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Tumour Volume of the Index Lesion in Prostate Cancer: Correlation between Results of Multiparametric Magnetic Resonance Imaging and the Histophatology

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ABSTRACT

Introduction
Prostate cancer is generally multifocal, presenting a lesion with a dominant focus (index lesion) that is characterized by being the lesion with the greatest volume and the biological capacity of invasion to adjacent tissues and distant metastases. With the advent of focal therapy and organ preservation in prostate cancer, it is essential to know the real tumour volume and thus, avoid the persistence of disease after treatments with curative intent. The aim of this study is to correlate the results of the dominant tumour volume obtained from the multiparametric magnetic resonance imaging (MRI) of the prostate and the histopathology.

Material and Methods
A retrospective study was performed which included all radical prostatectomies (RP) with previous MRI. A comparative analysis was performed between the tumour volume obtained from the MRI and the histopathology.

Results
A total of 46 patients were included in the study. The sensibility of the MRI in diagnosing the index lesion was 82.6%, highlighting that all tumours with a Gleason score ≥ 4+3 were diagnosed. The mean tumour volume in the MRI was 14.3 mm and in the histological result was 18.82 mm (p<0.05). The estimation tumour volume concordance was greatest in higher risk (International Society of Urological Pathology (ISUP)).

Conclusion
The MRI underestimates the real tumour volume of the prostate cancer index lesion when compared to the histological result of the surgical piece, being significantly lower in high-risk lesions.

Keywords
Prostate cancer; MRI; Radical prostatectomy; Index lesion; Tumour volume.

INTRODUCTION

Prostate cancer is the most frequent cancer in men and the second cause of cancer-specific death in developed countries.[1]

According to the recommendations of the clinical practice guidelines, high-levels of prostate-specific antigen (PSA), an abnormal digital rectal examination, positive family history and the density of PSA are indicators of suspected prostate cancer and motivate the indication of a confirmatory prostate biopsy.[2]

In the recent years, we focused on the need to increase the performance of our prostate biopsies to avoid the unnecessary biopsies that usually diagnostic an insignificant prostate cancer and in this way, avoid the overdiagnosis and overtreatment in low-risk prostate cancer.[3]

Multiparametric resonance imaging of the prostate (magnetic resonance imaging (MRI)) is a diagnostic tool used to find focal prostatic lesions of high-grade prostate cancer, with the ability to predict the tumour volume and allows the evaluation of which patients are candidates for different active treatment options. Currently, it is recommended to perform a MRI prior to the first biopsy, avoiding an overdiagnosis that can lead to an overtreatment in the clinically insignificant disease.[4]

Prostate cancer is generally multifocal, with a dominant focus (mainly determinate by the tumour volume) known as the 'index lesion'. This dominant lesion is characterized by being the largest lesion and presents the highest grade in the Gleason Score.[5] Furthermore, this 'index lesion' expresses the six hallmarcks of tumour lesions with metastatic biological characteristics.[6]

The advantages of MRI in predicting the true risk of prostate cancer and the prognosis of the disease are known, however, there are no strong correlations in the prediction of tumour volume, with limitations in the finding of smaller tumour focus and a negative impact on the real diagnosis of the risk of the prostate cancer.[7]

The diagnosis of the index lesion is fundamental to determinate the prognosis and the metastasic capacity of the disease.[8] The decision of an active treatment option depends on the relevance on this lesion and it needs to be diagnosed by the MRI. The sensitivity and positive predictive value of the MRI in the diagnosis of the index lesion is 75.9 and 82.6% respectively.[9]

The aim of this study is to evaluate the correlation between the MRI and the histopathology of the surgical piece in predicting the tumour volume of the index lesion and evaluate the sensitivity of the MRI in diagnosing it.

MATERIALS AND METHODS

A retrospective study was carried out between 2016 and 2018. All the surgical pieces of the radical prostatectomies performed in the Hospital Aleman in Buenos Aires were evaluated. A total of 102 patients were included, of whom 39 were excluded because they did not present a MRI prior to the surgery, 10 with a negative result in the MRI and 7 that did not present a MRI performed in our center or not reviewed by the diagnostic imaging service.

