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ORIGINAL PAPER

Magnetic resonance imaging target fusion biopsy vs. transrectal ultrasound-guided biopsy - A comparative study of ISUP score upgrading risk in the final radical prostatectomy specimen

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Summary *Objectives: The aim of this study was to compare the risk of International Society of Urological Pathology (ISUP) score upgrading between magnetic resonance imaging targeted fusion biopsy (MRI-TB) and transrectal ultrasound-guided biopsy (TRUS-B) in the final radical prostatectomy (RP) specimen pathological report.*
Materials and methods: This retrospective single center study included 51 patients with prostate cancer (PCa) diagnosed with MRI-TB and 83 patients diagnosed with TRUS-B between October/2019 and July/2021. We compared the rates of ISUP score upgrading between both groups after robotic-assisted radical prostatectomy (RARP) and the specific transition of each ISUP score based on biopsy modality. The rate of ISUP score concordance and downgrading were also assessed. To define the intra and interobserver concordance for each ISUP score in biopsy and RP specimen for each biopsy modality, the Cohen's Kappa coefficient was calculated. ISUP scores and biopsy modality were selected for multivariate analysis and a logistic regression model was built to provide independent risk factors of ISUP score upgrading.
Results: The difference of the rate of upgrading between MRI-TB group and TRUS-B group was statistically significant ($p = 0.007$) with 42.2% of patients of TRUS-B group experiencing an upgrade in their ISUP score while only 19.6% in MRI-TB group. Concordance and downgrading rates did not statistically differ between the two groups. Strength of concordance using Cohen's Kappa coefficient was fair in both groups but higher in MRI-TB group (TRUS-B group $k = 0.230$; $p < 0.001$; concordance: 47% vs. MRI/TB group $k = 0.438$; $p < 0.001$; concordance: 62.7%). Biopsy modality and ISUP 1 on biopsy were independent predictors of ISUP upgrading after RP.
Conclusions: MRI-TB is highly accurate with lower risk of PCa upgrading after RP than TRUS-B. Patients with ISUP 1 on biopsy have greater susceptibility to upgrading their ISUP score.

KEY WORDS: *Gleason Score; ISUP score; MRI-TB; Prostate cancer; TRUS-B; Upgrading.*

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INTRODUCTION

According to data from the *Global Cancer Observatory*, published in March 2021, 6750 new cases of prostate cancer (PCa) were diagnosed in *Portugal* in 2020, equivalent to 20% of all malignancy in men (1). In terms of incidence, PCa ranks first followed by colorectal cancer (19%) and lung cancer (11.6%) (1). PCa is a highly heterogeneous disease and therefore, the *European Association of Urology* (EAU) has established a risk group classification based on initial serum *prostate-specific antigen* (PSA), biopsy *Gleason Score* (GS), and clinical stage. There are several therapeutic strategies available according to the risk group (2). As a diagnostic assay, PSA clinical utility is ambiguous due to the lack of specificity and sensitivity for PCa, leading to many pointless biopsies with possibility of complications for the patient and potential overdiagnoses of low-risk tumors and its overtreatment (3).
In terms of prognosis, GS has a key role as a predictor of PCa clinical outcome (4). Donald Gleason developed this grading scoring system in 1966 (5). During the evolution and establishment of the GS grading system, multiple refinements were introduced to improve its performance. In 2014, the *International Society of Urological Pathology* (ISUP) proposed a modified grading system classification (ISUP grading system) based on GS, after reviewing in detail the main limitations of the previous 2005 version. This reviewed version of ISUP grading system was further adopted and disseminated worldwide by World Health Organization in 2016 (6, 7).
In recent years, there has also been a great development in the imaging field. The availability of *multiparametric magnetic resonance imaging* (mpMRI) in current clinical practice has revolutionized PCa diagnosis and staging. *Magnetic resonance targeted fusion biopsy* (MRI-TB) tends to be a valuable diagnostic method and more accurate for detecting clinically significant PCa (ISUP > 2 or GS > 7) than conventional strategies (PSA, *digital rectal examination* (DRE), and systematic biopsy) (8-10).
Despite scientific debate, several studies have shown that ISUP score of prostate biopsies is not always in concordance with the pathological report of RP specimens even when MRI-TB is performed (11, 12). The *transrectal ultrasound-guided biopsy* (TRUS-B) of the prostate may omit high-grade tumors areas because it is not targeted to a specific suspicious lesion but a random biopsy. On the

