Comparative analysis of multiparametric prostate MRI and ^{68}Ga-PSMA PET/MRI with radical prostatectomy specimens in prostate cancer staging

Engin Derekoylu[1] **MD,**
Kadir Can Sahin[1] **MD,**
Goktug Kalender[1] **MD,**
Mustafa Ozkaya[1] **MD,**
Iclal Gurses[2] **MD,**
Fatih Kantarcı[3] **MD,**
Haluk Burcak Sayman[4] **MD,**
Ahmet Erozenci[1] **MD**

1. Istanbul University - Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Urology,
2. Istanbul University - Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Medical Pathology,
3. Istanbul University - Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Radiology,
4. Istanbul University - Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Nuclear Medicine

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Corresponding author:
Engin Derekoylu MD,
Istanbul University - Cerrahpasa, Cerrahpasa Faculty of Medicine
Department of Urology
İstanbul Üniversitesi-Cerrahpaşa, Cerrahpaşa Tıp Fakültesi Yerleşkesi P-Blok Kocamustafapaşa Caddesi No:53 Cerrahpaşa 34098 Fatih / İstanbul
Phone: +90 553 741 75 30
engin.derekoylu@gmail.com

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Abstract

Objective: Because of low mortality rates and high treatment-related adverse effects in patients diagnosed early, active surveillance, focused treatments, and watchful waiting are currently advocated, emphasizing the importance of proper prostate cancer (Pca) staging using imaging techniques. We aimed to comparatively investigate the success rates of multiparametric prostate magnetic resonance imaging (MRI) and prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/MRI in predicting tumoral regions, seminal vesicle invasion, and extraprostatic extension. **Subjects and Methods:** Twenty six patients with a biopsy diagnosis of prostate cancer who underwent radical prostatectomy between January 2021 and September 2022 were included in the study. Preoperative evaluation was conducted through a combination of multi-parametric (Mp)MR and PSMA PET/MRI. Findings such as tumoral regions, seminal vesicle invasion, and extra-prostatic extension in prostatectomy specimens were compared with the MpMRI and PS MA PET/MRI images. **Results:** Prostate cancer was present in 103 foci of a total of 156 segments. In the context of identifying the aforementioned foci, the sensitivity of MpMRI was determined to be 74.8%, coupled with a specificity of 94.3%. Similarly, the sensitivity of PSMA PET/MRI was established at 70.9%, accompanied by a specificity rate of 90.6%. In the prediction of extraprostatic extension, MpMRI exhibited a sensitivity of 33.33% alongside a specificity of 78.57%. In contrast, PSMA PET/MRI displayed a sensitivity of 25% but achieved a higher specificity of 100%. Concerning the prediction of seminal vesicle invasion, MpMRI demonstrated a sensitivity of 40% and a specificity of 95.24%. Conversely, PSMA PET/MRI yielded a sensitivity of 60%, which was slightly superior to MpMRI's sensitivity with a close specificity rate of 95.24%. **Conclusion:** Multi-parametric MRI and PSMA PET/MRI are reliable methods for the local staging of prostate cancer and the prediction of tumor localization. No statistically significant advantage of either method was discerned in the course of our study.

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Introduction

Prostate cancer (PCa) is the 4th most common type of cancer and the 8th most common cause of cancer-related death [1]. It is estimated that 1 in 8 men will be diagnosed with Pca during their lifetime, and 1 in 41 men will succumb to PCa [2].

In today's healthcare landscape, PCa is diagnosed at an earlier age and at an earlier stage due to increased access to health services, screening programs, and advancements in imaging techniques. Consequently, curative treatments can often be offered to a majority of patients. Prostate cancer typically progresses slowly and is less aggressive, which often results in a protracted period before symptoms become evident. Many patients are diagnosed during the asymptomatic phase of the disease.

Due to the low mortality rates and high treatment-related side effects in patients diagnosed at early stages, clinicians may opt for approaches such as active surveillance, focal therapies, and watchful waiting. Therefore, the proper staging of PCa becomes crucial.