The final result is that 46 patients were included and different variables where evaluated: age, body mass index (BMI), PSA and PSA density, digital rectal examination, prostate volume measured by the MRI, clinical stage and pathological stage and we subdivided the different prognostic groups based on the classification on the International Society of Urological Pathology (ISUP).

The Student test (t) was performed for paired samples comparing the tumour volume obtained by the MRI and the histopathological result (HR) of the surgical piece, and associating this comparison in subgroups divided by the ISUP classification. A value of $p<0.05$ was considered statistically significant.

RESULTS

The mean age was 62.2-years (SD±7.2) and BMI was 26.1 (SD±2.5). A 21.7% (11 patients) had positive rectal examination prior to the diagnosis and the mean PSA was 9.8 ng/mL (SD±5.2). Prostate volume measured by MRI was 34 cc (range 25-49 cc). The average PSA density was 0.3 (SD±0.19) and 76% of the patients presented a T1c clinical stage (35 patients). The remaining percentage was divided into stages T2b (10 patients) and T2c (1 patients); 21.7% and 2.3% respectively.

The value of the sensitivity of the MRI in diagnosis the index lesion was 82.6%.

It is important to note that only 8 lesions were missed by the MRI and all of them had a volume < 5mm.

Regarding the pathological stage after radical prostatectomy was illustrated in Table 1.

The differences in tumour volume between the previous MRI and the surgical piece of each pathological stage was evaluated, without showing a significant difference in any evaluated stage ($p>0.05$).

A significant difference was obtained when compared the results obtained between the preoperative MRI and the HR of the surgical piece. The mean tumour volume of the index lesion reported by the MRI was 14.3 mm (SD±6.4) and the mean tumour volume of the index lesion in the radical prostatectomy was 18.8 mm (SD±6.2).

The mean difference in tumour volume was 4.4 mm, obtaining a significant result ($p<0.05$).

Of the 46 patients included, 8.6% (4 patients) did not show a difference when comparing the results and in 58.8% (27 patients) the difference in tumour volume was <5 mm. The remaining 41.2% (19 patients) presented a difference >5 mm. In this last subgroup, it is important to highlight that the maximum difference recorded was 9 mm and that this had no impact on the

Table 1. *Difference in the Tumour Volume (mm) between the MRI and the HR*

Patholofical Stage	pT2aN0 (n=12)	pT2bN1 (n=4)	pT2cN0 (n=20)	pT2cN1 (n=1)	pT3aN0 (n=3)	pT3aN1 (n=1)	pT3bN0 (n=2)	pT3bN1 (n=3)
Difference	5.25 mm	6.25 mm	4.4 mm	1 mm	3 mm	0 mm	4 mm	1.6 mm

MRI=Magnetic Resonance Imaging of the prostate; HR=Histopathological result of the radical prostatectomy

final result of the pathological anatomy. The greatest differences were seen in patients who did not present positive surgical margins in the HR of the radical prostatectomy.

Subsequently, a subdivision was performed by the ISUP classification into the different prostate cancer prognostic groups. Most of the patients were divided into ISUP 2 and 4 (17 patients in each group), 9 patients into ISUP 3 and only 3 patients were ISUP 1.

The difference in tumour volume of the index lesion in the ISUP 1 patients was 5.6 mm, 5.4 mm in the ISUP 2 group and 5.6 mm in ISUP 3 group. The difference drops to 2.5 mm in the ISUP 4 group (Table 2). Statistical comparison (Student test) was performed between the groups with the highest number of patients (ISUP 2 and 4) obtaining a significant difference ($p<0.05$).

Table 2. *Difference in the Tumour Volume (mm) between the MRI and the HR According the Subdivision by the ISUP Classification*

ISUP	ISUP 1 (n=3)	ISUP 2 (n=17)	ISUP 3 (n=9)	ISUP 4 (n=17)
Difference	5.6 mm	5.4 mm	5.6 mm	2.5 mm

MRI=Magnetic Resonance Imaging of the prostate; HR=Histopathological result of the radical prostatectomy

DISCUSSION

Previous studies have tried to find the correlation of the tumour volume between the results of the MRI and the surgical piece of the radical prostatectomy, obtained varied and limits results due to multiple reasons: low number of patients, lack of statistical comparison between both groups and the impossibility of an optimal recording of results.[10,11]

