

Role of contrast agent in evaluation of periprostatic invasion in prostate cancer

Papel del agente de contraste en la evaluación de la invasión periprostática en el cáncer de próstata

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Abstract

Objective: Our study aims to demonstrate the detection of invasion by biparametric prostate MRI (bpMRI). **Materials and methods:** The cases whose histopathological diagnosis was prostate cancer (PCa) and whose mpMRI report was reported as PIRADS 4 and 5 were evaluated retrospectively by two radiologists with different prostate imaging experiences. The images were grouped into two data sets. Dataset-1 was bpMRI, and dataset-2 was mpMRI. Two radiologists first evaluated dataset-1 independently of each other, and 1 month later, dataset-2. They recorded whether there was an invasion and where it was seen in the patients. Then, the results were compared. **Results:** A total of 75 patients were included in the study. Periprostatic invasion was detected in 33 of the patients. Both the 1st reader and the 2nd reader image detected all the cases with invasion (100%) separately between dataset-1 and set-2. Compatibility for image dataset-1 and dataset-2 between both readers was observed to be excellent. **Conclusions:** There is no need to use contrast agent to evaluate periprostatic invasion and to have an idea about local staging in PCa patients.

Keywords: Periprostatic invasion. Contrast agent. Prostate. Multiparametric. Biparametric.

Resumen

Objetivo: Nuestro estudio tiene como objetivo demostrar la detección de la invasión por resonancia magnética biparamétrica de próstata (BPMRI). **Material y métodos:** Los casos cuyo diagnóstico histopatológico fue PCA y cuyo informe MPMRI se informó como Pirads 4 y 5 fueron evaluados retrospectivamente por dos radiólogos con diferentes experiencias de imágenes de próstata. Las imágenes se agruparon en dos conjuntos de datos. DataSet-1 fue BPMRI, DataSet-2 fue MPMRI. Dos radiólogos evaluaron por primera vez el conjunto de datos 1 independientemente el uno del otro, y 1 mes después, el conjunto de datos-2. Registraron si había una invasión y dónde se vio en los pacientes. Luego se compararon los resultados. **Resultados:** Se incluyeron un total de 75 pacientes en el estudio. La invasión periprostática se detectó en 33 de los pacientes. Tanto el primer lector como la imagen del segundo lector detectaron todos los casos con invasión (100%) por separado entre el conjunto de datos-1 y el set-2. Se observó que la compatibilidad para el conjunto de datos de imágenes-1 y el conjunto de datos entre ambos lectores era excelente. **Conclusiones:** No es necesario usar el agente de contraste para evaluar la invasión periprostática y tener una idea sobre la puesta en escena local en pacientes con PCA.

Palabras clave: Invasión periprostática. Agente de contraste. Próstata. Multiparamétrico. Biparamétrico.

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Introduction

Prostate cancer (PCa) is one of the most diagnosed and leading causes of cancer-related death in men^{1,2}. Prostate cancer is suspected in the presence of a positive digital rectal examination and/or elevated prostate-specific antigen (PSA). This antigen, which is widely used in PCa screening in the clinic, is secreted from both normal prostate epithelium and malignant cells². Conventional radiological evaluations such as ultrasonography (US), computed tomography (CT), and contrast-enhanced lower abdomen magnetic resonance imaging (MRI) are insufficient in detecting and staging prostate cancer. Therefore, with the publication of Prostate Imaging Reporting Data System version 1 (PIRADS v1) in 2012, multiparametric prostate MRI (mpMRI) was brought into the literature and routine practice, and the reporting system was simplified with PIRADS v2 in 2015³. PIRADS v2.1 was published in 2019 by the PIRADS committee due to the feedback of the uncertainties and limitations of PIRADS v2 in many studies⁴. The use of mpMRI in the diagnosis of PCa has been increasing in recent years, and mpMRI is also used for treatment planning, local staging, determination of biopsy localization, and estimation of tumor aggressiveness⁵. According to the PIRADS guideline published by the European Society of Urogenital Radiology (ESUR) in 2012, the mpMRI protocol consists of multiplanar T1-weighted (T1W) and T2-weighted (T2W) images, diffusion-weighted images (DWI), and dynamic contrast-enhanced (DCE) sequences³. In local staging, which is an important step after the diagnosis of PCa, the specificity of MRI is high, but the specificity is low in demonstrating microscopic extraprostatic extension. The current method used to determine whether the tumor has exceeded the prostate border is PSA, Gleason score, positive core percentage, and digital rectal evaluation⁶. These data are combined with the patient's clinic to predict possible extraprostatic extension, seminal vesicle invasion, lymph node involvement, and distant metastasis. Prostate MRI directly visualizes the extraprostatic extension instead of these evaluations. Although MRI has relatively low sensitivity (38%) in demonstrating extraprostatic extension in early studies, it is highly specific⁷.