The aim of this study is to compare preoperative gallium-68 (^{68}Ga) prostate-specific membrane antigen emission tomography/magnetic resonance imaging (PSMA PET/MRI) and multi-parametric prostate magnetic resonance imaging (MpMRI) with final pathology in cases diagnosed with PCa and scheduled for radical prostatectomy (RP). The study seeks to evaluate the ability of these imaging modalities to predict lesion location, size, and local staging during the preoperative period.

Subjects and Methods

A retrospective analysis was conducted on patients who underwent surgery between January 2021 and September 2022 in our clinic. Pre-biopsy PSA values, MpMRI findings, biopsy pathology results, preoperative PSMA PET/MRI images, and final pathology reports were examined. Patients who underwent pelvic radiotherapy, castration, received neoadjuvant hormone therapy, or had missing data were excluded from the study. The final analysis included 26 patients who met all of the inclusion criteria and provided consent to participate.

All PSMA PET/MRI studies were analyzed by an experienced nuclear medicine physician (HS), blind to the final pathology results. Only the T2A images from MpMRI were utilized for the localization of PSMA uptake. Any elevated PSMA uptake, distinguishable from background and physiological uptake, was considered tumoral involvement.

Suspicious areas of malignancy within the prostate were marked on the PI-RADS v2.1 prostate sector map. Maximum and average standardized uptake values (SUVmax and SUVmean) and metabolic tumor volume (MTV) were measured by delineating a volume of interest (VOI) around the prostate tumor. Whole-body PET images were utilized to detect the presence of lymph nodes and organ metastases.

The MpMRI studies were re-evaluated by an experienced urogenital radiologist (FK), who was blinded to the pathological findings. Suspicious areas of malignancy within the prostate were delineated on the PI-RADS v2.1 prostate sector map [3]. Parameters such as prostate volumes, lesion localization and dimensions, PI-RADS v2.1 scores, extraprostatic extension (EPE), seminal vesicle invasion (SVI), and the presence of periprostatic lymph nodes were documented. The highest PI-RADS score was assigned to patients whose multiple lesions had varying PI-RADS scores.

Pathological evaluations were conducted in accordance with the ISUP (International Society of Urological Pathology) Consensus Conference 2019 recommendations [4]. A standard pathological assessment was performed by an experienced uropathologist (IG). The upper (base) and lower (apex) 6-8mm segments of the prostate were sliced in a pie-shaped manner and horizontally arrayed. Subsequently, the intervening prostate tissue was sliced at 3-4mm intervals. All regions of tumor involvement were demarcated in red under the microscope. Areas with pathological involvement that were not identified in imaging studies were re-evaluated following examinations conducted by nuclear medicine and radiology physicians. Pathology served as the gold standard for assessment.

The decision to incorporate pelvic lymph node dissection into the patients' surgeries was made in accordance with the Briganti 2018 nomogram [5]. The surgeries were performed either via open or robot-assisted laparoscopic approaches. Pelvic lymph node dissection was planned to encompass the bilateral removal of lymph nodes located in the obturator fossa, both cranial and caudal to the obturator nerve, and medial and lateral to the internal iliac artery, which overlies the external iliac artery and vein.

The prostate was divided into six segments: right apex, right mid, right base, left apex, left mid, and left base (a total of 156 segments for 26 patients). In pathologic examination, as well as in MpMRI and PET/MRI imaging, these prostate regions containing the tumor were recorded. Furthermore, the locations of positive foci in preoperative prostate biopsies were similarly documented. Tumor foci that were not detected in MpMRI and PET/MRI were re-evaluated, and their findings were recorded.

The evaluation and analysis of the data were performed using IBM SPSS (The Statistical Package for the Social Sciences, Armonk, NY: IBM Corp.) version 25.0 software package. Descriptive data were expressed as frequencies (n) and percentages (%) for categorical variables, while mean±standard deviation and median (25^{th}–75^{th} percentile) were used for numerical variables. The Mann-Whitney U test was employed to compare non-normally distributed continuous or discrete variables between the two groups. Spearman's correlation analysis was applied to assess the relationship between two numerical variables. A significance level of $P<0.05$ was considered statistically significant.

