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ORIGINAL PAPER

Lesion location agreement between prostatic multiparametric magnetic resonance, cognitive fusion biopsy and radical prostatectomy piece

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Summary ***Introduction: Prostatic multiparametric magnetic resonance (mpMRI) allows for guided prostate biopsy (PB).***
Objective: To evaluate localization agreement between mpMRI lesions and histology obtained by cognitive PB and radical prostatectomy (RP) surgical specimen (SS).
Methods: Out of 115 consecutive cognitive biopsied patients, 37 with positive PB were studied. Sample was characterized regarding age, prostatic volume, PI-RADS, location of lesion on mpMRI, lesion dimension, total number of fragments obtain by PB, number of fragments directed to the lesion, number of fragments with prostatic adenocarcinoma (PCa) and ISUP classification. The relationship between mpMRI and SS piece was analysed in 15 patients who underwent RP.
Results: Regarding agreement between mpMRI and PB, agreement of location was observed in 26 (70.3%); 7 (18.9%) presented PCa positive fragments in the suspected zone plus others in the same lobe; 3 (8.1%) in the suspected zone plus the contralateral lobe and 1 (2.7%) had no PCa in the suspected zone but had bilateral PCa. The total number of fragments with PCa was lower in cases with agreement between mpMRI and PB ($p < 0.05$). Regarding agreement between mpMRI and SS, 5 cases (33.3%) presented the same location as described by mpMRI, 5 (33.3%) showed ipsilateral lesions in other zones of the prostate; 4 (26.7%) presented extensive bilateral lesions on all prostate zones and 1 (6.7%) showed previously unknown contralateral lesions. None of the factors studied related mpMRI and RP ($p > 0.05$).
Conclusions: Localization agreement of mpMRI vs PB and mpMRI vs SS was present in 26/37 (70.3%) and 5/15 (33.3%), respectively. That suggests the existence of other lesions (multifocality) not identified on mpMRI.

KEY WORDS: *Prostate biopsy; Cognitive prostate biopsy; Multiparametric magnetic resonance imaging; Prostate cancer; Localization agreement; Multifocality.*

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INTRODUCTION

The incidence of *prostate cancer* (PCa) has increased in the last decades, being the most common male malignant disease and a major cause of morbidity and mortality (1-3). This increase is due to the increasing use of screening techniques such as the *Prostate Specific Antigen* (PSA) testing which allows for the detection of lesions at an earlier stage including lesions that may not develop into significant disease (1, 3). PCa has high prevalence in the male population (3-4% in northern *Europe*) but low mortality rates (1). Currently, the standard method for the diagnosis of PCa is *digital rectal exam* (DRE) or PSA measurement followed by transrectal ultrasound guided *prostate biopsy* (PB) in suspected patients although it lacks sensitivity and specificity for lesion detection (1, 2, 4). Prostate ultrasound can demonstrate some lesions that appear hypo-echoic when compared to the normal echogenic peripheral zone. However, more than 40-50% of cancerous lesions may appear as iso-echoic allowing for many false negatives even when protocols that sample normal prostate are used, such as double sextant biopsy (1, 4, 5). Due to this fact, the use of multiparametric magnetic resonance (mpMRI), applying the PI-RADS scoring system, to complement and in some cases avoid PB has increased (1, 4, 6-10).
Multiparametric magnetic resonance allows for detection, characterization, staging and assessment of metabolic, morphological and cellular changes of lesions that correlate with tumour aggressiveness; mpMRI can also decrease the detection of indolent disease. The combination of mpMRI with biopsy (fusion biopsies) increases its value as a diagnostic tool (1, 4, 6, 7, 11-13). The use of mpMRI with its ability to detect lesions larger than 0.2 ml, permits in some cases the identification of multiple lesions (multifocality) of localized PCa. In fact, prostate can have coexistence of more than one lesion with different Gleason score (2, 7, 9, 14). Thus, the term *Index Lesion* (IL) or dominant lesion, has been introduced to define the lesion with the highest Gleason score orthe largest lesion in the case of lesions with the same Gleason score (6, 7, 14). The multifocality of PCa, expressed by the presence of satellite lesions, also underestimates the size and extent of PCa. The clinical significance of these factors is still undetermined: in high-risk patients where treatment option is *radical prostatectomy* (RP) they may not alter prognosis, but they are of high importance when focal treatment is regarded as an option. The use of fusion biopsy may allow for identifi-

