# Prostate Multiparametric-MRI (mp-MRI) Accuracy for Localization of Clinically Significant Prostate Cancer: A Retrospective Comparative Study between MRI and Whole-mount Histopathology

## *Precisão da Ressonância Magnética Multiparamétrica da Próstata (mp-RM) na Localização do Cancro da Próstata Clinicamente Significativo: Um Estudo Retrospetivo Comparativo entre RM e Histopatologia de Peça Total*

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## Abstract

**Introduction:** Multiparametric magnetic resonance imaging (mpMRI) has been increasingly used to guide prostate cancer management. Most studies are focusing on the detection of prostate cancer rather than localization of tumors within the gland, which is fundamental to plan treatment. We aimed to evaluate mpMRI for accurate localization of tumor nodules and examining the predictors of detection.

**Methods:** Retrospective study of 30 prostate cancer (PCa) patients who underwent mp-MRI before radical prostatectomy (RP). Suspicious lesions on mpMRI were localized using a standardized prostate map of 24 regions of interest (ROI) and compared with whole-mount histopathology.

**Results:** Seven hundred and twenty ROIs were evaluated and 160 had clinically significant PCa (lesions ≥5 mm or Gleason ≥6). Sensitivity and specificity for the detection of PCa on hemiprostates was 82% and 80%. PCa mapping was less sensitive for octants - 52%, but specificity was higher, at 95.9%. mpMRI had better performance for Gleason >7 and tumor dimension ≥1cm. MRI correctly identified the location of 80% of index lesions. The extracapsular invasion was correctly detected in 90% of patients. Tumor volume had a strong correlation between mpMRI and RP analysis, with an approximate 10% underestimation of tumor dimensions. (rho =0.73; $p$ <0.001).

**Conclusion:** mpMRI is capable of accurate localization of clinically significant PCa within whole mount prostate, with moderate sensitivity and good specificity. mpMRI performance increases with ISUP ≥3 and size ≥1 cm. Extracapsular invasion detection and high sensitivity of hemiprostatic localization make this exam vastly relevant for nerve-sparing treatment planning.

**Keywords:** Multiparametric Magnetic Resonance Imaging; Prostatic Neoplasms/diagnosis; Prostatic Neoplasms/diagnostic imaging

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## *Resumo*

***Introdução:*** *A ressonância magnética multiparamétrica (RMmp) tem sido cada vez mais utilizada para orientar a abordagem ao cancro da próstata (CaP). A maioria dos estudos está a concentrar-se na detecção do cancro da próstata em vez da localização de tumores no interior da glândula, que é fundamental para planear o tratamento. Este estudo tem por objetivo avaliar a acuidade da RMmp na localização de CaP e averiguar os preditores de detecção.*

***Métodos:*** *Estudo comparativo retrospectivo de 30 pacientes com CaP submetidos a RMmp antes da prostatectomia radical (PR). As lesões suspeitas na mpMRI foram localizadas utilizando um mapa de próstata padronizado de 24 regiões de interesse (ROI) e comparadas com a histopatologia da peça cirúrgica de PR.*

***Resultados:*** *Foram avaliadas 720 ROIs, sendo que 160 tinham CaP clinicamente significativos (lesões ≥5mm ou Gleason ≥6). A sensibilidade e especificidade para a detecção de CaP em hemipróstatas foi de 82% e 80%. O mapeamento do CaP era menos sensível para os octantes prostáticos (52%), mas a especificidade era mais elevada (95,9%). A RMmp teve melhor desempenho para Gleason >7 e dimensão tumoral ≥1 cm e identificou correctamente a localização de 80% das lesões índex. A invasão extracapsular foi correctamente detectada em 90% dos doentes. O*

*volume do tumor teve uma forte correlação entre a RMmp e o estudo histopatológico, com cerca de 10% de subestimação das dimensões do tumor. (rho =0,73; p <0,001).*

*Conclusão: a RMmp é capaz de localizar com precisão carcinoma da próstata clinicamente significativo, com sensibilidade moderada e elevada especificidade. o desempenho da RMmp aumenta com ISUP ≥3 e o tamanho ≥1 cm. A detecção de invasão extracapsular e a alta sensibilidade da localização hemiprostática tornam este exame extremamente relevante para o planeamento de um tratamento cirúrgico "nerve-sparing".*

