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Original Article

The efficacy of multiparametric prostate magnetic resonance imaging in the diagnosis and treatment of prostate cancer

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ABSTRACT

Aim: To investigate the accuracy of multiparametric prostate magnetic resonance imaging (mpMRI) in determining the diagnosis and treatment options of prostate cancer (PCa), and its pathology correlation.

Methods: Between October 2017 and January 2018, 73 patients were subjected to an mpMRI at our clinic. Of these patients, 11 were radical prostatectomy (RP) after treatment, and four were post-radiation therapy (RT) follow-up. The remaining 58 patients were assigned to the PSA elevation and / or positive digital rectal examination (DRE) patient group in this study and their outcomes were evaluated.

Results: Of the 58 patients included in the study, 13 were found to have a PI-RADS 5 on mpMRI and in 9 (90%) of 10 patients undergoing simultaneous biopsy, PCa was detected. The biopsy results of all cases evaluated as PI-RADS 1 were benign. All of the patients who were ISUP 3 and above had a PI-RADS 5. Patients with a PI-RADS score of 4 and above being ISUP 2 and above was statistically significant *(p=0.011)*. A case had undergone a previous radical prostatectomy assessment revealed that tPSA increased to 2 ng/ml during the follow-up, and so RT was added to the treatment; although LAP was identified in the left iliac region on an mpMRI performed upon the continued increase of tPSA. During the follow-ups of the patient who had regional RT, the tPSA dropped below 0.01 ng/ml.

Conclusion: The results of our study show that mpMRI can gain a new and important place in urology due to the guidance it provides in biopsies, facilitating targeted biopsy, its effectiveness in determining treatment modalities and its importance in post-PCa treatment follow-ups.

Keywords: Multiparametric prostate magnetic resonance imaging, mpMRI, prostate cancer, PI-RAD.

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Introduction

Prostate cancer (PCa) is the second most common cancer among men in the United States of America (USA) and the second-leading cause of cancer-related deaths [1, 2]. The leading risk factor for prostate cancer is age, with the average age of diagnosis of PCa being 66 [3].

Although prostate cancer is common, the mortality risk is low. At this point, a risk classification has been made in order to answer the "Which PCa is fatal?" question. The National Comprehensive Cancer Network (NCCN) guidelines identifies six different risk groups, being very low, low, intermediate, high, very high and metastatic. This classification is based on "whether the cancer is limited to the prostate, the Gleason score, the number of specimens with cancer, the prostate-specific antigen (PSA) value, PSA density (PSAd) and the presence of metastasis to lymph nodes or other organs" [4, 5].

PSA and digital rectal examinations (DRE) are the current screening methods, with a biopsy recommended in cases where PSA≥4ng/ml or a suspicious exam finding is present. The systematic biopsy of the prostate involves the use of a thick needle to take specimens of the peripheral zone, in line with certain standards. At this point, two basic issues need to be taken into account, the first of which is the failure to diagnose cancers in the areas that cannot be accessed by the needle due to the random sampling of cancers that cannot be viewed using ultrasonography (US), and the second issue is the over-diagnosis of low grade cancer. In this sense, an important weakness has emerged in PCa imaging. With the increased clinical use of 3 Tesla (T) devices, PCa can be viewed with a high accuracy rate, which has led to the development of multiparametric prostate magnetic resonance imaging (mpMRI) [6, 7].

An mpMRI is usually performed to identify localized cancers, along with elevated PSA. An mpMRI is aimed mainly at identifying clinically significant cancers (CSC: a tumor > 0.5 cc, Gleason ≥3+4, extracapsular extension) [8], although some make use of mpMRI as the primary screening method [9].

The current guidelines differ in their recommendations on the use of mpMRI. The European Association of Urology (EAU) identifies two main strategies for mpMRI prior to biopsy: The first involves performing a systematic biopsy in all cases, regardless of the mpMRI result (positive or negative), and to add a targeted biopsy in the presence of a positive mpMRI; while second one involves only a targeted biopsy in the presence of a positive mpMRI, with no biopsy recommended in the event of a negative mpMRI. The EAU guidelines also point out that mpMRI is safer prior to a repeated biopsy [10].