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other hand, targeted biopsy may overestimate the presence of a high-grade tumor (13). The potential for undertreatment or overtreatment resulting from the lack of correlation between the ISUP score of the prostate biopsy and RP specimen may seriously impair the patient's quality of life and prognosis. Here we aim to compare ISUP score of prostate biopsy and RP specimen when MRI-TB or TRUS-B is performed and identify potential predictive factors associated with ISUP score upgrading.

Materials and methods

Study design and case selection

We retrospectively analyzed a database of prospectively collected demographics and clinicopathological data from our institution. All consecutive patients subjected to *robotic-assisted radical prostatectomy* (RARP) by four different surgeons, between 10/2019 and 07/2021 were included in the study cohort. Those patients were divided into 2 groups according to the biopsy modality used for PCa diagnosis: MRI-TB group or TRUS-B group. Patients underwent prostate biopsy due to PSA elevation (> 4 ng/mL), abnormal DRE, or/and at least suspicious abnormalities in ultrasound or mpMRI findings. We decided that patients who were submitted to neoadjuvant hormones or chemotherapy and/or radiotherapy before surgery should be excluded because these treatments may influence the histopathology of the RP specimen. Patients with PCa diagnosed by *transurethral resection of the prostate* (TURP) were also discharged. Patient's age at diagnosis, preoperative serum PSA, the time interval between biopsy and surgery, prostate specimen volume, ISUP score of the biopsy and RP specimen, and also other features of the pathological RP specimen including pathological stage, surgical margins, and presence of cribriform pattern were also examined.

Imaging acquisition and MRI-TB protocol

MRI-TB was performed in all patients with mpMRI-detected abnormalities (PIRADS > 3-5). The imaging acquisition protocol followed the PI-RADS v. 2.1 criteria according to the European Society of Urogenital Radiology, based on the DWI and T2Wl sequences (14). In our institution, all mpMRI examinations were performed with a 3T MRI scanner (*Magnetom Skyra, Siemens, Erlangen, Germany*). All suspected lesions were evaluated by a genitourinary radiologist with expertise in mpMRI, unblinded to clinical information, and further discussed with the urologist for the identification and demarcation of suspicious lesions as well as possible landmarks. All outside patients sent to our hospital with previous mpMRI abnormalities findings were also reviewed by a genitourinary radiologist and urologist. All MRI-TB were performed using a mpMRI and transrectal ultrasound fusion software MIM Symphony BxTM (*MIM Software Inc, Ohio, USA*) and a cart-based ultrasound system (*BK PRO Focus ultrasound system, BK Medical, Massachusetts, USA*). At our institution, this MRI-TB has been used since 2017 by two experienced urologists. The patients were placed in lithotomy position, and subjected to general or spinal anesthesia after antibiotic prophylaxis and rectal and perineal disinfection. We obtained at least 4 cores of each selected target of the prostate and systematic biopsies using a transperineal ultrasound-guided prostate biopsy approach with the ultrasound probe in the rectum.

TRUS-B protocol

All TRUS-B were performed using a cart-based ultrasound system Hitachi EUB-7500A (*2013, Hitachi, Ltd, Tokyo, Japan*). TRUS-B were performed by 6 urologists of our department. The patients were placed in the left lateral decubitus position and subjected to a periprostatic nerve block (10 mL of 1% lidocaine) after rectal povidone-iodine disinfection by enema in addition to antimicrobial prophylaxis. A double-sextant protocol was used with a collection of 2 fragments in the apex, middle and base regions, bilaterally, resulting in a total of 6 regions covered and 12 fragments.

