided more accurate diagnosis than MRI-targeted or systematic biopsy alone. Consistent with earlier studies, we found higher cancer detection rates on TBx when compared to SBx.[7,9,23] However, 13 out of 127 prostate cancers (10.2%) were missed by TBx alone. Missed cancers by TBx may reflect the underlying limitation of mpMRI which might result from factors such as PCa not visible on mpMRI, varying inter-reader agreement on the mpMRI results and/or missing the target lesion in biopsy.

Our results have shown that MRI-targeted biopsies are significantly better for the detection of clinically significant PCa (ISUP 2

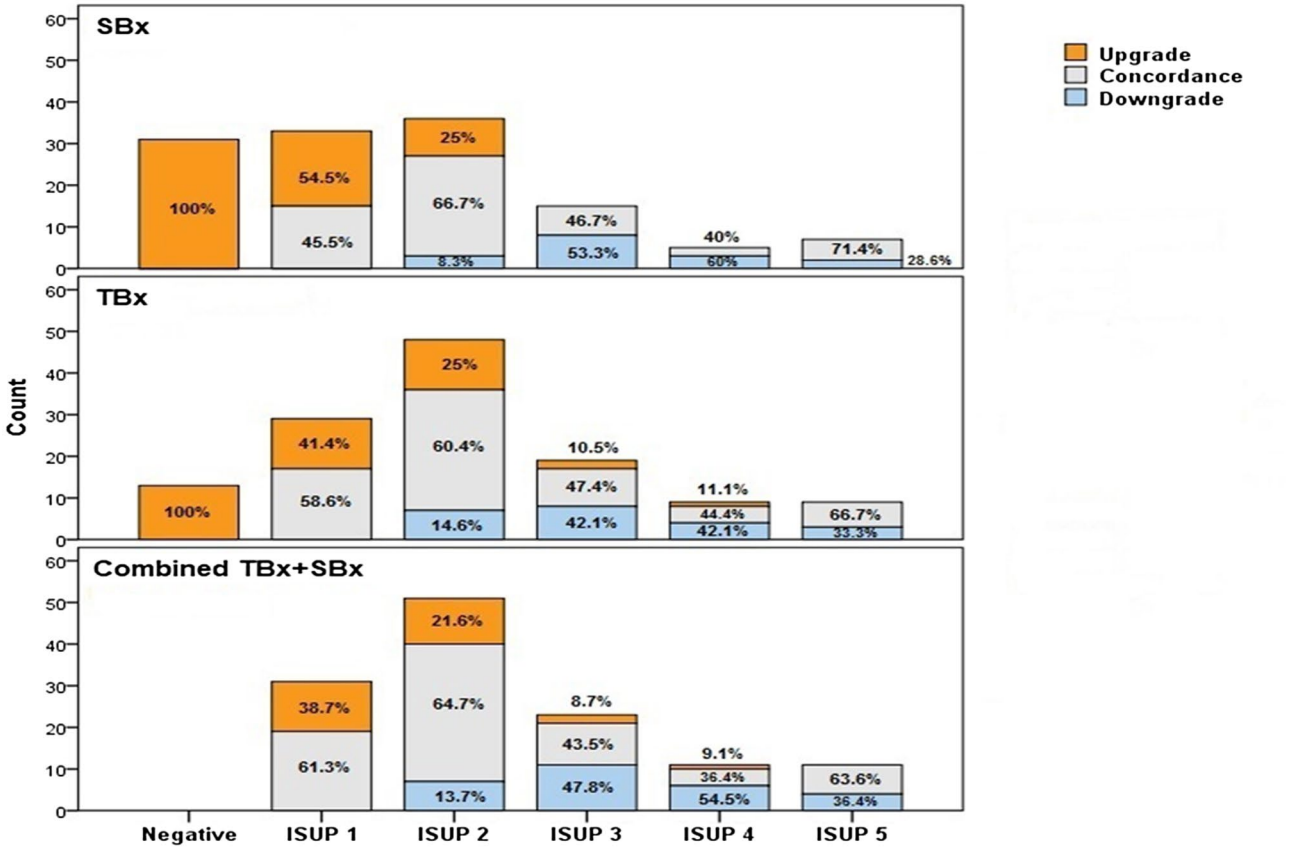


**FIGURE 2** Concordance, upgrading and downgrading of biopsy compared to RP ISUP grades stratified by biopsy approach

or higher) than TRUS-Bx. Almost half of the cancers detected by TRUS-Bx were in ISUP grade 1 category. When TBx alone is compared to SBx alone for the detection rate of significant prostate cancer diagnosis, overall targeted biopsy alone tends to detect more significant PCa but this superiority does not reach statistical difference. In the present study, SBx had superior performance to TRUS-Bx in determining high-grade cancers. This could be a result of the cognitive fusion bias within the SBx that the urologist performing the SBx was aware of the localisation of the suspicious lesion on mpMRI. In our study, if a pure TBx strategy omitting SBx is applied, this will lead to missing significant prostate cancer in 11 patients. Our results support the notion that in order to obtain the most accurate assessment of the entire prostate gland especially for patients at risk of significant disease, SBx remains necessary, in addition to the TBx due to limitations of mpMRI performance/reading and of precision during lesion targeting.