In PIRADS v2 published by ESUR, the level of contribution of DCE to diagnosis was reduced. In the differentiation of clinically significant PCa, DWI was used for the peripheral zone (PZ) and T2W images were

used as the dominant sequence for the transitional zone (TZ). It was also suggested that the contribution of DCE to the diagnosis in PCa is minimal for PZ lesions and is useless for TZ lesions⁸. According to PIRADS v2, DCE only elevates PZ lesions from the PIRADS-3 category to the PIRADS-4 category. In some studies, it is argued that DCE does not contribute significantly to the diagnosis of clinically significant PCa, and it is suggested that only T2-weighted images and DWI images are sufficient⁹⁻¹¹. In this situation, the place of contrast series in diagnosing clinically significant PCa has become controversial. Accordingly, biparametric prostate MRI (bpMRI), in which only T2-weighted images and DWI images are considered, has been discussed. There are many studies in the literature comparing mpMRI and bpMRI in detecting clinically significant PCa¹²⁻¹⁴. However, bpMRI studies focusing on detecting extraprostatic invasion used in local staging are very limited in the literature.

The main purpose of this study is to demonstrate the diagnostic accuracy of bpMRI in detecting extraprostatic invasion, which is especially important in local staging. In addition, in this study, we aimed to show the agreement of two radiologists with different experiences in the evaluation of extraprostatic invasion with bpMRI.

Materials and method

The study was carried out retrospectively and the study was started after the approval of the local ethics committee dated 28 July 2022 and numbered 22-KAEK-155. Our study was carried out according to the "Helsinki Declaration".

Case selection

In our study, patients diagnosed with PCa histopathologically between January 2019 and June 2022 were examined. Inclusion criteria for the study were patients with elevated PSA and/or positive digital rectal examination findings, patients with mpMRI examination before and within 6 months of prostate biopsy, patients with mpMRI examination within 6 months before prostatectomy, mpMRI report PIRADS 4 and 5 according to PIRADS v2.1 reported patients. Apart from the two readers who performed the study, the PIRADS score was performed by a genitourinary system radiologist with 5 years of prostate MRI reading experience. Exclusion criteria were history of previous

surgery for the prostate, incomplete histopathological data, inadequate mpMRI image quality (artifactual image due to patient movement, presence of magnetic susceptibility artifact due to pelvic surgery such as total hip replacement, presence of artifact on DWI images due to full rectum and inability to comment on the presence of invasion due to collapsed seminal vesicles), and hormonal therapy before mpMRI.

MRI protocol

All patients underwent MRI examination on a 1.5 T device (SIGNA™ Explorer-60 cm GE Healthcare) without using an endorectal coil. MRI sequences used axial fast-spin echo T1W without fat suppression, axial, coronal, and sagittal turbo-spin echo T2W without fat suppression, axial single-shot spin echo-planar DWI images, and T1 Lava three-dimensional spoiled gradient echo pulse sequences without fat suppression. The technical parameters of the sequences are T1W; TR/TE 817/11; slice thickness 3 mm; no slice gap; matrix 256 × 256, and field of view (FOV) 200 × 200 mm for axial images. T2W; TR/TE 8590/108; slice thickness 3 mm; no slice gap; matrix 256 × 256 and FOV 200 × 200 mm for axial images. For DWI, TR/TE 7100/66, slice thickness 3 mm, no slice gap, matrix 256 × 256 and FOV 200 × 200 mm for axial images and b values are 0, 500, and 1500 s/mm². The apparent diffusion coefficient map was calculated for each patient and T1 Lava; TR/TE 4/1, slice thickness 3 mm, no slice gap, matrix 256 × 256 and FOV 200 × 200 mm for axial images. Gadolinium-based contrast agents 0.1 mmol/kg were used for contrast images. Dynamic images were acquired with 30 phases every 7 s. The examination time for the patients lasted approximately 40–45 min.