Pathological assessment of biopsy and RP specimen

All biopsies and RP specimens were examined and reported by a selected team of genitourinary pathologists. The processing and histopathological reports by the pathologists of biopsies and RP specimens followed the EAU guidelines recommendations (2). The PCa was classified using the modified ISUP grading system (6, 7): ISUP 1 =

Table 1.
Characteristics of study population.

	MRI-TB group	TRUS-B group	Total	P value
Total (n)	51	83	134	
Age (years; median [IQR])	69 (7)	64 (11)	67 (9)	0.001*
Preoperative serum PSA (ng/mL; median [IQR])	6.95 (5.03)	7.81 (5.57)	7.4 (5.60)	0.126
Prostate specimen volume (g; median [IQR])	48 (22)	41 (13)	42 (16)	0.109
The time interval between biopsy and surgery (days; median [IQR])	117(125)	126(143)	120 (129)	0.521
Biopsy ISUP score				0.098
ISUP 1 (n %)	7 (13.7%)	8 (9.6%)	15 (11.2%)	
ISUP 2 (n %)	17 (33.3%)	49 (59.0%)	66 (49.3%)	
ISUP 3 (n %)	20 (39.2%)	18 (21.7%)	38 (28.4%)	
ISUP 4 (n %)	5 (9.8%)	5 (6.0%)	10 (7.5%)	
ISUP 5 (n %)	2 (3.9%)	3 (3.6%)	5 (3.7%)	
Pathology specimen ISUP score				0.352
ISUP 1 (n %)	4 (7.8%)	5 (6.0%)	9 (6.7%)	
ISUP 2 (n %)	18 (35.3%)	27 (32.5%)	45 (33.4%)	
ISUP 3 (n %)	27 (52.9%)	42 (50.6%)	69 (51.5%)	
ISUP 4 (n %)	0 (0.0%)	1 (1.2%)	1 (0.8%)	
ISUP 5 (n %)	2 (4.0%)	8 (9.6%)	10 (7.5%)	
Pathology specimen - Cribform pattern				0.031*
Yes (n %)	3 (5.9%)	16 (19.3%)	19 (14.2%)	
No (n %)	48 (94.1%)	67 (80.7%)	115 (85.8%)	
Pathological stage				0.482
pT2 (n %)	25 (49.0%)	40 (48.2%)	65 (48.5%)	
pT3a (n %)	23 (45.1%)	33 (39.8%)	56 (41.8%)	
pT3b (n %)	3 (5.9%)	10 (12.0%)	13 (9.7%)	
Positive surgical margins				0,035*
Yes (n %)	21 (41.2%)	50 (60.2%)	71 (53%)	
No (n %)	30 58.8%)	33 (39.8%)	63 (47%)	
Surgeon				0.082
A (n %)	10 (19.6%)	33(39.8%)	43 (32.1%)	
B (n %)	12 (23.5%)	19(22.9%)	31 (23.1%)	
C (n %)	19 (37.3%)	20(24.1%)	39 (29.1%)	
D (n %)	10 (19.6%)	11(13.3%)	21 (15.7%)	

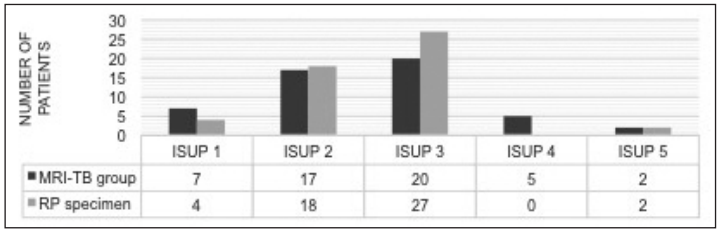
IQR: Interquartile Range; MRI-TB: magnetic resonance imaging targeted fusion biopsy; PSA: Prostate-Specific Antigen; TRUS-B: transrectal ultrasound-guided biopsy.