In this study, combined TBx + SBx showed significantly better concordance than any biopsy method alone in ISUP Grade 1. Also, combined TBX + SBx prostate biopsy resulted in significantly less pathologic upgrading in ISUP 1 grade group as compared with TRUS-Bx at prostatectomy (38.7% vs 62.1%). Men under active surveillance in ISUP Grade 1 group diagnosed by TRUS-Bx are at significantly greater risk of subsequent reclassification by confirmatory biopsies. It has been reported that up to 40% of men potentially suitable for AS had unfavourable disease at RP and these high rates of adverse pathologic findings which can underestimate aggressiveness of the disease.[24-26] Upgrading is particularly a great concern in the context of active surveillance. Pathologic upgrading has been shown to be associated with adverse outcomes, including higher rates of biochemical recurrence.[27,28] A recent study by our group has shown that men suitable for AS, but elected immediate RP, proved to have a GS upgrade rate of 30.6% and a pathological upstaging rate of 13.2%.[29] In the present study, our results clearly suggest that TRUS-Bx based active surveillance decision should be questioned unless confirmatory mpMRI TBx + SBx is done. In the active surveillance scenario, it is imperative to decrease the risk of missing a high-grade disease and delaying a radical treatment, providing more confidence to the urologist and the patient with conservative management of PCa. Based on our data, multiparametric MRI TBx + SBx is the best available strategy to stratify men to AS with reliable eligibility and should be included in the AS protocols for a more accurate grading of PCa.

Among all biopsy methods, the lowest concordance was achieved in ISUP Grade 4. Combined TBx + SBx showed significantly better concordance than TRUS-Bx in ISUP Grade 4. At this group, TRUS-Bx showed increased upgrading (47.1%) but in contrast TBx + SBx showed increased downgrading (54.6%). Downgrading may be due to oversampling that small foci of Gleason 5 detected at biopsy but not documented at radical prostatectomy.[4] In ISUP Grade 4, SBx was better than TRUS-Bx. This, again, shows that inadequate diagnostic biopsy sampling is high in TRUS-Bx and most of the SBx are not blind and affected by MRI cognition.