Results

Thirteen patients underwent retropubic RP, while thirteen patients underwent robot-assisted laparoscopic RP. Of the operated patients, seventeen underwent bilateral pelvic lymph node dissection as well. The median age of the patients was determined to be 65.42 years, ranging from 55 to 75 years.The median PSA value for patients was 12.49ng/mL, ranging from 1.2 to 90. Clinical staging revealed that 18 patients were classified as T1C, 7 patients as T2a, and 1 patient as T2C. Patient characteristics are summarized in Table 1.

Regarding preoperative MpMRI findings, one patient exhibited a PI-RADS 3 lesion, while 19 patients had PI-RADS 4, and 6 patients had a dominant PI-RADS 5 lesion. In MpMRI, the median diameter of the dominant lesion was measured at 13.34mm, ranging from 6.2 to 26.9mm. In preoperative PSMA PET/MRI, the mean intraprostatic SUVmax value was 10.4, with a range of 3.95 to 38.43. For RP specimens, the median tumor diameter was calculated to be 15.85, with values ranging from 0 to 87.7 (Table 1).

In the RP specimens, SVI was observed in 5 patients. Seminal vesicle invasion was detected in 3 patients in MpMRI and again in 3 patients in PSMA PET/MR imaging. Capsular invasion (CI) was noted in 12 patients in the RP specimens. Multi-parametric MRI identified CI in 7 patients, while PSMA PET/MR imaging identified it in 3 patients.

Out of a total of 156 prostate segments, tumors were detected in 103 of them, while 53 segments showed no evidence of tumors in final pathology reports. Both tumoral and non-tumoral foci that are correctly revealed by mpMRI and PSMA PET/MRI, as well as transrectal biopsy (TRUS-Bx), are summarized in Table 2 (Figures 1-3).

In our study, the sensitivity of MpMRI in predicting tumoral areas was found to be 74.8%, with a specificity of 94.3%. The positive predictive value (PPV) for predicting tumoral areas was 96.2%, while the negative predictive value (NPV) was 65.8%. Prostate-specific membrane antigen PET/MR's sensitivity in predicting tumoral areas was 70.9%, with a specificity of 90.6%. PPV was 93.6%, and NPV was 61.5%. For the detec-

Table 1. *Patient characteristics (n=26).*

Age	**65.42 (55-75)**
ASA score	
1	4 (15.4)
2	21 (80.7)
3	1 (3.8)
PSA (ng/mL)	12.49 (1.2-90)
Clinical staging	
T1c	18 (69.2)
T2a	7 (26.9)
T2c	1 (3.8)
PI-RADS scores of lesions detected in MpMRI	
3	1 (3.8)
4	19 (73)
5	6 (23.1)
Diameter of dominant lesion in MpMRI (mm)	13.34 (6.2-26.9)
Intraprostatic SUVmax value in ^{68}Ga PSMA PET/MRI	10.4 (3.95-38.43)
Median tumor diameter in RP specimens (mm)	15.85 (0-87.7)

Note: Data were expressed as median (min.-max.) or number (%) whenever appropriate. Abbreviations: PSA; prostate specific antigen, PI-RADS; Prostate Imaging Reporting and Data System, ASA; American Society of Anesthesiologists, MpMRI; multiparametric prostate magnetic resonance imaging, ^{68}Ga PSMA PET/MRI; ^{68}Ga prostate-specific membrane antigen emission tomography/magnetic resonance imaging, RP; radical prostatectomy.

Table 2. Numbers of positive foci captured by the techniques in analysing 156 segments of 26 patients.