Before the examination, the patients were advised to sexual abstinence for 3 days. During the examination, care was taken to ensure that the rectum of the patients was empty. Buscopan 20 mg/kg intravenous injection was administered to reduce intestinal peristalsis if there were no contraindications during the examination.

Image analysis

The images were evaluated by two radiologists (1st reader 5-year prostate MRI reading experience and 2nd reader 2-year prostate MRI reading experience) with different experiences on evaluating

prostate MRI. Images were evaluated from a 21.3 inch 3MP IPS Screen medical monitor through Sectra IDS 7 Picture Archiving and Communication Systems. The images were divided into two sets. It was classified as image set-1 bpMRI (T2W, T1W, and DWI sequences) and image set-2 mpMRI (T2W, T1W, DWI, and DCE sequences). While evaluating patients in the study, readers did not look at contrast-enhanced images for bpMRI. Contrast-enhanced images were eliminated in the computer environment, and readers only viewed bpMRI images of the same patients. First, image set-1 was evaluated by both readers. After 1 month, in the second session, evaluation of the same patients, the image set-2 was examined by both readers. Readers evaluated the images independently of each other. At the end of the evaluation, periprostatic invasion was recorded for each patient as present/absent. Invasion sites; it was localized as extraprostatic (extension beyond the prostatic capsule to the fat planes), seminal vesicle invasion, and bladder invasion. In addition, protrusions and irregularities in the prostate contour, obliteration of the rectoprostatic angle, tumor-capsule interface larger than 1 cm, and neurovascular bundle involvement, defined as invasion criteria according to PIRADS v.2.1, were also recorded in the extraprostatic extension. The presence of invasion for image set-1 was accepted in cases where an extraprostatic soft-tissue lesion extending to the seminal vesicle and bladder and causing restriction in diffusion was detected. For image set-2, the presence of invasion was accepted when extraprostatic, seminal vesicle, and a contrasting soft-tissue lesion extending to the bladder were detected. Then, the obtained data were compared in terms of the presence and localization of invasion between readers and between image sets.

Statistical analysis

The SPSS 24 statistical software package (IBM Corp., Armonk, NY, USA) was used for all data analysis. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean, deviation, and minimum-maximum. Normality of distributions was evaluated using the Kolmogorov–Smirnov and Shapiro–Wilk W tests. Independent samples *t*-test was used as our data showed a normal distribution. $p < 0.05$ was considered statistically significant. The Cohen's kappa test was used to determine the level of compatibility among readers. Kappa coefficient; If it is < 0 , weak

agreement, 0-0.20 agreement insignificant, 0.21-0.4 low agreement, 0.41-0.6 medium agreement, 0.61-0.8 high agreement, and 0.81-1 was evaluated as a perfect agreement.

Results

A total of 75 male patients were included in the study. The mean age of these patients was calculated as 66.49 ± 7.57 (48-86 years). On mpMRI, 35 (46.7%) of the patients were reported as PIRADS 4 and 40 (53.3%) as PIRADS 5. The mean PSA of the patients was 16.17 ± 13.95 ng/mL (3.58-66 ng/mL). The histopathological report of all patients was reported as adenocancer. The mean age of the patients reported as PIRADS 4 was 65.46 ± 8.69 years and the mean PSA of these patients was 9.05 ± 5.89 ng/mL. The mean age of the patients reported as PIRADS 5 was 67.4 ± 6.4 years and the mean PSA of these patients was 22.4 ± 15.94 ng/mL (Table 1). There was no statistically significant difference between PSA values and age for patients reported as PIRADS 4 and 5.