GS ≤ 6; ISUP 2 = GS 7 (3+4); ISUP 3 = GS 7 (4+3); ISUP 4 = GS 8 (4+4); ISUP 5 = GS 9 or GS10.

Statistical analysis

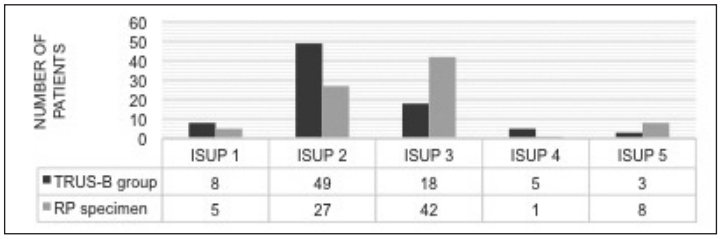
Our primary endpoint in this study was the risk of ISUP score upgrading for each modality of biopsy. The rate of concordance and downgrading were also assessed. Descriptive statistics were used for patients' demographic. Approximation to Gaussian distribution for continuous variables was not met on the Shapiro-Wilk test. Accordingly, a non-parametric statistic was used. Continuous variables were compared using Mann-Whitney Test. To define the intra and interobserver concordance for each ISUP score in biopsy and RP specimen evaluation for each biopsy modality, the Cohen's Kappa coefficient was calculated. Categorical variables were analyzed by chi-square test. ISUP scores and biopsy modality were selected for multivariate analysis and a logistic regression model was built. The models' goodness of fit was assessed by the *Hosmer-Lemeshow test* (HL) test. Statistical significance was considered for $p < 0.05$. All Statistical analysis was performed using SPSS v.25 (*IBM SPSS Statistics for macOS, Version 25.0. Armonk, NY: IBM Corp.*).

Figure 1.
Distribution of ISUP score after MRI-TB and RP specimen pathological examination.



MRI-TB: Magnetic resonance imaging targeted fusion biopsy; RP: Radical Prostatectomy.

Figure 2.
Distribution of ISUP score after TRUS-B and RP specimen pathological examination.



TRUS-B: transrectal ultrasound-guided biopsy; RP: Radical Prostatectomy.

Results

Groups characteristics

Group's baseline characteristics of patients subjected to prostate biopsy between October/2019 and July/2021 are detailed in Table 1. Overall, there were 51 patients in the MRI-TB group and 83 patients in TRUS-B group. There were no statistically significant differences in preoperative serum PSA, prostate specimen volume, the time interval between biopsy and surgery, ISUP score of biopsy and RP specimen, pathological T stage, and surgeons between both groups. Patients were statistically different in age ($p < 0.001$), presence of cribriform pattern ($p = 0.031$) and positive margins ($p = 0.035$). Figure 1 and 2 show the different distribution of ISUP scores between each biopsy group and the RP specimen pathology. The total proportions of ISUP score in MRI-TB were: ISUP 1 13.7%, ISUP 2 33.3%, ISUP 3 39.2%, ISUP 4 9.8% and ISUP 5 3.9%. In TRUS-B group, the proportions were: ISUP 1 9.6%, ISUP 2 59%, ISUP 3 21.7%, ISUP 4 6% and ISUP 5 3.6% (in each group, most PCa in biopsy were ISUP 2 or ISUP 3). At final RP specimen pathology report, the total proportions of ISUP scores in MRI-TB group were: ISUP 1 7.8%, ISUP 2 35.3%, ISUP 3 52.9%, ISUP 4 0% and ISUP 5 4%. In TRUS-B group the proportion were: ISUP 1 6%, ISUP 2 32.5%, ISUP 3 50.6%, ISUP 4 1.2% and ISUP 5 9.6% (in each group, most PCa in RP specimen were ISUP 2 or ISUP3).