*Palavras-chave: Neoplasias da Prostata/diagnóstico; Neoplasias da Prostata/diagnóstico por imagem; Ressonância Magnética Multiparamétrica*

## Introduction

Prostate cancer (PCa) is the second most common cancer worldwide and the fifth most common cause of cancer death among men.[1] Prostate multiparametric magnetic resonance imaging (mpMRI) has been rapidly adopted to fill the unmet need for a non-invasive, accurate PCa screening tool. The European Association of Urology (EAU) and American Urology Association (AUA) both advocate mpMRI use in biopsy naïve patients or patients with previous negative biopsy. Several studies demonstrated the value mpMRI in terms of improved cancer detection via targeted biopsy, decreased detection of indolent disease, improved risk stratification, clinical staging and surgical and radiotherapy planning.[2-9]

A recent meta-analysis including 29 included studies reported that the diagnostic accuracy of mpMRI for detecting PCa, in both biopsy naïve and previous biopsy negative, was high with a sensitivity of 0.87 and a specificity of 0.68 respectively.[10]

Despite these advantages, there is considerable variation in the reported accuracy of mpMRI for the detection of significant prostate cancer, with significant heterogeneity among studies.[10] Most of them compare mpMRI results with histopathology from the systematic and MRI-guided biopsies, which only represents a small sample of tissue. And there is a known disparity between systematic prostate biopsy results and final histopathological results at radical prostatectomy (RP).[11] Therefore, whole-mount histopathology of RP specimen provides a definitive evaluation of the prostate gland and must be considered the reference gold standard for the assessment of detection and localization of tumour.

Additionally, the majority of studies focus on the detection of prostate cancer, rather than on the localization of tumours within the gland.[12] There are a few recent studies, that evaluate localization against RP specimens, but tumor location analysis was performed using the limited anatomical zones (peripheral or transitional).[13] Studies performed with more detailed prostate zonal mapping were more motivated to determine mpMRI parameter performance rather than on clinical features and application of MRI.[12,14]

Pre-operative prostate lesion volume and maximal dimensions estimation is a key metric for predicting the likelihood of positive surgical margins, biochemical prostate-specific antigen recurrence and cancer-specific survival post-prostatectomy.[15-18] The precise localization and dimensions are the necessary bridge for minimally invasive focal therapies and to tailor nerve sparing in radical prostatectomy (RP).

Therefore, the aim of this study was to evaluate the value of multiparametric MRI for accurate localization of intraprostatic tumour nodules, with whole-mount histopathology as a reference standard. Secondary endpoints were examining the predictors of tumour detection, index lesion localization performance, correct estimation of tumour dimension and extraprostatic extension (EPE).

## Methods

### Study Population

Using the institutional Prostate mpMRI database, we selected consecutive patients who 1) underwent MRI between January 2015 and April 2018, and 2) had a radical prostatectomy for the treatment of PCa within 9 months of MRI. Patient characteristics are summarized in Table 1.

### Prostate mpMRI

Multiparametric MRI studies were obtained in a 3-Tesla machine (Magnetom Trio Tim, Siemens). Studies were performed with acquisition of T2-weighted images (T2WI) in the sagittal, coronal and axial planes, axial diffusion-weighted imaging (DWI) using low and b-values (50 s/mm2 and 1000 s/mm2, respectively) and with generation of ADC maps, and dynamic contrast-enhanced (DCE) study after intravenous administration of gadobutrol (Gadovist®, Bayer) at a dose of 0.1 mL/kg and a rate of 2.5 mL/s.

After the selection of the study patients, all MpMRI were reviewed by a single radiologist (with 10 years of experience reading mpMRI) and free-hand regions of interest (ROIs) encompassing suspicious areas were delineated in the images and then drawn in a twenty-four sector map and classified according to PI--RADSv2.19 The radiologist had access to the subject's clinical data (e.g. age, PSA level, DRE, results of previous biopsies).