	Tumoral segments in RP specimens (n=103)	Non-tumoral segments in RP specimens (n=53)
MpMRI	77/103	50/53
^{68}Ga PSMA PET/MRI	73/103	48/53
TRUS-Bx	68/103	40/53

MpMRI; multiparametric prostate magnetic resonance imaging, TRUS-BX; transrectal ultrasound prostate biopsy, ^{68}Ga PSMA PET/MRI; ^{68}Ga prostate-specific membrane antigen emission tomography/magnetic resonance imaging, RP; radical prostatectomy.

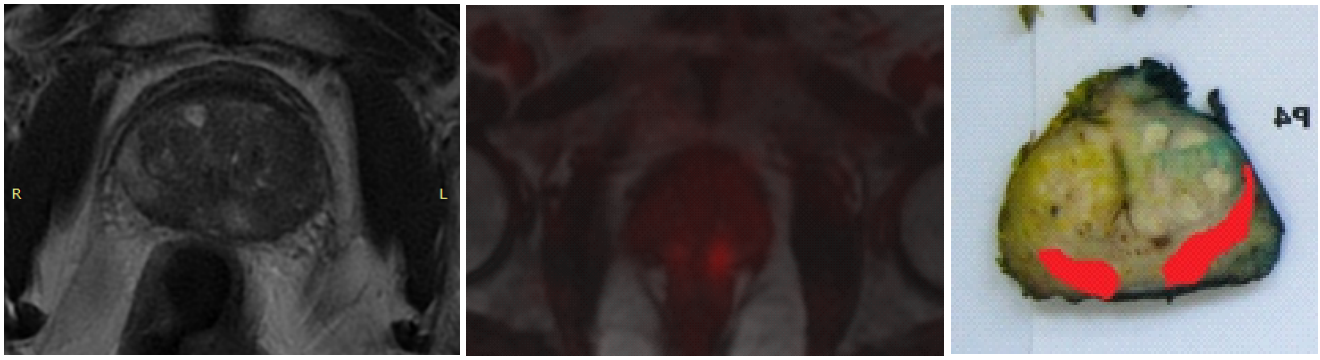

Figure 1. Tumoral regions located in the mid-apical region of the prostate, which have been identified and correlated across MpMRI T2 images, PSMA PET/MRı, and pathological examinations. (Archives of the Department of Radiology, Nuclear Medicine, and Medical Pathology at Istanbul University-Cerrahpaşa).