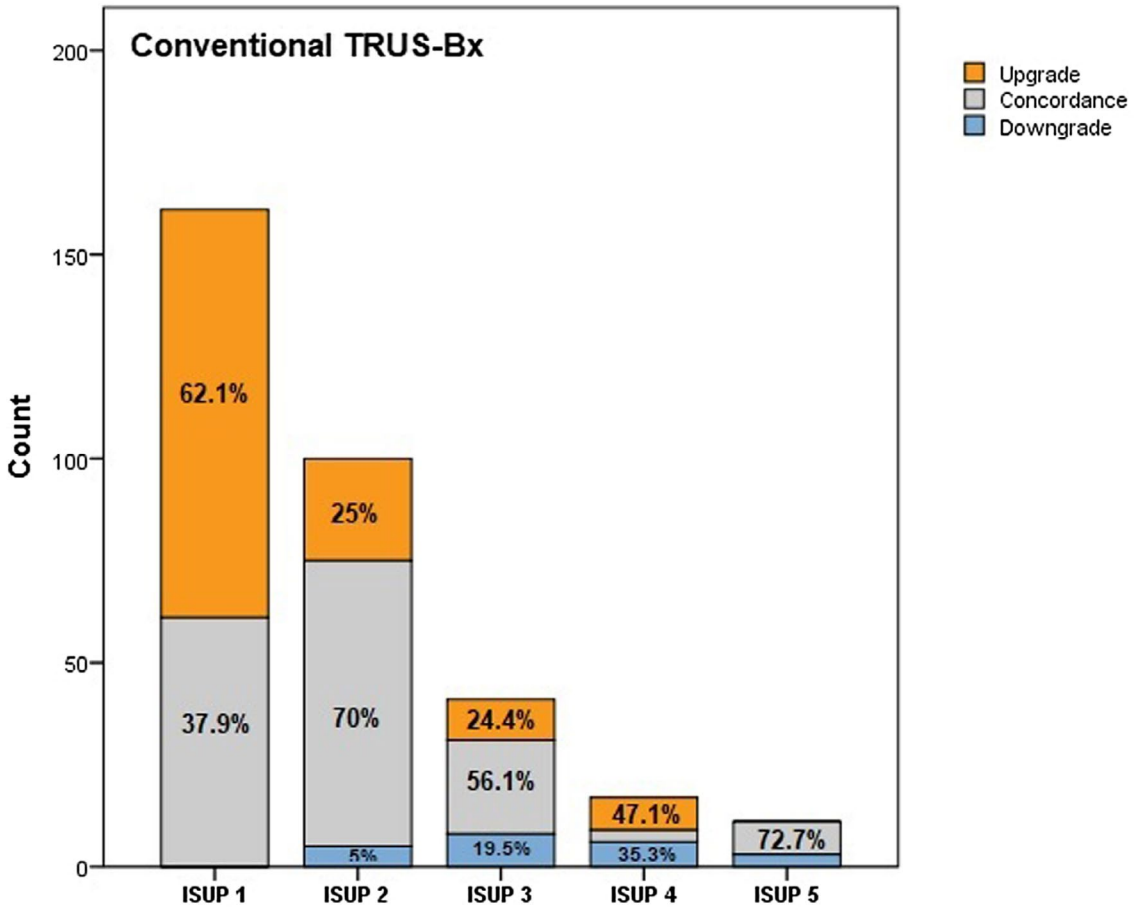


**FIGURE 3** Concordance, upgrading and downgrading of conventional TRUS biopsy compared to RP ISUP grades

Our study has demonstrated that TRUS-Bx concordance was superior for ISUP 2, 3 and 5 Grade Groups than TBx + SBx. In all ISUP groups except 1 and 4, TRUS-Bx showed better performance in predicting final pathology with higher concordance. MRI-Targeted biopsies are more prone to downgrading and TRUS biopsies are more upgraded. In the present study, downgrading was higher in TBx + SBx biopsy group compared to conventional TRUS-Bx. Downgrading may occur for several reasons, including over-sampling of the very small (less than 5%) foci of Gleason pattern 4 or 5 cancer.[4,30] There is a risk of oversampling with increased number of targets registered by radiologist and increased number of biopsy cores taken at discretion of the biopsy performer. A very small foci of Gleason pattern 4 or 5 tumour might be missed by the routine radical prostatectomy pathologic examination or might be noted as the presence of a tertiary Gleason pattern if these small tumours are detected. It is reported that the issue of accounting for tertiary grade patterns is significant as can be seen in almost 20% of RP specimens.[4] An increased number of target lesions on mpMRI and thus, an increased number of core biopsy per lesion may cause needle biopsy to sample a tertiary higher grade pattern in the RP, which is not recorded in the standard GS reporting, resulting in apparent overgrading on the needle biopsy. Our results suggest that if the physician is assigning the patient as high-risk group solely based on biopsy pathology, there would be a risk of overtreating quite a few patients. Having increased the percentage of surgical pathology downgrading, MRI fusion biopsy implies a high rate of overdiagnosis of Gleason sum 8 scores on biopsy, potentially leading to suboptimal treatment strategies and patient distress.

Although conventional TRUS-Bx is a blind, nontargeted and not always anatomically systematic biopsy, our findings portray that TRUS-Bx is superior but not yet significant over SBx in accurate prediction of final pathology. However, there is a difference of 7.6% and 22.4% for ISUP 1 and 4 grades between the schemes respectively favouring SBx. This may be a result of cognitive impact of MRI findings that the unblind nature of systematic biopsies after mpMRI were probably contaminated by MRI findings and not even described to be so, in practice it influences and orients biopsy.

The major limitations of our study are its retrospective nature and analysis. Another limitation is that TBx data were obtained from five different centres performed by seven different urologists using different MRI and MRI-US Fusion devices. Failure of mpMRI fusion biopsy due to mpMRI incorrect image registration or mismatch of image planes, inaccurate sampling and intralesional Gleason Score heterogeneity may have impacted our results. Another important limitation is that there was no centralised pathological examination, multicentric pathological examinations by uropathologists at respective centres. However, our data reflect the real-life nationwide picture.

In conclusion, our results have shown that MRI-targeted biopsies are significantly better for the detection of clinically significant PCa than TRUS-Bx. However, superiority in significant cancer detection appears at least in part as a result of oversampling of higher grade areas within an otherwise low grade cancer rendering a risk of overtreatment if biopsy GGG was taken as a unique parameter for treatment decision. TRUS-Bx has superior concordance with radical prostatectomy for ISUP 2-4 grade groups, but increased upgrading should also be taken into account leading to undertreatment. MRI-Targeted biopsies combined with systematic biopsies has the greatest concordance in ISUP Grade 1 which is of utmost importance for active surveillance indicating that active surveillance decision should be based on MRI-targeted + systematic biopsies either at initial diagnosis or in confirmatory biopsy.

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## APPENDIX

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