Periprostic invasion was detected in 33 (44%) of the patients. All of the patients with invasion were reported as PIRADS 5. The mean age of the patients with invasion was 67.97 ± 6.35 years and the mean PSA of these patients was 24.95 ± 16.32 ng/mL. The mean age of the patients without invasion was 65.33 ± 8.29 , and the mean PSA of these patients was 9.27 ± 5.74 ng/mL (Table 1). A statistically significant difference was found between PSA values for patients with and without invasion ($p < 0.001$). The most common invasion was extraprostatic (extension beyond the prostatic capsule into the fat planes) in 14 patients (42.4%) (Figs. 1 and 2). Seminal vesicle invasion was detected in 13 patients (39.4%), both seminal vesicle and bladder invasion were detected in 3 patients (9.1%), and both seminal vesicle and extraprostatic invasion were detected in 3 patients (9.1%).

Both the 1st and 2nd reader image data set-1 (bpMRI) and set-2 (mpMRI) detected all the cases with invasion (100%) separately. The compatibility between both readers for image data set-1 and set-2 was observed to be excellent (Kappa value +1) (Table 2).

Discussion

In our study, since all cases with invasion detected on mpMRI could be detected with bpMRI and excellent agreement was observed between two radiologists with different prostate imaging experiences in

Table 1. Descriptive data of the patients

Radiopathological data	Number/Percent	Age $\pm$ SD (year)	PSA $\pm$ SD (ng/mL)
PIRADS 4	35/46.7%	65.46 ± 8.69	9.05 ± 5.89
PIRADS 5	40/53.3%	67.4 ± 6.4	22.4 ± 15.94
Cases with invasion	33/44%	67.97 ± 6.35	24.95 ± 16.32
Cases with no invasion	42/56%	65.33 ± 8.29	9.27 ± 5.74
Total	75/100%	66.49 ± 7.57	16.17 ± 13.95

SD: standard deviation; PSA: prostate-specific antigen; PIRADS: prostate imaging reporting data system.

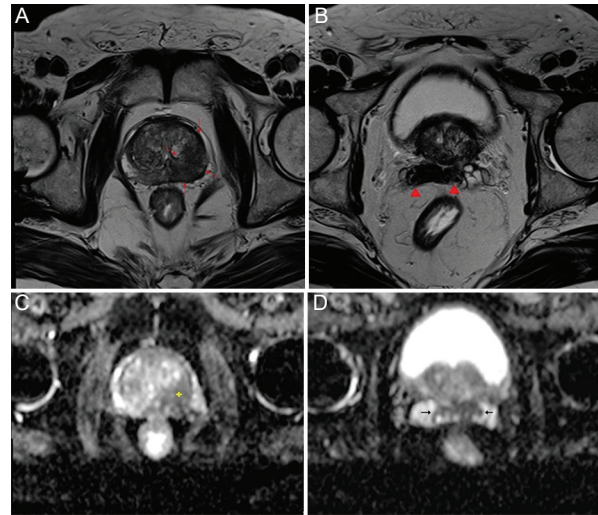


Figure 1. A-D: a 68-year-old male patient. PIRADS 5 lesion involving the anterior and posterior compartments of the middle peripheral zone on the left and involving the transitional zone anterior and posterior zone. The lesion extends to the base of the prostate in more superior sections and invades both seminal vesicles from there. **A:** T2-weighted image shows signal loss at the described location of the lesion (between the red arrows). **B:** T2-weighted image, it is observed that the lesion has invaded both seminal vesicles (red arrowheads). **C:** the apparent diffusion coefficient map, lesion appears hypointense (yellow mark). **D:** the apparent diffusion coefficient map shows that the lesion has invaded both seminal vesicles (between black arrows).

the detection of invasion on bpMRI, gross local staging of PCa could be performed by showing periprostic invasion by bpMRI.