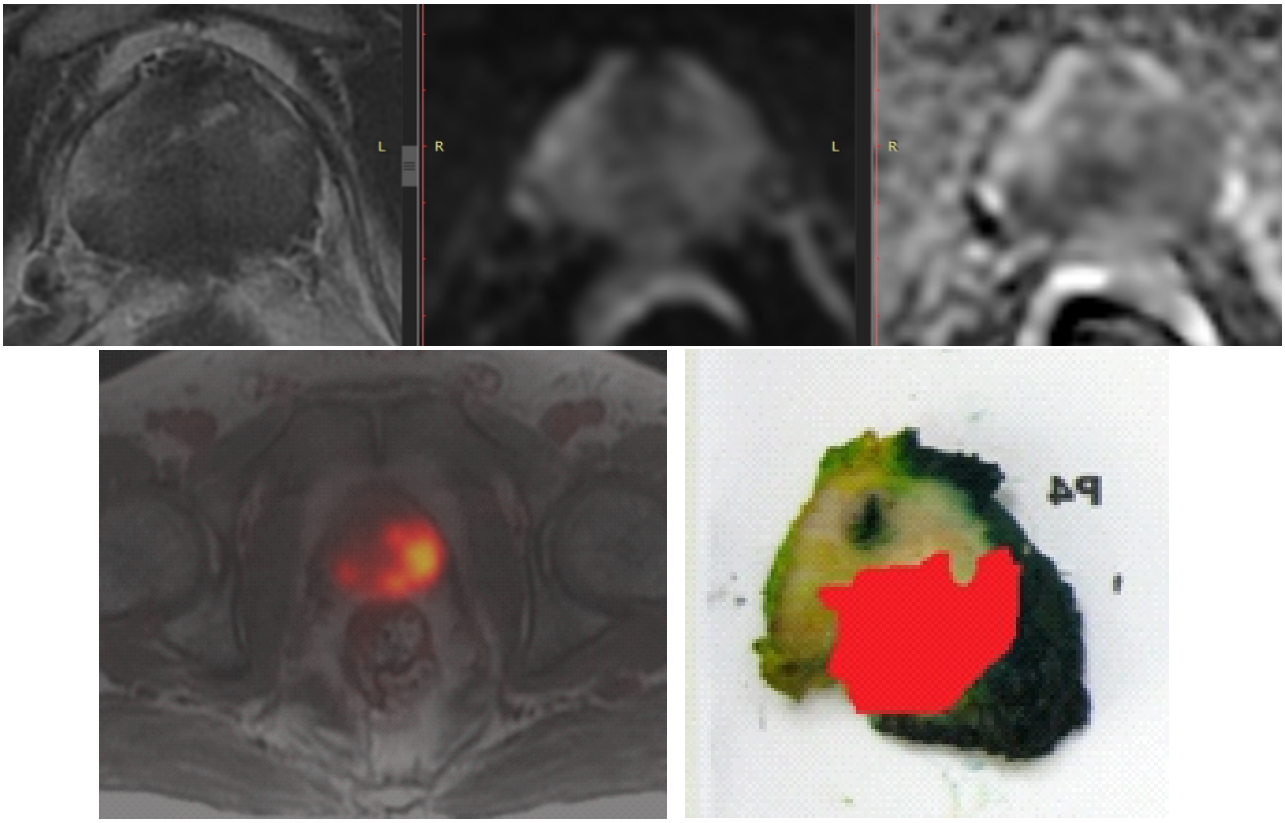

Figure 2. Tumoral regions identified in the apical peripheral zone, which have been correlated across MpMRI sections, PSMA PET/MRI, and pathological examinations. (Archives of the Department of Radiology, Nuclear Medicine, and Medical Pathology at Istanbul University-Cerrahpaşa).

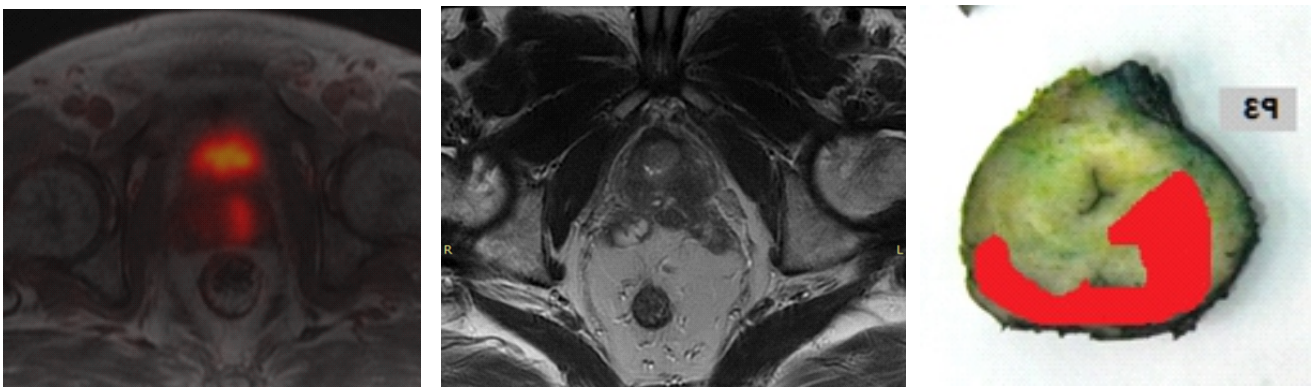

Figure 3. A PI-RADS 5 lesion identified in the bilateral prostatic lobes on MpMRI, specifically indicating left seminal vesicle invasion. Simultaneously, PSMA PET/MR imaging reveals the presence of seminal vesicle invasion and bilateral involvement (SUVmax: 15.71). The final pathology report also confirms bilateral tumor involvement and left seminal vesicle invasion in areas corresponding to the sections. (Archives of the Department of Radiology, Nuclear Medicine, and Medical Pathology at Istanbul University-Cerrahpaşa).

tion of cancer foci in TRUS-Bx, the sensitivity was 66%, with a specificity of 75.5%. PPV was 84%, and NPV was 53.3%.