### Radical Prostatectomy and Histopathological Assessment

Microscopic assessment of RP specimens was performed after routine preparation – prostate gland was weighed, inked and sectioned at 4-5 mm intervals perpendicular to the urethra – to allow proper orientation and comparison with the MRI slices. Each section was stained with haematoxylin and eosin. A dedicated experienced uropathologist delineated all tumour regions and

**Table 1 –** Patient, Radical Prostatectomy and mpMRI Characteristics

| Characteristic | Number of patients |
|---|---|
| **Patients** | |
| Number of patients (n) | 30 |
| Age – median (Q1-Q3) | 68 (63 – 72.) |
| Days between mpMRI and RP (days) – median (Q1-Q3) | 105 (67-173) |
| PSA (mg/dL) – median (Q1-Q3) | 7.97 (5.82 – 12.5) |
| Previous biopsies – median (Q1-Q3) | 2 (1-3) |
| Last biopsy Gleason Score – n (%) | |
| 6(3+3) | 6 (20%) |
| 7(3+4) | 18 (60%) |
| 7(4+3) | 5 (16.7%) |
| 9(4+5) | 1 (3.3%) |
| **RP Specimen** | |
| Weight (g) – median (Q1-Q3) | 50 (43-60.5) |
| Tumor max dimension (mm) – median (Q1-Q3) | 20.7 (14.75-27) |
| Number of focal tumors – n (%) | |
| 1 | 25 (83.3%) |
| 2 | 3 (10%) |
| 3 | 2 (6.7%) |
| RP Gleason Score and ISUP grade – n (%) | |
| 6(3+3) – ISUP 1 | 3 (10%) |
| 7(3+4) – ISUP 2 | 20 (66.7%) |
| 7(4+3) – ISUP 3 | 6 (20%) |
| 9(4+5) – ISUP 5 | 1 (3.3%) |
| TMN stage – n (%) | |
| pT2a | 1 (3.3%) |
| pT2c | 15 (50%) |
| pT3a | 11 (36.7%) |
| pT3b | 3 (10%) |
| **mpMRI** | |
| Prostate Volume (cm3) – median (Q1-Q3) | 53 (38.75-64.25) |
| Tumor max dimension (mm) – median (Q1-Q3) | 17 (13.75 – 2.2) |
| Tumor Volume (cm3) – median (Q1-Q3) | 1.23 (0.54-2.98) |
| Number of focal tumors – n (%) | |
| 1 | 28 (93.3%) |
| 2 | 2 (6.7%) |
| Extraprostatic extension | |
| Present | 11 (36.7%) |
| None | 19 (63.3%) |

ISUP – International Society for Urological Pathology

attributed the pathological tumour stage (pT), histopathological type, Gleason and ISUP grade and surgical margins according to the 2017 TNM classification.

### Correlation between mpMRI Images and RP Specimen

We used 4 different strategies to calculate MRI performance: per octant, quadrant, hemiprostate and index lesion identification.

Therefore, we considered 3 axial sections (basal, middle and apical prostate) and the following ROIs:

- Octant analysis: 24 ROIs (8 octants x 3 axial regions);
- Quadrant analysis: 12 ROIs (4 quadrants x 3 axial regions);
- Hemiprostate analysis: 6 ROIs (2 hemiprostates x 3 axial regions);
- Index lesion analysis: number of ROIs occupied by index lesion on RP octant grid.

The index lesion was defined as the largest lesion in the whole-mount prostate.

Isolated Gleason 6 lesions with less than 5 mm were excluded from the analysis – considered as clinical non-significant lesions.[20] As for the MRI, corresponding ROIs were analysed for the presence of tumour in the different strategies, resulting in ROIs labeled as positive or negative according to the radiologist reviews.

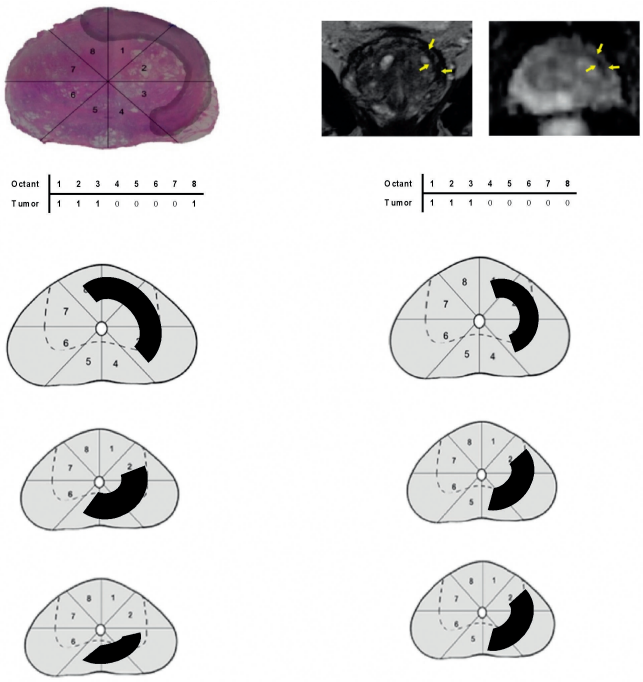
The numbers of true positives, true negatives, false positives and false negatives were determined. Fig. 1 summarizes the model of octant analysis and Fig. 2 shows an example of a true positive case.