Additionally, mpMRI is recommended if there is any clinical suspicion of PCa prior to the biopsy, and that every lesion identified should be biopsied in a targeted and systematic way [10]. According to NCCN guidelines, mpMRI should be considered in the active follow-up group with a life expectancy of more than 10 years in the very low- and low-risk groups. In cases where the biopsy is negative, yet a clinical suspicion still exists, mpMRI should be considered to allow observation of the anterior tumor in particular. mpMRI has also been recommended in the presence of elevated PSA in treated cases [5]. mpMRI has the same diagnostic power as computed tomography (CT) in identifying the pelvic pathological lymph node [11, 12]. mpMRI is also superior to bone scintigraphy and direct radiography in determining bone metastasis [13].

In the light of the above information, the present study assesses the accuracy of mpMRI

in the diagnosis and the determination of treatment options in PCa, and its pathology correlation.

Materials and Methods

A total of 73 patients underwent an mpMRI at our clinic between October 2017 and January 2018, of which 11 were radical prostatectomy (RP) cases and four were post-RT follow-up cases.

Patient exclusion criteria were standard MR contraindications and any previous prostate specific treatment (hormonal therapy, radiotherapy, or radical prostatectomy). Since no prostate imaging, reporting and data system (PI-RADS) categorization was made among the cases that had undergone treatment, so 15 cases were excluded from the study. The remaining 58 patients were assigned to the PSA elevation and/or positive DRE patient group in the present study, and their outcomes were evaluated. PI-RADS assessments were made prospectively, and then the mpMRI results of the cases were compared with their pathology results. The study was conducted in accordance with the ethical approval of the University Ethics Committee (Number: 47104536-000-8728). The rights of all participants were protected and written informed consents were obtained before the study according to the Helsinki Declaration.

Transrectal ultrasonography-guided biopsies

Biopsies were performed from 12 quadrants with a length of 15–22 mm by the guidance of a transrectal probe using a biopsy gun (Geotek® Estacore). 18 gauge needles were used. All patients were given antibiotic prophylaxis with ciprofloxacin before the procedure and bowel preparation was performed with an enema on the day of the procedure. The first dose was taken 1 day prior to biopsy and the second dose on the morning of the biopsy. The antibiotic prophylaxis was continued for 1–3 days after biopsy. Rectal swab culture or targeted antibiotic therapy was not performed as a standard prior to the biopsies.

Multiparametric prostate magnetic resonance imaging (mpMRI)

Multiparametric prostate MRI comprises three basic sequences to achieve anatomical and functional imaging [8]. The first sequence is T2-weighted (T2A) imaging with a high spatial resolution, which allows for the differentiation between structures, such as the transitional zone (TZ), peripheral zone (PZ), capsule, pseudocapsule and urethra, providing anatomical detail. The second basic sequence is diffusion-weighted imaging (DWI), which incorporates two different images: high b-valued images (b=0, 200, 800 and 1400 sec/mm^2) and an apparent diffusion coefficient (ADC) map. DWI basically provides the image of the motion of water. Water moves freely in every direction in the extracellular space in normal prostate tissue, meaning that it displays an accelerated diffusion. In cases of increased cellularity and impaired tissue microarchitecture, the water cannot move freely in every direction, meaning that it displays a restricted diffusion. This manifests as a high signal on high b-value images and a low signal on the ADB map in DWI. The third basic sequence is dynamic contrast-enhanced (DCE) imaging, which provides details on tissue perfusion (in DCE, an at least 2-minute image is obtained in total every 15 seconds following the intravenous administration of a contrast agent. This allows information to be obtained on how fast the tissue gets blood, and how much, and how much of the blood it retains) [14].

PI-RADS v2 scoring

The scoring (categorization) was made based

on the recommended PI-RADS v.2 guidelines, which advise some dominant sequence scoring. Accordingly, peripheral zone (PZ) lesions are categorized based on the DWI score, while the transitional zone (TZ) lesions are based on the T2 score.