ISUP score concordance rates from biopsy and RP specimen in study cohort and in each group

The Table 2 shows the rate of concordance or not (downgrading or upgrading) between biopsy and pathological ISUP scores in all study cohort and the two groups. The rate of upgrading between MRI-TB group and TRUS-B group was statistically significant ($p = 0.007$) with 42.2% of patients of TRUS-B group experiencing an upgrade in their ISUP score while only 19.6% in MRI-TB group. Concordance and downgrading rates did not statistically differ between the two groups.

Specific ISUP scores transition between biopsy and RP specimen

Specific ISUP scores transition between biopsy and RP specimen when considering all study cohort is depicted in Table 3. The major rates of upgrading were seen in

Table 2.
ISUP score downgrading, concordance and upgrading per groups.

Study group	ISUP score Downgrading	Concordance	Upgrading
MRI-TB group (n %)	9 (17.7%)*	32 (62,7%)**	10 (19.6%)***
TRUS-B group (n %)	9 (10.8%)*	39 (47%)**	35 (42.2%)***
Total (n %)	18 (13.4%)*	71 (53%)**	45 (33.6%)***

*IMRI-TB: Magnetic resonance imaging targeted fusion biopsy; TRUS-B: Transrectal ultrasound-guided biopsy; *: Downgrading rates; **: Concordance rates; ***: Upgrading rates.*

Table 3.
ISUP score downgrading, concordance and upgrading rates in both groups (MRI-TB group plus TRUS-B group).

ISUP score-biopsy	ISUP score – RP specimen ISUP 1	ISUP 2	ISUP 3	ISUP 4	ISUP 5	Total (n%)
ISUP 1 (n %)	6 (40%)**	6 (40%)***	3 (20%)***	0 (0%)***	0 (0%)***	15 (100%)
ISUP 2 (n %)	3 (4.5%)*	33 (50%)**	27 (41%)	0 (0%)***	3 (4.5%)***	66 (100%)
ISUP 3 (n %)	0 (0%)*	5 (13.2%)*	30 (78.9%)**	0 (0%)***	3 (7.9%)***	38 (100%)
ISUP 4 (n %)	0 (0%)*	1 (10%)*	5 (50%)*	1 (10%)**	3 (30%)***	10 (100%)
ISUP 5 (n %)	0 (0%)*	0 (0%)*	4 (80%)*	0 (0%)*	1 (20%)**	5 (100%)
Total (n)	9	45	69	1	10	134

*RP: Radical prostatectomy; *: Downgrading rates; **: Concordance rates; ***: Upgrading rates.*

Table 4.
ISUP score downgrading, concordance and upgrading rates (MRI/TPB group).

ISUP score-biopsy	ISUP score – RP specimen					Total (n%)
	ISUP 1	ISUP 2	ISUP 3	ISUP 4	ISUP 5	
ISUP 1 (n %)	3 (42.9%)**	3 (42.9%)***	1 (14.3%)***	0 (0%)***	0 (0%)***	7 (100%)
ISUP 2 (n %)	1 (5.9%)*	12 (70.6%)**	4 (23.5%)***	0 (0%)***	0 (0%)***	17 (100%)
ISUP 3 (n %)	0 (0%)*	3 (15%)*	17 (85%)**	0 (0%)***	0 (0%)***	20 (100%)
ISUP 4 (n %)	0 (0%)*	0 (0%)*	3 (60%)*	0 (0%)**	2 (40%)***	5 (100%)
ISUP 5 (n %)	0 (0%)*	0 (0%)*	2 (100%)*	0 (0%)*	0 (0%)**	2 (100%)
Total (n)	4	18	27	0	2	51

*RP: Radical prostatectomy; *: Downgrading rates; **: Concordance rates; ***: Upgrading rates.*

Table 5.
ISUP score downgrading, concordance and upgrading (TRUS-B group).