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cation of more lesions and better planning of treatment (12, 15). It is theorized that the IL drives disease progression and that multifocality does not alter prognosis, although a consensus has not been achieved because of divergent results of different studies (6, 15). The use of mpMRI to guide biopsies, as a first line diagnostic tool (rather than as second line when PB fails to detect lesions) is increasing, as it is its use to determine the need of prostatic biopsy in some individuals (16).
Nevertheless, a normal mpMRI does not exclude the presence of PCa because mpMRI can detect lesions with high Gleason score and miss lesions with lower Gleason and areas deemed non-suspicious can still reveal significant disease with PB (2, 4, 12, 17, 18). Correlation between mpMRI identified lesions and radical prostatectomy was found to be accurate in lesions equal or superior to 0.2 ml, validating its use for fusion biopsy and possibly guided therapy (12, 17, 19-21). In patients with a negative mpMRI, the risk of significant disease (Gleason ≥ 7) is still present, although recent studies show a very high negative predictive value. Therefore, some studies still recommend PB even with negative mpMRI (12, 15, 17, 21). The interobserver variability of prostate mpMRI still represents a challenge, as rates are still very variable between studies (8, 11, 13).
The aim of this work was to evaluate the correlation between lesions described in mpMRI and the histology results obtained by prostate biopsy and RP.

Methods

Patients selection
A retrospective analysis of 291 consecutive diagnostic mpMRI conducted by the same team of radiologists in a tertiary hospital was performed. One hundred fifteen biopsied patients were selected, of whom 56 had a positive biopsy for prostate adenocarcinoma. The data available allowed for the evaluation of agreement between lesion location on mpMRI and PB in 37 patients or on mpMRI and RP in 15 patients (Figure 1).

Data collection
Clinical and biochemical data was obtained from consulting patients' charts.
Imaging data was obtained from analysis of reports conducted by the same team of radiologists, or by revision of images if insufficient data was present in the reports.
Anatomopathological data from PB and RP was obtained from consulting reports by the medical team of the pathology department.

Technical characteristics
All mpMRI were conducted and described by the same team of radiologists and were revised by a single senior radiologist. Of the 291 mpMRI, 161 were conducted utilizing the PI-RADS v1 classification, while the remaining were evaluated applying the PI RADS v2. In this study, being our main endpoint the location of the tumour, no distinction between PI-RADS versions was made in order to increase available numbers. Exams were performed on a 3T MR scanner.

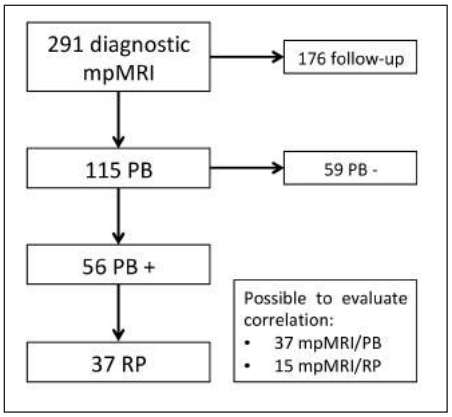

Figure 1. *Patients method selection.*

Prostate biopsies were conducted by different urologists (non-studied variable) under ultrasound guidance according to cognitive fusion. All patients were submitted to guided biopsy and systematic biopsy (with variable number of cores collected).

Studied variables
The sample obtained was characterized in relation to age, prostate volume, PI-RADS score, location of lesion [side (left, right, bilateral, medial), floor (apex, base, medial), zone (peripheral, transition, central, stroma)] and dimension on mpMRI. Regarding prostate biopsy it was assessed the total number of fragments obtained, the number of fragments directed to the lesion, number of fragments with PCa, ISUP classification and agreement between location of PCa in fragments in relation to mpMRI. In the 15 patients submitted to RP, the agreement between location of lesion on *surgical specimen* (SS) and mpMRI was evaluated.
We included patients with PI-RADS score 2 that had any mpMRI modification possible to localize (hypointensity lesions in the peripheral zone; circumscribed hypointense or heterogeneous nodules) and had a positive PB.

Definition of agreement
Agreement between mpMRI/PB and mpMRI/SS was defined as agreement of the presence of PCa only on the regions identified by mpMRI.

Statistical analysis
Evaluation of the effect of variables studied on location agreement was conducted utilizing the Mann-Whitney test (utilizing the statistic program SPSS v21). The values $p < 0.05$ were considered statistically significant.