Located in PZ, the linear or wedge lesions that are slightly low on ADC and isointense on high b-value image are categorized as score 2; those intermediately low on ADC and with a slightly high signal on high b-value image are categorized as score 3; those that are prominently low on ADC with a high signal on a high b-value image and <15 mm are categorized as score 4; those ≥15 mm with characteristics of a score 4 signal or lesions with an extraprostatic extension are categorized as score 5; and those with score 3 and early focal contrast involvement on DCE are categorized as score 3+1=4.

Located in the TZ, lesions that are regular, encapsulated and nodular are categorized as score 2; those with heterogeneous signals and irregular contours are categorized as score 3; those that are homogeneous, hypointense and limited to the prostate and <15 mm are categorized as score 4; and those measuring ≥15 mm with characteristics of a score 4 signal, or lesions with extraprostatic extensions, categorized as score 5 [8].

ISUP classification

Today, pathology reports are required to include a grade classification, from 1 to 5, in addition to the Gleason score assignment for PCa [15]. Such classifications are made based on the guidelines for prostate cancer, which are graded in accordance with the scale identified at a consensus conference organized in 2014 by the International Society of Urological Pathology (ISUP). Upon the recommendations of the 2014 consensus conference, the 2005 ISUP classification has been changed (Table 1).

Table 1. The International Society of Urological Pathology (ISUP) grading system**.**

ISUP grade	Gleason scores	Definition
Grade 1	**2–6**	Only individual discrete well-formed glands
Grade 2	**3+4=7**	Predominantly well-formed glands with lesser component of poorly formed/fused/ cribriform glands
Grade 3	**4+3=7**	Predominantly poorly formed/fused/ cribriform glands with lesser component of well-formed glands
Grade 4	**4+4=8**	Only poorly formed/fused/cribriform glands
	3+5=8	Predominantly well-formed glands and lesser component lacking glands (or with necrosis)
	5+3=8	Predominantly lacking glands (or with necrosis) and lesser component of well-formed glands
Grade 5	**9–10**	Lacking gland formation (or with necrosis) with or without poorly formed/fused/ cribriform glands

Statistical analysis

Data analysis was performed with SPSS software, version 22 for Windows. Numerical parameters were expressed as mean ± standard deviation, minimum and maximum values, while categorical variables were expressed as frequency and percentage. The Mann-Whitney U test for nonparametric data was used to determine the significance of differences between the groups. $P < 0.05$ was considered to be statistically significant.

Results

Of the 58 patients included in the study, 13 were found to have a PI-RADS score of 5 on an mpMRI, 10 of which underwent concurrent biopsy and 9 (90%) were identified as having PCa (One of them; Figure 1). Based on the biopsy results of the group with a PI-RADS score of 4, 71% were diagnosed with PCa, although 11 of the 20 patients evaluated as PI-RADS 1 underwent a biopsy, and all were found to be benign (Table 2).

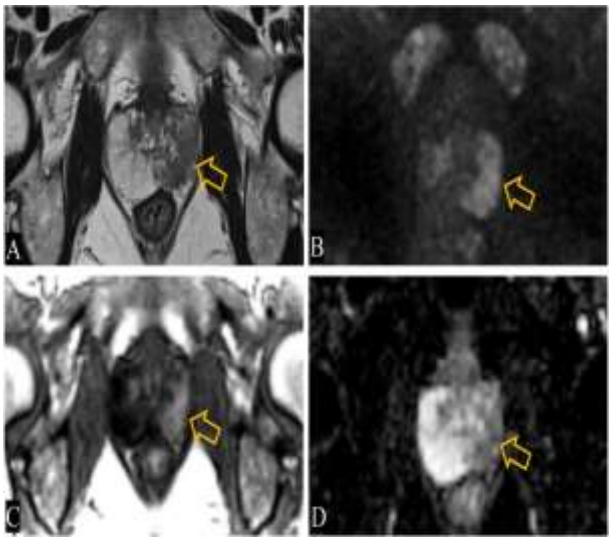

Figure 1. The left mid peripheral zone lesion (yellow arrows) was hypointense on T2WI (a), hyperintense on high b-value (b). It was vividly enhancing in early arterial dynamic imaging (c) and hypointense on ADC (d). This was a PI-RADS category 5 lesion with a 31 mm diameter. It was diagnosed Gleason 4+3 after radical prostatectomy.