With the change on prostate imaging over the years, the areas of use of contrast media are narrowing. Because, besides its minimal contribution to diagnostic accuracy, it has disadvantages that cannot be ignored. There are three major advantages to removing DCE from the protocol. These shorten the examination time, reducing the cost of the examination, and eliminating the possible undesirable effects of the contrast agent. Some known side effects linked to the use of gadolinium-based contrast agents include:

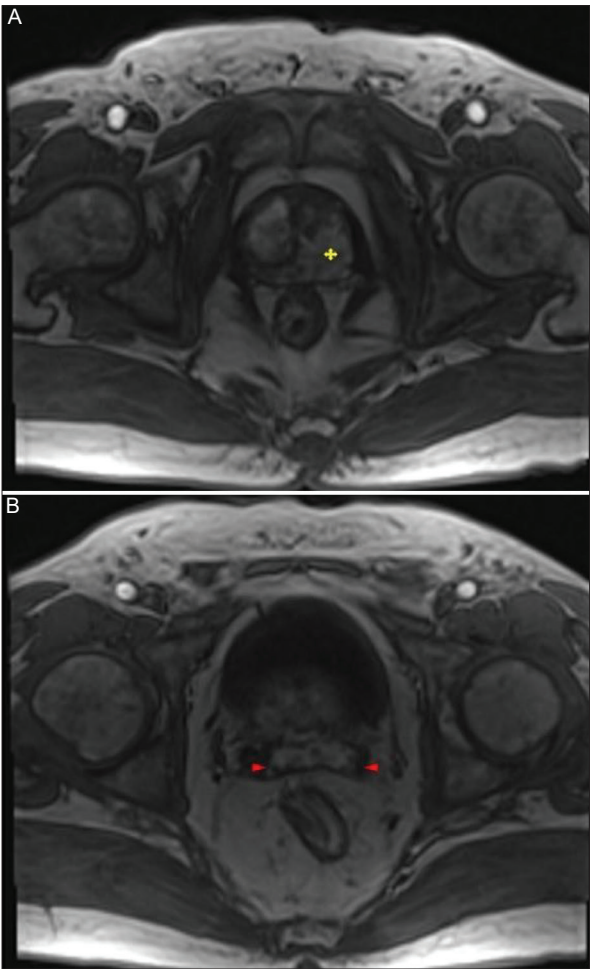


Figure 2. A and B: post-contrast T1-weighted image of the same patient without fat suppression. A: the lesion has heterogeneous contrast (yellow mark). B: seminal vesicle invasion is seen as a contrasting space-occupying formation (between the red arrowheads).

development of allergic reaction, systemic nephrogenic fibrosis and accumulation of contrast agent in the brain¹⁵. Other side effects are seen at a rate of 0.004-0.7% and include coldness or warmth at the injection site, pain at the injection site, nausea, vomiting, headache, paresthesia, and dizziness¹⁶. DCE is still included in clinical use and in the PIRADS v2.1 guideline. Because DCE has advantages such as detecting small PCa and following patients after radical prostatectomy^{11,17}. In addition, the use of contrast agent has additional advantages such as increasing the diagnostic accuracy of some inexperienced radiologists and supporting the correct diagnosis if the image quality of DWI and/or T2W sequences is low¹⁶. However, it has also been shown that the use of DCE causes false positives in some benign conditions such as prostatitis and fibrosis¹⁸. The role of DCE in

Table 2. Compatibility among readers

Observers	Invasion detection (number/percent)		Kappa
	Data set-1 (bpMRI)	Data set-2 (mpMRI)	
Reader I	33/100%	33/100%	1
Reader II	33/100%	33/100%	

bpMRI: biparametric prostate magnetic resonance imaging; mpMRI: multiparametric prostate magnetic resonance imaging.