Results

Agreement in location mpMRI/PB
In relation to PB, location was assessed only as side. Agreement between mpMRI/PB was of about 26 (70.3%), meaning that 11 (29.9%) presented lesions out of the suspected zone. Results concerning location of lesions are summarized in Table 1.
The characterization of studied variables and its effect on agreement are summarized in Table 2. Of the factors

Table 1.
Agreement in location between mpMRI and lesions objectified in prostatic biopsy and by radical prostatectomy specimen.

Agreement mpMRI vs PB (n = 37)		Agreement mpMRI vs SS (n = 15)	
Agreement	26; 70.3%	Agreement	5; 33.3%
PCa in SZ + PCa in the same lobe	7; 18.9%	PCa in SZ + ipsilateral lesions in other floors	5; 33.3%
PCa in SZ + PCa in contralateral lobe	3; 8.1%	PCa in SZ + contralateral lesions	1; 6.7%
No PCa in SZ + bilateral PCa	1; 2.7%	Bilateral lesions in all floors	4; 26.7%

PB = prostatic biopsy; PCa = prostate cancer; SS = surgical specimen; SZ = suspicious zone.

Table 2.
Effect of clinical and imaging variables on agreement in location between suspicious lesion of prostate adenocarcinoma on mpMRI and prostate biopsy.

	All patients (n = 37)	With agreement (n = 26)	p
Average age (years)	66.6	65.9	NS
Average PSA (ng/ml)	9.1	10.0	NS
Average volume (cc)	53.5	54.4	NS
Average number of previous PB	1.3	1.1	NS
Average diameter of suspicious lesion on mpMRI (mm)	24.3	22.9	NS
Location of lesion in mpMRI			NS
· Right	15; 40.5%	10; 38.5%	
· Left	15; 40.5%	11; 42.3%	
· Medial	3; 8.1%	1; 3.8%	
· Bilateral	4; 10.8%	4; 15.4%	
Average total number of fragments	13.0	13.0	NS
Average number of guided fragments	4.7	4.9	NS
PI-RADS			NS
· 2	7; 18.9%	5; 19.2%	
· 3	3; 8.1%	3; 11.5%	
· 4	4; 10.8%	4; 15.4%	
· 5	23; 62.2%	14; 53.8%	
Average number of fragments with PCa	3.5	3	Statistically significant
ISUP after PB			NS
· 1	10; 27.0%	8; 30.8%	
· 2	18; 48.6%	10; 38.5%	
· 3	5; 13.5%	5; 19.2%	
· 4	3; 8.1%	2; 7.7%	
· 5	0; 0.0%	0; 0.0%	
· Unknown	1; 2.7%	1; 3.8%	

PSA = Prostatic specific antigen; PB = Prostatic biopsy; mpMRI = multiparametric magnetic resonance; PCa = prostate adenocarcinoma; NS = Non significant (p > 0.05); StS = statistically significant (p ≤ 0.05).

studied, only the total number of fragments with PCa was lower in cases with agreement between mpMRI and PB ($p < 0.05$).
Agreement on location between mpMRI/PB for lesions PI-RADS 2,3,4 and 5 was 71.4% (n = 5), 100.0% (n = 3), 100% (n = 4) and 60.9% (n = 23), respectively.
Agreement in location mpMRI/PB for lesions ISUP (PB result) 1,2,3 and 4 was 80% (n = 8), 55.6% (n = 10), 100.0% (n = 3) and 66.7% (n = 2), respectively.

Agreement in location mpMRI/SS

Agreement on location between mpMRI/SS was of 5 (33.3%) (Table 1).
The characterization and effect of variables on agreement are summarized in Table 3, being that no variable had a statistically significant effect. In relation to side, agreement for lesions localized on the right side, left, medial and bilateral was 33.3% (n = 2), 33.3% (n = 2), 0.0% (n = 0) and 50.0% (n = 1), respectively. In relation to the floor, agreement for lesions localized at the base, medium and apex was 33.3% (n = 2), 28.6% (n = 2) and 50.0% (n = 1), respectively. In relation to anatomical zone, agreement for lesions localized in the peripheral zone, transition zone and central zone was 36.4% (n = 4), 33.3% (n = 1) and 0.0% (n = 0), respectively.
Agreement in location between mpMRI/SS for PI-RADS lesion score 2,3,4 and 5 was off 0.0% (n = 0), 100% (n = 1), 50.0% (n = 2) and 33.3% (n = 3), respectively.
Agreement in location for ISUP 1,2 and 5 (evaluated by SS) was 50.0% (n = 2), 33.3% (n = 4), and 0.0% (n = 0), respectively.
In the five exams that showed agreement, all patients presented with an ISUP SS smaller or similar to the ISUP obtained by PB (only one patient was reclassified with ISUP 3 on PB and of ISUP 2 on SS, having the remaining patients maintained ISUP classification).