We assessed the existence of pre-MRI predictors for the correct identification of index lesion: Serum PSA levels (<4 ng/dL; ≥4 ng/dL); ISUP grade (<3 or ≥3), maximal dimension (<1 or ≥1cm) and TMN stage (<T3; ≥T3).

Finally, correlations between tumour maximal dimensions in the mpMRI and the PR specimen were evaluated. Tumour volume was compared using an ellipsoid formula (LxWxHx[π/6]).

### Statistical Analyses

Continuous variables were summarized using medians and ranges, and categorical variables were summarized using frequencies and percentages. Sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) where determined to evaluate MRI performance on localising prostate tumours in the three different mapping strategies: hemiprostates, quadrants and octants. McNemar test and Cohen's measurement of agreement were determined for each of the strategies. Index lesion identification was also evaluated in terms of sensitivity, PPV and accuracy. Pearson correlation and T-Test were used to determine the relations between the tumour dimensions at histopathology and MRI. Preliminary analyses were performed to ensure no violation of normality and linearity. Nonparametric tests, Spearman Rho and Wilcoxon Signed Rank Test were conducted to compare tumour volume on the two exams. The extra-




| Histopathology | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Octant | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| Base | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 1 |
| Mid | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 |
| Apex | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 |

| mpMRI | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Octant | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| Base | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| Mid | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 |
| Apex | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 |

| Performance | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Octant | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| Base | TP | TP | TP | TN | TN | TN | TN | FN |
| Mid | TN | TP | TP | TP | FN | TN | TN | TN |
| Apex | TN | FP | TP | TP | FN | TN | TN | TN |

**Figure 1 –** Illustration of summarized comparison between histology and mpMRI
A grid with eight regions of interest (octants) is shown on top left image, prostate base histopathology. The corresponding image on mpMRI on top right.
Example of the summarized comparison of whole mount prostate (left) and the corresponding mpMRI (right). With schematic representation of true positive (TP), false negative (FN), false positive (FP) and true negative (TP) on mpMRI analysis.

-capsular invasion was compared using K of Cohen. All analyses were performed using SPSS version 25 (SPSS IBM, Armonk, NY, USA). Statistical significance was defined as $p < 0.05$.

## Results

A total of 30 patients with PCa who underwent mpMRI before RP were included. PCa was detected in all histopathologic analysis

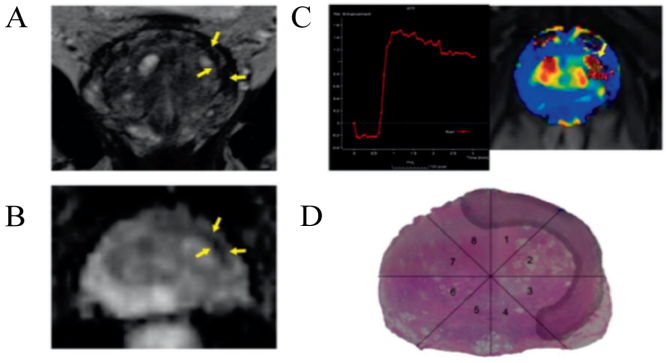



**Figure 2 –** True Positive case
The lesion is delimitated by the arrows on (A) and (B).
(A) T2-weighted imaging (T2WI), (B) diffusion-weighted imaging (DWI), (C) dynamic contrast-enhanced (DCE) imaging and (D) Mid slice of RP specimen

and MRI detected tumour presence in 29 of the 30 patients (96.7%). Patient and tumour characteristics are presented in Table 1.