ISUP score-biopsy	ISUP score – RP specimen					Total (n%)
	ISUP 1	ISUP 2	ISUP 3	ISUP 4	ISUP 5	
ISUP 1 (n %)	3 (37.5%)**	3 (37.5%)***	2 (25%)***	0 (0%)***	0 (0%)***	8 (100%)
ISUP 2 (n %)	2 (4.1%)*	21 (42.9%)**	23 (46.9%)***	0 (0%)***	3 (6.1%)***	49 (100%)
ISUP 3 (n %)	0 (0%)*	2 (11.1%)*	13 (72.2%)**	0 (0%)***	3 (16.7%)***	18 (100%)
ISUP 4 (n %)	0 (0%)*	1 (20%)*	2 (40%)*	1 (20%)**	1 (20%)***	5 (100%)
ISUP 5 (n %)	0 (0%)*	0 (0%)*	2 (66.7%)*	0 (0%)*	1 (33.3%)**	3 (100%)
Total (n)	5	27	42	1	8	83

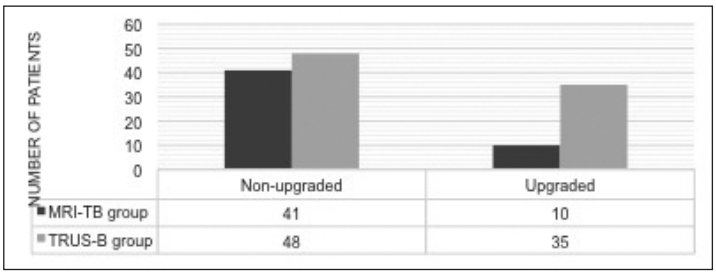
*RP: Radical prostatectomy; *: Downgrading rates; **: Concordance rates; ***: Upgrading rates.*

patients with ISUP 1 and 2 in biopsy (60% and 50% of those patients upgraded their initial ISUP score respectively). In TRUS-B group there were a higher upgrading rates in ISUP 1 and 2 (62.5% and 53%) while in MRI-TB group, the rates of upgrading were notable higher in ISUP 1 (57.2%) (Table 4 and Table 5, respectively). Strength of concordance using Cohen's Kappa coefficient was fair in both groups but higher in MRI-TB group (TRUS-B group $k = 0.230$; $p < 0.001$; concordance: 47%/MRI/TB group $k = 0.438$; $p < 0.001$; concordance: 62.7%).

Demographics, clinical and pathological features according to upgrade status

Overall, ISUP of 89 patients was upgraded in the final pathological report against 45 whose ISUP was not upgraded. On univariate analysis, as displayed in Table 6, there were no statistically significant differences in patients who were upgraded or not in PSA, prostate specimen volume, time interval between biopsy, presence of surgical positive margins or cribform patterns in PR specimen. Upgrading of biopsy ISUP score were associated with the biopsy modality (higher in TRUS-B biopsy - Figure 3) and ISUP score in biopsy ($p = 0.07$ and $p = 0.001$, respectively). In our regression logistic model, biopsy modality and ISUP 1 on biopsy were independent predictors of ISUP upgrading after RP (Table 7).

Figure 3.
Upgrading status comparison between MRI-TB group and TRUS-B group.



MRI-TB: Magnetic resonance imaging targeted fusion biopsy; TRUS-B: transrectal ultrasound-guided biopsy.

Table 6.
ISUP upgrading status - univariate analysis.

Upgrading status	Non-upgrading group	Upgrading group	P-value
Total (n)	89	45	
Age Standard (ng/mL; median [IQR])	68 (9)	66 (24)	0.245
Preoperative serum PSA (ng/mL; median [IQR])	7.25 (5.14)	7.7 (6.25)	0.481
Prostate specimen volume (ng/mL; median [IQR])	44 (19.75)	41 (12)	0.061
The time interval between biopsy and surgery (standard) (days; median [IQR])	122 (129)	112 (125)	0.984
Biopsy ISUP score	0.001*		
ISUP 1 (n %)	6 (40%)	9 (60%)	0.022*
ISUP 2 (n %)	36 (54.5$)	30 (45.5%)	0.004*
ISUP 3 (n %)	35 (92.1%)	3 (7.9%)	< 0.001*
ISUP 4 (n %)	7 (70%)	3 (30%)	1.000
ISUP 5 (n %)	5 (100%)	0 (0%)	
Biopsy modality	0.07*		
MRI-TB (n %)	41 (80.4%)	10 (19.6%)	
TRUS-B (n %)	48 (57.8%)	35 (42.2%)	
Surgical margins (n (%))			0.247
Negative (n %)	45 (50.6%)	44 (49.4%)	
Positive (n %)	18 (40%)	27 (60%)	
Cribform pattern			0.170
Negative (n %)	79(88.8%)	36 (80%)	