Upon re-examination of areas in RP specimens where tumors were detected but not visible on imaging methods, it was found that there were 26 tumoral foci that were not identified on MpMRI. Out of these, 24 were ISUP grade 1, one was ISUP grade 2, and one focus located in the transitional zone was ISUP grade 3. The long axis of tumoral areas was less than 5 mm in 15 foci, with eight of them being less than 1mm in size.

There were 30 foci that were detected on pathological examination but not visible on PSMA PET/MRI. Among these areas, nine had a long axis smaller than 1mm, while 11 had a size larger than 5mm. Within these areas, ISUP grade 1 was observed in 21 of them, ISUP grade 2 in 3, ISUP grade 3 in 4, and ISUP grade 4 in 2. In adjacent ISUP grade 4 regions that were not identifiable on PSMA PET/MRI, the tumor exhibited a perineural growth pattern (Figure 4). It was hypothesized that there was no involvement in this region due to the relative absence of vascular structures within the perineural region.

Fifteen foci were identified that were not visible on both MpMRI and PSMA PET/MR imaging (Figure 5). Among these foci, 14 were ISUP grade 1, and only one was ISUP grade 2. When the boundaries of the tumoral area in these foci were determined under the microscope, it was found that only 2 foci had a long axis greater than 5 mm, while 6 foci had a long axis of 1mm or less (Figure 6).

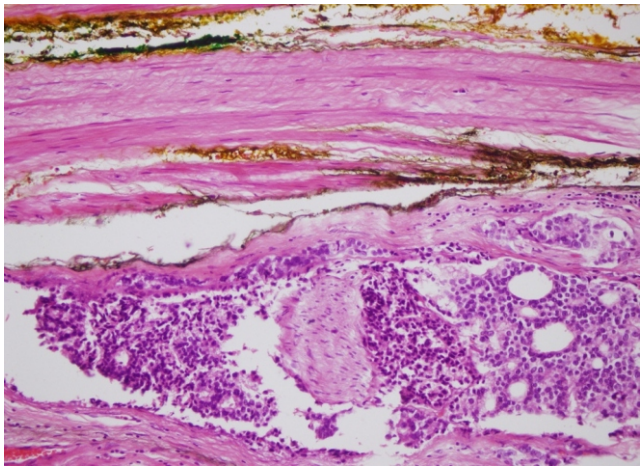

Figure 4. An area identified as Gleason pattern 4 with perineural invasion in the right peripheral zone of RP specimen, which was not discernible on PSMA PET/MRI (H&E; x200) (Archives of the Department of Medical Pathology at Istanbul University-Cerrahpaşa).

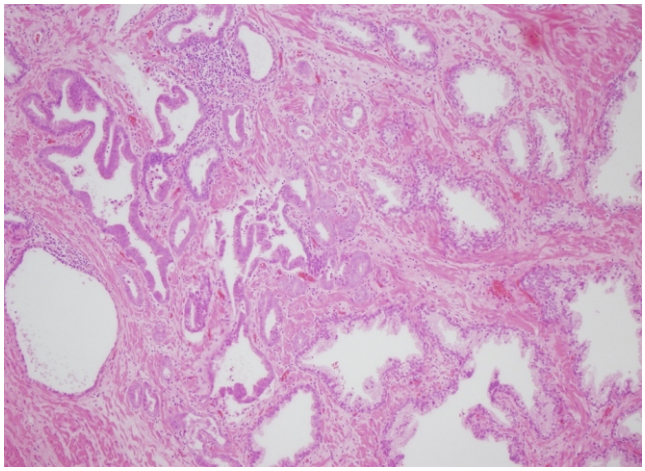

Figure 5. A microinvasive acinar adenocarcinoma area located at the left apical level of a RP specimen that was not detectable on both MpMRI and PSMA PET/MR imaging. (H&E; x100) (Archives of the Department of Medical Pathology at Istanbul University-Cerrahpaşa).