### mpMRI Performance Analysis

In octant analysis, histopathologic study was conducted in 720 octants and clinically significant tumours was present in 160 of them (22.2%) – with a mean 7 positive segments per patient (range 1-17). One hundred and seven octants (14.9%) were classified as positive by mpMRI according to PI-RADSv2.[19]

MRI performance results are shown in Table 2: Sensitivity and specificity for the detection of PCa on hemiprostates was 82% and 80%, respectively. Kappa measurement of agreement was 0.56 ($\sigma$=0.116; $p$<0.001). Prostate cancer mapping by MRI was less sensitive in the quadrant and octant analysis - 51% and 52%, respectively. Specificity was higher in the quadrant (95.6%) and octant (95.9%) analysis. Cohen's Kappa was 0.51 ($\sigma$=0.047; $p$<0.001) and 0.55 ($\sigma$=0.039; $p$<0.001) for quadrant and octant analysis, respectively.

Pathological study of the 30 index lesions revealed 123 segments with cancer and mpMRI was able to detect 78 positive segments with a sensitivity of 59% and a PPV of 92%. Kappa coefficient of agreement was 0.69 ($\sigma$=0.09; $p$<0.001). 80% of the index lesions were correctly identified by mpMRI.

### Predictors of Tumour Detection

Specificity and Sensitivity for detection of PCa in octants, quadrants and hemiprostates were higher in ISUP grade ≥3 (OR=1.5, $p$<0.05) and tumour dimension ≥1 cm (OR=2.96<0.05).

### Tumour Dimension and Extracapsular Invasion Analysis

Baseline characteristics of tumour volume and dimensions are summarized in Table 1. There was a strong correlation between

Table 2 – mpMRI Performance: Sensitivity (Sen), Specificity (Spe); Positive Predictive Value (PPV), Negative Predictive Value (NPV) and Accuracy

| MRI PERMORMANCE | | | | | |
|---|---|---|---|---|---|
| | Sen IC95% | Spe IC95% | PPV IC95% | NPV IC95% | Accuracy IC95% |
| Hemiprostate | 82.2% (68.0-92.0%) | 80.0% (51.9-95.7%) | 92.5% (81.6-97.1%) | 60.0% (43.2-74.7%) | 81.7% (69.6-90.5%) |
| Quadrants | 52.3% (43.4-61.0%) | 96.5% (93.2-98.47%) | 89.6% (81.1-94.6%) | 77.7% (74.5-80.7%) | 80.3% (75.8-84.3%) |
| Octants | 52.5% (44.5-60.4%) | 95,9% (93.9-97.3%) | 78.3% (70.2-84.7%) | 87.7% (85.9-89.4%) | 86.3% (83.6-88.8%) |
| Index lesion | 58.5% (49.3-67.4%) | N/A | 92.3% (91.2-93.3%) | N/A | 80.0% (61.4-92.3%) |
| **Octants** | | | | | |
| ISUP<3 | 49.5% (39.7-59.4%) | 95,9% (93.7-97.6%) | 74.7% (64.3-82.8%) | 88.8% (86.7-90.5%) | 86.9% (83.8-89.6%) |
| ISUP≥3 | 60.7% (46.7-73.5%) | 97,3% (92.4-99.5%) | 91.9% (78.4-97.3%) | 83.3% (78.3-87.4%) | 85.2% (78.9-90.2%) |
| MD<1 cm | 28.57% (3.7-70.9%) | 96,9% (89.3-99.6%) | 50.0% (14.2-85.7%) | 92.6% (88.7-95.2%) | 90.3% (90.0-96.0%) |
| MD≥1 cm | 54.5% (46.3-62.5%) | 96,1% (94.1-97.7%) | 81.7% (73.8-87.6%) | 87.0% (84.9-88.8%) | 86.1% (83.2-88.7%) |

ISUP – International Society for Urological Pathology; MD – maximal dimension.

measurements of tumour maximal dimensions in RP and mpMRI ($r$=0.80; $n$=30; $p$<0.001), but dimensions were significantly lower on mpMRI measurements (M=1.84 mm; σ=0.16) when compared to anatomopathological analyses (M=2.07 mm; σ=0.15, with t(29)= -2.31, $p$<0.001) - 0.22 mm lower, which means an 11% underestimation of the tumour dimensions by mpMRI.

There was a strong correlation between mpMRI and RP tumour volume (rho=0.73; n=28; $p$<0.001), but again with a statistically significant difference in volume measurements between the two exams (z=-2.28; n=28; $p$<0.05), with the median 1.66 $cm^3$ in PR specimens and 1.24 $cm^3$ in mpMRI.