IQR: Interquartile Range; MRI-TB: magnetic resonance imaging targeted fusion biopsy; PSA: Prostate-Specific Antigen; TRUS-B: transrectal ultrasound-guided biopsy.

Table 7.
ISUP upgrading status - multivariate analysis.

ISUP score - biopsy	Variable	P value	Odds Ratio	CI 95%
	ISUP 1	0.028*	6.579	1.230-35.204
	ISUP 2	0.134	2.877	0.723-11.451
	ISUP 3	0.244	0.353	0.061-2.036

CI: Confidence Interval.

Discussion

The current way to further evaluate the prostate when there is a doubt of a tumor is with a prostate biopsy. However, with only a small sample of prostate tissue collected by a needle, physicians may not have a representative knowledge of the main structural features of cancer to predict its aggressiveness. GS and consequently ISUP score grading system are an essential prognostic tool in PCa and are included in many risk predictor normograms (4, 15, 16).

The concordance between the ISUP score of biopsies and the RP specimens is essential to confirm the physicians and patients' expectations regarding the risk group in which the cancer is assigned, the most appropriate treatment strategy, and the patient's prognosis. Unfortunately, the expected concordance does not always meet expectations and PCa aggressiveness might be underestimated or overestimated resulting in a delay of treatment in patients initially qualified for active surveillance (AS);

undertreatment in case of high-risk PCa that could benefit not from monotherapy (surgery or radiation) but multimodal therapy or clinical trial; or overtreatment in patients disqualified to a low-risk disease after surgery who would be better candidates for AS (2). Risk normograms may also be imprecise in terms of whether or not pelvic lymphadenectomy is required. Therefore, it's not surprising that previous studies have reported an increased risk of biochemical recurrence, distant metastasis, and death when ISUP score is underestimated (17-20). The vast majority of those studies only assessed the upgrading risk regarding TRUS-B, the most widely accepted method for PCa diagnosing. Therefore, this study provides further evidence of the clinical utility of MRI-TB in daily clinical practice. The lower reliability of TRUS-B in our study is aligned with the results obtained by *Kvale et al.* and other historical studies that have determined the upgrading risk when a systematic biopsy is performed (21). We demonstrated that 42.2% of patients in the TRUS-B group were upgraded. In fact, our results are similar to *King et al.* study' which reported a GS upgrading rate after TRUS-B of 35-43% (22). However, it should be noted that those studies used the GS system to classify PCa, rather than ISUP score which ranges from 1 to 5 with Gleason Score 9 and 10 assigned to ISUP 5. Therefore, our study does not assess the risk of upgrading from Gleason Score 9 to 10. Nevertheless, it should be recognized that we use ISUP grading system, a more recent and updated grading system which is based on GS. There are a few studies in the literature that specifically assessed the transition of ISUP scores between prostate biopsy and RP.

When both modalities of biopsy are compared, as shown in Table 8, previous studies reported different upgrading rates but lower when magnetic resonance imaging ultrasound guided biopsy is performed (23-25). MRI-TB provides a lower incidence of ISUP score upgrading, although there is still a non-negligible risk of upgrading of 19.6%. The major rates of upgrading were detected in patients with ISUP 1 in both groups. This has implications mainly for those patients who have postponed RP due to active surveillance. On the other hand, 53% (*vs.* 23.5% in MRI-TB group) of patients classified as ISUP 2 after TRUS-B were upgraded. These data are consistent with data from the study by *De Lucca et al.* who demonstrated a lower risk of ISUP 2 upgrading after MRI-TB *vs.* systematic biopsy (26). In our study, 6.8% (n = 3) of those patients with ISUP 2 in the TRUS-B group upgraded to ISUP 5 (*vs.* 0% in the MRI-TB group) as demonstrated in Table 5. Despite a small number of patients, this is particularly relevant when patients with ISUP 2 in the biopsy are subjected to radiotherapy. Due to the lack of confirmatory ISUP score of RP specimen, those patients are at risk of undertreatment.