As a general result, it is understood that the MRI underestimates the real tumour volume and this is a consequence of the low training to report the real size of the dominant lesion, the technology of the images and, finally, the lack of knowledge of the real definition of the 'index lesion'.[12]

Mc Neal et al[13] published one of the first studies that postulated the tumour volume, the dominant pattern of the Gleason Score and the lymphovascular invasion as the prognostic factors of clinical progression. They concluded that, although the prostate cancer is generally multifocal, a tumour volume >12 cc from a dominant lesion, which they called 'index lesion', was an independent factor of progression and treatment failure.

The index lesion is the dominant lesion in tumour volume, strongly related to the one with the highest Gleason Score and the biological capacity to invade adjacent tissues and generate distant metastases.[14]

The knowledge of the real tumour volume or the volume of the dominant lesion is crucial and fundamental prior to planning the different therapeutic options to achieve successful treatments. It has been shown that a tumour volume >5 mm has a 10% capacity to invade the prostate capsule, a volume >40 mm has a 10% capacity to invade the seminal vesicles and a tumour volume >50 mm a 10% capacity to develop distant metastases.[15]

In 1993, Stamey et al[16] defined insignificant prostate cancer as that lesion with a histological pattern of Gleason Score 6 and a tumour volume <0.5 cc. This definition was updated and Wolters et al[17] increased the cut-off point of the tumour volume to <1.3 cc. In a recent review on the management of low-risk prostate cancer, Klotz et al[18] cited this definition of insignificant prostate cancer and homologate a tumour volume of 1.3 cc=14 mm.

There are studies that suggest that prostate tumours, due to their multifocality characteristics, present areas of low tumour volume that are invisible in the MRI or generate a dismissal of the volume of the index lesion.[19] The sensitivity of MRI to diagnose the index lesions is estimated to be 75.9% with a positive predictive value of 82.6%.[9] In a recent study with a greater number of patients, Le et al[20] published a sensitivity of 80%. In our study, the value of sensitivity was similar (82.6%) and we missed only 8 lesions which presented a tumour volume <5 mm and multifocality characteristics.

As in the present study, Le Noblin et al[21] correlated the results of prostate tumour volume of MRI and the HR using a correlation software and they found that dismissal of MRI was less when the prostate cancer was more aggressive. They hypothesize that higher grade tumours have solid areas of growth that extend beyond the margins of the lesion, manifesting themselves darker in diffusion (ADC) and captures the radiologist's attention estimating more accurately the real tumour volume.

The precision in the diagnosis of the real index lesion volume is fundamental especially with the advent and the increase indication in the different options of the prostate focal therapy. In a recent study where evaluated the precision of MRI, suggested that at least 20% of the tumour volume reported by the MRI should be increase of the area where the focal treatment will be performed and it would be treating the complete area in up to 95% of cases.[22] They proposed to increase the cut-off point to 9 mm from the lesion reported by the MRI and with this margin the entire tumour volume would be treated. In our study the greatest discrepancies reached a maximum of 9 mm difference, thus increasing the margins ≥ 9 mm from the MRI result would totally treat the dominant lesions in our series.

Generally, the discrepancy is more relevant in the non-capsular margin of the dominant lesion, and this is due to the tendency of tumours that originate close to the prostate capsule to grow centripetally.[23] This point is very important because the extraprostatic extension in patients undergoing a radical prostatectomy resided within the first capsular 3 mm.[24] To achieve the optimal focal treatment, the margins would have to increase to 9 mm from centripetal shape (non-capsular margin) and 3 mm from the capsular margin. This is important in terms of oncological results, since up to 20% of positive prostate biopsies

were reported in a recent review after focal treatment.[25]

Nevertheless, in the present study the location of the index lesion and its growth were not evaluated and it could be an important limitation.

Other limitations are the retrospective design and carried out in a single center with a low number of patients evaluated. The MRI were reported by a two different radiologist and may have some bias in the result of the reported tumour volume.

CONCLUSION

The MRI significantly underestimates the real tumour volume of the index lesion. However, this discrepancy between the MRI and the HR of the surgical piece was significantly less in high-grade prostate cancer.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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