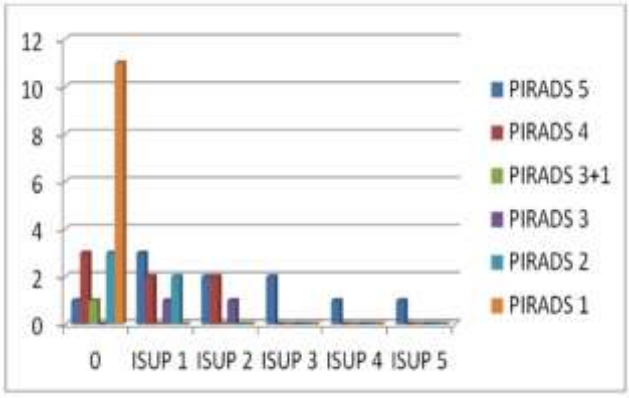

Figure 2. The PI-RADS distribution according to the ISUP classification (58 cases).

surgical contour was negative and no metastasis was identified, and therefore RT was administered. An mpMRI performed upon the continued increase of tPSA during the follow-up identified a 15x9 mm LAP in the left iliac region (Figure 3). During the follow-ups of the patient who had regional RT thereafter, the tPSA dropped below 0.01 ng/ml.

Table 2. The PI-RADS and ISUP results of 58 cases with PI-RADS scoring.

Scoring	Patients (n)	0	ISUP 1	ISUP 2	ISUP 3	ISUP 4	ISUP 5	Non-Biopsy (n)	PSA	PSA D
PIRADS 5	13	1	3	2	2	1	1	3	19 (4,6-124,91)	0,409
PIRADS 4	10	2	3	2	0	0	0	3	6,79 (3,25-12,16)	0,159
PIRADS 3+1	3	1	0	0	0	0	0	2	3,53 (1,99-5,23)	0,067
PIRADS 3	4	0	1	1	0	0	0	2	4,55 (1,09-7,63)	0,098
PIRADS 2	8	3	2	0	0	0	0	3	7,62 (2,12-18,74)	0,109
PIRADS 1	20	11	0	0	0	0	0	9	5,69 (0,34-13,79)	0,072

All of the patients who were 3 and above according to the ISUP classification had a PI-RADS category of 5 (Figures 2). Patients with a PI-RADS score of 4 and above being ISUP 2 and above (CSC) was statistically significant *(p=0.011)*.

The additional case assessment revealed that tPSA increased to 2 ng/ml during the follow-up of one patient with a tPSA=9.94 ng/ml in 2014 who was diagnosed with Gleason =3+4 upon the systematic biopsy, and who had undergone a previous radical prostatectomy, although the

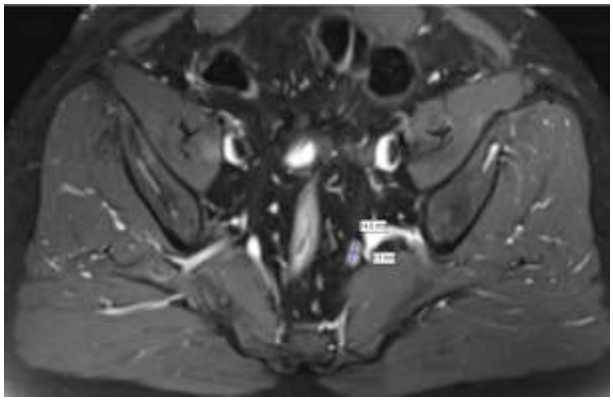

Figure 3. 15x9-mm left main iliac LAP on contrasted T1A on mpMRI.

Discussion

Prostate MRI was first used to evaluate extraprostatic invasion during PCa staging. Combining different sequences of MR imaging, mpMRI has gained in popularity in recent years, and has started to be used to guide TRUS biopsies for PCa diagnosis [16]. The significance of using mpMRI, especially prior to a prostate biopsy, was also emphasized in the 2012 European Society of Uroradiology Guidelines [17].