Table 3. bpMRI and mpMRI advantages

bpMRI (T2W, DWI) advantages	mpMRI (T2W, DWI, DCE) advantages
Examination time is short	Diagnostic accuracy increases if T2W and DWI image quality is poor
Possible side effects of the contrast agent are eliminated	Diagnostic accuracy increases in the presence of inexperienced radiologist
Cost is lower	Detection of small lesions becomes easier
Evaluation is easier	Contributes to diagnostic accuracy in uncertain cases

bpMRI: biparametric prostate magnetic resonance imaging; mpMRI: multiparametric prostate magnetic resonance imaging; T2W: T2 weighted; DWI: diffusion-weighted imaging; DCE: dynamic contrast enhanced.

diagnosis and staging is controversial. One advantage of using the bpMRI protocol is that it is easier to evaluate images than mpMRI. The comparison of mpMRI and bpMRI in terms of advantages is shown in table 3.

Studies on the use of bpMRI in local staging, which is the focus of our study, are limited. Although the specificity of prostate MRI is high in local staging, the sensitivity is low due to the inability of MRI to show microscopic extraprostatic extension⁴. In this instance, we think that imaging with DCE will not be of additional benefit in showing the microscopic extension. Our results also detected periprostatic invasion at the same rate in contrast-enhanced and non-contrast series, regardless of microscopic extension.

There are some studies showing that bpMRI has the same diagnostic accuracy as mpMRI in detecting clinically significant PCa according to PIRADS v2^{14,19-21}. In a study that divided patients with suspected PCa into low-risk, intermediate-high-risk, and very high-risk patients, it was reported that only bpMRI evaluation would be sufficient in the very high-risk patient group (having a very high PSA and positive digital rectal examination finding)²². According to this study, our patient group

falls into the very high-risk category, and we argue that bpMRI will be sufficient to evaluate patients in this category. Recent evidence has revealed that the bpMRI protocol may be sufficient in the diagnosis for PCa of 10 mm and above¹¹. In another study, the bpMRI protocol for clinically significant PCa was shown to have the same diagnostic accuracy as mpMRI²⁰. In a similar study, bpMRI focused on the detection of cancer in the anterior fibromuscular stroma and TZ, and they showed that the rates of clinically significant PCa detection by bpMRI were not lower than mpMRI²³.

Detection of periprostatic invasion (extraprostatic extension, seminal vesicle invasion, bladder invasion) is an important step in treatment planning. Our findings contribute to local staging with bpMRI at this stage. This stage will be more advantageous than mpMRI in shortening the examination time, reducing the cost, and eliminating possible side effects.

Ga68 Prostate Specific Membrane Antigen (Ga68-PSMA) is a new monitoring agent used on PET. Ga68 PSMA-positron emission tomography-computed tomography (PET/CT) is used in the diagnosis, evaluation of the extent of prostate cancer, and treatment follow-up. Ga68 PSMA-PET/CT examination was accepted as the gold standard for demonstrating the presence of invasion. However, this method has some limitations in diagnosis and staging. Ga68 PSMA-PET/CT is confusing and false-positive in conditions such as benign prostatic hypertrophy that increases PSA levels and in conditions such as prostatitis. In this case, Ga68 PSMA-PET/CT can provide additional diagnostic benefits in demonstrating periprostatic invasion of bpMRI, and it can also be used instead of Ga68 PSMA-PET/CT.

The limitations of our study are the fact that the study is retrospective and single center, and the number of patients is low, which is in the first place. The second limitation is that the endorectal coil is not used on MRI sequences. The third limitation is that the images were obtained with a 1.5 T MRI device. Since the second and third limitations will reduce the signal-to-noise ratio, the image quality is low. Another limitation of our study is that the Gallium-68 PSMA-PET/CT examination, which is used in routine practice in demonstrating invasion and metastasis, was not included in the study.

Conclusion

There is no need to use contrast agent to evaluate periprostatic invasion and to have an idea about local staging in PCa patients. With this method, prolongation of dynamic contrast sequence-based examination,

increase in cost, and undesirable side effects of contrast agent are eliminated. With adequate image quality, T2W and DWI images, radiologists experienced on prostate imaging will not need contrast-enhanced series in the evaluation of periprostatic invasion. We hope that more comprehensive studies will be conducted with images in which the contrast agent is eliminated.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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