Table 3.
Effect of clinical and imaging variables on agreement between location of prostate adenocarcinoma suspicious lesion, between mpMRI and findings in surgical specimen after radical prostatectomy.

	All patients (n = 15)	With agreement (n = 5)	p
Average age (years)	65.1	63.6	NS
Average PSA (ng/ml)	8.6	10.0	NS
Average volume (cc)	49.1	53.4	NS
Average diameter of suspicious lesion on mpMRI (mm)	26.4	23.5	NS
Location of lesion in mpMRI			NS
a) Side			
· Right	6; 40.0%	2; 40.0%	
· Left	6; 40.0%	2; 40.0%	
· Medial	1; 6.7%	0; 0.0%	
· Bilateral	2; 13.3%	1; 20.0%	
b) Floor			
· Base	6; 40.0%	2; 40.0%	
· Medial	7; 46.7%	2; 40.0%	
· Apex	2, 13.3%	1; 20.0%	
c) Zone			
· Peripheral	11; 73.3%	4; 80.0%	
· Transition	3; 20.0%	1; 20.0%	
· Central	1; 6.7%	0; 0.0%	
PI-RADS			NS
· 2	3; 20.0%	0; 0.0%	
· 3	1; 6.7%	1; 20.0%	
· 4	2; 13.3%	1; 20.0%	
· 5	9; 60.0%	3; 60.0%	
ISUP SS			NS
· 1	2; 13.3%	1; 20.0%	
· 2	12; 80.0%	4; 80.0%	
· 3	0; 0.0%	4; 80.0%	
· 4	0; 0.0%	0; 0.0%	
· 5	1; 6.7%	0; 0.0%	

PSA = Prostatic specific antigen; PB = Prostatic biopsy; mpMRI = multiparametric magnetic resonance; PCa = prostate adenocarcinoma; NS = Non significant; SS = Surgical specimen.

In the 10 nonagreeing exams, the ISUP SS values were superior to the ISUP BP values in 5 (50.0%) of cases (regarding the five ISUP 1 patients in PB, four were reclassified as ISUP 2 in SS and one maintained ISUP classification).

Discussion

Currently the use of "*blind*" biopsy in the search for PCa with the objective of "*finding*" the neoplasic lesion constitutes an exception when compared to other cancer diagnostic procedures (22). The development of mpMRI and the subsequent rise of guided prostate biopsy has been associated with excellent results in detecting significant PCa. This has various potential applications of great relevancy, such as reducing the number of unnecessary biopsies, reducing the diagnosis of indolent PCa and better planning of focal therapy (2, 19, 23). To make it possible, mpMRI has to present high sensitivity and high negative predictive values, which can be evaluated by comparing characteristics of identified lesions on mpMRI with findings obtained from prostate biopsy (guided and systematic) and with histopathological result from radical prostatectomy specimens.

In this study, agreement between mpMRI and PB was 70.3%. In relation to patients without agreement, all presented multifocality. In an interesting way, we observed that all bilateral suspicious lesions on mpMRI (n = 4) presented agreement on PB. Of all factors studied, only having a small number of positive PB cores for PCa, was related to higher agreement between mpMRI and PB. This data can be explained by the fact that a higher number of positive cores can be associated to the presence of multifocal lesions not identified by mpMRI. The agreement was higher for lesions PI-RADS ≤ 3 that for lesions PI-RADS > 3 (80.0% *vs.* 66.7%).

Agreement between location for mpMRI and SS was only 33.3% and multifocality was responsible for the lack of agreement in the 66.7% remaining patients.

Interestingly, patients with non-agreeing lesions presented with an increased ISUP classification in relation to PB in 50.0% of cases (*vs* 0.0% of patients with agreement). None of the factors studied related to agreement (probably by the reduced sample size).