In a review of the success of mpMRI, a study with 3T reported that CSC was detected in 99 of 100 patients [18]. In another study, involving 114 patients with no lesions identified on mpMRI, found identified no lesions in a systematic biopsy in 88 (77.2%) cases, while a Gleason 3+3 tumor and a Gleason 3+4 tumor was identified in 22 (19.3%) and 4 (3.6%) cases, respectively. The success in ruling out CSC was found to be 96.5%. All of the Gleason 3+4 cases were observed to be patients with active follow-ups [19]. Another study also reported a very high rate of negative prediction for mpMRI (97–98.7%) [20].

In light of the updated knowledge, a positive mpMRI (PI-RADS score of 4 or 5) allows a targeted biopsy to be performed in patients who have not undergone a biopsy, but who have an elevated PSA and/or positive DRE. With the negative mpMRI (PI-RADS score 1 or 2), the biopsy can be delayed and a PSA follow-up can be considered. A negative mpMRI has a very high success rate in ruling out CSC. A positive mpMRI can reveal anterior tumors or CSC in the region that cannot be accessed by a biopsy needle in patients with a negative biopsy history, despite an elevated PSA. A negative mpMRI, on the other hand, can reveal the causes of elevated PSA, such as prostatis, an enlarged prostate gland and BPH nodules. In patients with a positive biopsy history, a positive mpMRI can detect extracapsular extension, seminal vesicular invasion and neurovascular bundle invasion. This changes the treatment strategy (extended surgery or higher-dose radiotherapy rather than neuroprotective surgery). An active follow-up may be considered in the presence of a negative or minimal abnormal mpMRI, a low tumor volume, a Gleason 3+3 score or a short life expectancy (the NCC recommends monitoring only in the very low, low and intermediate risk groups, and with a life expectancy lower than 10 years). However, mpMRI may not reveal high-risk cancer in some cases, and therefore careful PSA monitoring should be carried out during the active follow-up. In patients with a post-treatment elevated PSA, a positive mpMRI can display a recurrence, leading to early treatment. Again, these patients require close follow-up in the presence of a negative mpMRI, as in such cases, a systemic disease may be present [9].

In the present study, the identification of PCa in most of the cases with PI-RADS 4 or 5, and in groups of patients with pathologies of ISUP 2 or more, allows for patient prediction prior to biopsy. Furthermore, it increased the rate CSC identification, and helped in the differentiation of a patient group that might require active follow-up. The benign biopsy result in all of the patients biopsied among the cases evaluated with PI-RADS 1 suggests that a biopsy may be avoided in patient groups recording such results. The study by Wang et al., which is in line with the present study, also reported reduced unnecessary diagnosis for the low-grade cancer group, and avoided repeated biopsied through the performance of targeted biopsies [21].

mpMRI plays a significant role also in local assessment following prostate cancer treatment. An mpMRI following a radical prostatectomy,

RT and focal treatment may be used to visualize normal post-treatment changes and to detect recurrent diseases locally [22]. In the additional case assessment provided in our study, the tPSA of one patient who underwent a radical prostatectomy had increased, although the surgical contour was negative and no metastasis was identified during follow-ups, and the patient received RT. However, an mpMRI performed after a continued increase of tPSA was identified during follow-up revealed a LAP in the left iliac region. A regional RT was administered and tPSA dropped below 0.01 ng/ml during the follow-up, which supports its usefulness in viewing recurrences.

This study has some limitations. Firstly, it is retrospectively designed. Secondly, our sample number is a little low, but it is acceptable for a pilot study. Also, the mpMRI has started to be applied in the near future.

It can be understood from the findings of the present study that mpMRI has gained a novel and significant place in urology in providing guidance to biopsies, in allowing targeted biopsies to be performed, in aiding in the determination of treatment modalities and in its significant contributions to post-PCa treatment follow-ups. That said, the number of participants in our study needs to be increased in order to reflect the general population, and so further studies are required.

Conclusion

MpMRI has gained a novel and significant place in urology in providing guidance to biopsies, in allowing targeted biopsies to be performed, in aiding in the determination of treatment modalities and in its significant contributions to post-PCa treatment follow-ups. Additionally, mpMRI can also be considered an appropriate imaging method for revealing localized tumors in cases with recurrent PSA. Our study observed that a targeted biopsy is required at the diagnostic stage, and the PI-RADS classification is an important indicator of biopsy.

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