In addition to the biopsy modality, to be classified as ISUP 1 in biopsy was identified as a predictive risk for upgrading in multivariate analysis. As suggested by *Altok et al.*, when the RP specimen is analyzed, a "*regression to the mean GS7*" (ISUP 2-3) appears also to occur with our data even with patients who graduated as ISUP 1 in the biopsy, with 100% of patients transiting to ISUP 2-3 (27). In fact, one of the challenges of the pathologist is to differentiate Gleason patterns 3 and 4 due to several reasons based on inherent subjectivity of reporting borderline-cases (28). Therefore, it is essential to have a dedicated and experienced team of pathologists to minimize variations in interpretations of ISUP score and discrepancy between biopsy and RP specimens.

Although our study did not find a relation between prostate specimen volume and upgrading risk, many studies report a higher risk of upgrading in prostate of smaller size (25). We expected that the longer the time interval between biopsy and surgery, the greater the risk of upgrading but we did not find this relation in our study (21). Our study has several limitations concerning its retrospective and non-randomized design. It was also a single-institution study that targeted Portuguese population. Other limitations are the small number of patients in each group and heterogeneity between the two groups; the non-inclusion of other variables likely to be related to upgrading risk according to previous studies such as the number of cores collected, biopsy core lengths and PSA density (23, 29). Other variables, such as the specific number, extent, location and PIRADS classification of suspicious lesions on mpMRI, and their respective association with the PCa diagnosis in both biopsy cores and surgical specimens were not assessed in our study. However, *Lourenço et al.* suggest that PCa multifocality can be an indicator of ISUP upgrading risk in patients who were discordant in mpMRI location of the suspicious lesions either in the cognitive fusion biopsy cores or PR specimens (30). Nevertheless, we believe that this study reinforces the key role of MRI as a diagnostic and staging tool in PCa. Physicians should be aware of potential upgrading risk factors during the decision-making process. The development of normograms and biomarkers that can predict the risk of upgrading may be essential to improve the assertiveness of the clinical decision (31-33). According to *Lacetera et al.*, the incidence of clinically significant PCa in patients under AS protocol is higher in the subgroup of patients who underwent confirmatory and follow-up MRI-TB *vs.* random biopsy (69% *vs.* 31%) (34). We strongly recommend that patients on AS protocol should be counseled about the risk of ISUP upgrading and informed about the advantage of MRI-TB to detect clinically significant PCa.

Table 8.
Our study and selected previous series that evaluated the risk of upgrading.

Series citation	Groups	Patients (n)	Upgrading (%)	P value
Guimarães et al.	MRI-US	51	19.6%	
	TRUS-B	83	42.2%	0.07*
(25)	MRI-US	73	16.4%	
	TRUS-B	89	31.5%	0.027*
(24)	MRI-US	145	33.5%	
	TRUS-B	221	31.7%	0.8
(23)	MRI-US	92	26.9%	
	TRUS-B	137	73.1%	0.027*

MRI-TB: Magnetic resonance imaging targeted fusion biopsy; TRUS-B: tTansrectal ultrasound-guided biopsy.

Conclusions

MRI-TB is highly accurate with lower risk of PCa upgrading after RP than TRUS-B. Patients with ISUP 1 on biopsy

have greater susceptibility to upgrading and we strongly recommend mpMRI on patients in AS protocol. Additional studies are necessary to identify predictive risk factors for ISUP score upgrading to better categorize patients into risk groups and select the best treatment option according to the biological behavior of PCa and prognosis.

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