Extracapsular invasion was present in 11 cases, with mpMRI identifying 90% of them accurately (Kappa measurement of agreement of 0.8; σ=0.109; $p$<0.001).

## Discussion

The main aim of our study was to evaluate mpMRI for accurate localization of intraprostatic tumour nodules. When analysed in octants model, mpMRI had moderate sensitivity for detection of significant PCa and for its correct localization, with high specificity and high negative predictive value (Sensitivity – 52.5%; Specificity – 95.9%; NPV – 87.7%). These findings were consistent with other studies. In a similar 24-segment study, with eight ROIs grid mapping, Isebeaert *et al*[12] reported sensitivities of 58.5%, specificities of 84.3% and NPV of 79.1% for PCa localization. The largest study that reported the PI-RADSv2-based performance for PCa detection was conducted by Wibulpolprasert *et al*[14] and reported 56.0% sensitivity, 97.9% specificity and 93.7% negative predictive value. When the hemiprostatic model was analysed, sensitivity was considerably superior (82%), with a specificity of 80%. These findings are relevant for selection criteria for focal therapies and active surveillance.

Index lesion localization with the 24 segments mapping had a higher sensitivity and PPV when compared with previous studies of Wibulpolprasert *et al.*[14] Index lesion was accurately detected in 80% with a good concordance of results between the two exams (K=0.69).

The maximum diameter of tumour has been shown as a simple clinical tool for assessment of the grade of prostate tumours.[21] We found that maximal tumour dimensions and volume in mpMRI were correlated to the dimensions and volume of tumour in anatomopathological analyses, yet with an 11% underestimation of the tumour dimensions by mpMRI. These findings were consistent with other studies, where volume estimates of prostate cancer using MRI tended to substantially underestimate histopathological volumes.[22]

Extracapsular invasion was correctly detected in 90% of the patients, which confirms the relevance of mpMRI for staging purposes. This result is superior to the reported by a previous meta-analysis (71%) for a per patient analysis,[23] probably justified by the use of higher field strengths and the use of functional imaging techniques. Combined with the high sensitivity (82.2%) of hemiprostatic localization, mpMRI is vastly relevant for surgical planning and nerve sparing treatment options, which may decrease morbidity without influencing oncological results. These results are also applicable for focal therapy planning.

In the present study, there was a significant increase in MRI performance for lesions with dimension of 1cm or more and ISUP grade ≥3. These outcomes, along with 80% of index lesion detection, confirm the ability of MRI to accurately detect dominant tumours, while missing non-significant lesions. This helps excluding patients with low risk of progression from radical treatments and their possible complications.

Prostate MRI can improve diagnostic accuracy and risk stratification at initial diagnosis, and at the same time, be a strategic tool on active surveillance (AS) protocols, reducing the need for surveillance biopsies and their complications. In this study, we found that mpMRI can estimate tumour size with sufficient accuracy. Consequently, it can be used as part of an active surveillance strategy to monitor tumour growth and extension. The potential use of MRI as part of AS protocols is supported by the high specificity of this exam and the high accuracy of index lesion detection, correct localization, dimensions, and extracapsular invasion. Index lesion grade could be monitored with fusion biopsies.

We must acknowledge several limitations of our study. This is a retrospective study, with a limited number of participants. A selection bias was present because all patients had PCa and underwent RP. Consequently, our sample is not representative of the use of mpMRI in biopsy naïve patients. The radiologist who prospectively reviewed the MRI images was aware that all patients had PCa, but despite that, he was blinded for the final pathology of the surgical specimen. A technical limitation of our study was the comparison between RP specimens with 4 to 5 mm of height with mpMRI slices with a thickness of 3mm. We were not able to calculate specificity and NPV in index lesions analysis because there was no ROIs without tumour (true negatives).

## Conclusion

Multiparametric MRI is capable of accurate localization of clinically significant PCa, with moderate sensitivity and excellent specificity. Extracapsular invasion detection and high sensitivity of hemiprostatic localization make this exam vastly relevant for nerve sparing or focal therapy planning, and as a tool for following up the tumour volume on active surveillance protocols.

### Responsabilidades Éticas

**Conflitos de Interesse:** Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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RC, VQ – first co-author.

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LC – Conceção do estudo, análise das imagens e revisão do manuscrito.

CF – Conceção do estudo, análise das amostras e revisão do manuscrito.

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