The accuracy of mpMRI for detecting PCa has been widely studied. Multiple studies have shown that guided prostate biopsy of the suspected lesion on mpMRI detects more clinically significant tumours that systematic biopsy, whereas systematic biopsy detects more non-significant tumours. Due to this fact, most authors still recommend conducting both techniques at the same time as to increase diagnostic accuracy (2, 3, 5, 22). Given that mpMRI has a high negative predictive value (between 63 and 98% (24), various authors have defended that mpMRI can significantly reduce the number of prostatic biopsies conducted, particularly in patients with previously negative biopsy (3, 4, 21).

The accuracy of mpMRI is especially high in detecting index lesions, with various recent studies showing values > 85% (7, 14, 19, 20, 25).

In our study, the low correlation between lesions identified on mpMRI with biopsy and surgical specimen, was related to multifocality, as in our methodology we considered the existence of unidentified multifocal lesions on mpMRI as nonagreeing exams. Various studies have shown that PCa is multifocal in most cases, with a variation of 57 to 91% (26-29). In this context, it is important to assess the characteristics of unidentified lesions on mpMRI, being they index or satellite lesions. *Radtke et al.* (19), in a study correlating surgical specimen of radical prostatectomy, objectified that 94% of lesions not identified by mpMRI presented with Gleason ≤ 3+4. In a study by *Borkowetz et al.* (7), that also related mpMRI to SS, mpMRI failed to identify 13% of index lesions, that in half of cases presented with a Gleason score ≥ 4+3. *Baco et al.* (14) obtained a diagnostic acuity of 95% for IL with biopsy guided by mpMRI, where the remaining 5% were identified by systematic biopsy. The high sensitivity obtained by combining guided biopsy with systematic biopsy was equally proved in other studies (19, 30). *Le et al.* (6) described the multifocality of PCa in 64% of cases, being the mpMRI detection rate for all tumours of only 47% (132/283).

The sensitivity of mpMRI was higher in lesions larger than 1 cm (72%), Gleason score ≥ 7 (72%) and for index lesions (80%). In a study conducted by *Tan et al.*, mpMRI was capable of identifying 46.7% of all tumour foci (31). Better results concerning the ability of mpMRI in detecting multifocal lesions was described by *Hegde et al.* (12), who described an accuracy of 62.0% in detecting satellite lesions by mpMRI (that in 55.3% presented with Gleason score ≥ 3+4).

Analysing therapeutic applications, particularly focal therapies, it is relevant to highlight that satellite lesions do not necessarily present adjacent to the index lesion, being the average distance of approximately 1 cm (32).

The importance of satellite lesions is not totally explained. Currently, the most widespread idea supports that potentially metastatic and lethal PCa originates from the same aberrant progenitor cell (in other words, with the same monoclonal origin) (33, 34) and that IL (correctly identified by mpMRI) most likely originates from the same lethal parent cell (35). Nevertheless, other studies showed that non-index lesions can be responsible for local invasion (36) and for metastatic PCa (37).

The identification of PCa lesions by mpMRI is dependent on multiple factors, namely lesion volume (> 1cc), Gleason score (≥ 7), histology, location (inferior to lesion located at the apex) and of the contrast to normal adjacent tissue (14, 31).

Currently another matter of debate is the influence of the technique of guided biopsy utilized, namely the difference between cognitive fusion biopsy (utilized in our work), MRI-transrectal ultrasound fusion and in-bore MRI target biopsy. A recent systematic review showed that in-bore MRI target biopsy is superior to cognitive fusion biopsy for the detection of all PCa (regardless of Gleason score), although it was not superior in detecting significant tumours. The MRI-transrectal ultrasound fusion biopsy did not show advantages in relation to cognitive fusion biopsy (38).

In this study, all the exams were conducted or revised by the same radiologist, which eliminates the subjective variation in reading mpMRI. Some studies showed that

for index lesion the interobserver variation is not significant (15, 39), while other studies showed a clear effect of the radiologist´s experience in reading mpMRI (13).
This work presents with various limitations, namely its retrospective nature and the small number of surgical specimens evaluated. Also, histology was assessed by report, which can reduce agreement concerning location (10, 15). Another limitation was the inclusion of patients with a PI-RADS score of 2, which by definition signifies a negative mpMRI (although during PB the areas of the prostate where alterations were present where considered, namely hypointensity lesions in the peripheral zone). Lastly, agreement between index lesion and satellite lesion was not evaluated, nor was histopathological characteristics for tumour foci.

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