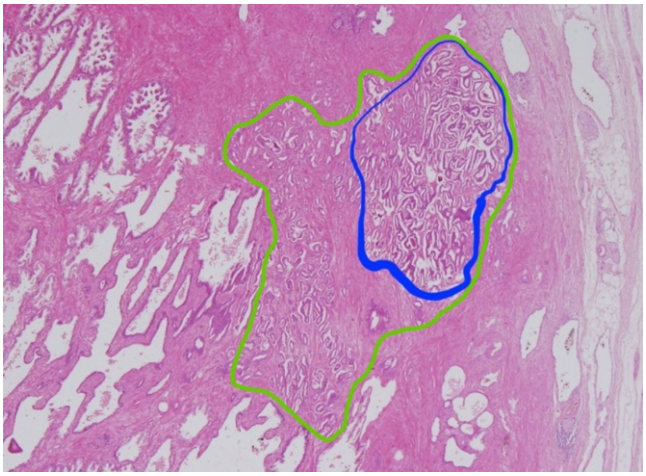

Figure 6. Gleason pattern 3 (outlined in green), 3x2mm area located at the right base level of a RP specimen, that was not visible on both MpMRI and PSMA PET/MR imaging (outlined in blue). (H&E; x40) (Archives of the Department of Medical Pathology at Istanbul University-Cerrahpaşa).

Seminal vesicle invasion and CI are significant predictors that can advance the disease to a locally advanced stage, and their prediction is crucial. In our study, the sensitivity of MpMRI for SVI was 40%, with a specificity of 95.24%. Positive predictive value was calculated as 66.67%, while NPV was 86.96%. When examining PSMA PET/MRI, the sensitivity for SVI was 60%, with a specificity of 95.24%. PPV was 75%, and NPV was 90.91% (Table 2).

In the detection of CI, MpMRI exhibited a sensitivity of 33.33% and a specificity of 78.57%. PPV was calculated as 57.14%, while NPV was 57.89%. PSMA PET/MRI, on the other hand, had a sensitivity of 25% and a specificity of 100% in identifying CI. PPV was 100%, while NPV was 60.87% (Table 2).

When the groups were divided into ISUP grades 1-2 and grade 3 or higher, MpMRI exhibited a sensitivity of 76.1% and a specificity of 92.1% for tumoral region detection in the low-grade group. In the high-grade group, the sensitivity was 73.7% and the specificity was 100%. In the low-grade group, the PPV and NPV were 92.1% and 76.1%, respectively, while in the high-grade group, they were 100% and 50%, respectively (Table 2).

When tumoral region detection is examined for the low-grade group, PSMA PET/MR exhibited a sensitivity of 63% and a specificity of 89.5%, while in the high-grade group, the sensitivity was 77.2% and the specificity was 93.3%. The PPV and NPV were calculated as follows: in the low-grade group, PPV was 87.9% and NPV was 66.7%, while in the high-grade group, PPV was 97.8% and NPV was 51.9% (Table 2).

In patients with a Gleason pattern 4 ratio of less than 10% in RP specimens, MpMRI exhibited a sensitivity of 79.5% and a specificity of 89.3% for tumoral region detection. In cases where the Gleason pattern 4 ratio was 10% or higher, the sensitivity was 71.2% and the specificity was 100%. In patients with a Gleason pattern 4 ratio of less than 10%, PPV and NPV were calculated as 92.1% and 73.5%, respectively. In cases where the Gleason pattern 4 ratio was 10% or higher, the PPV was 100% and the NPV was 59.5% (Table 2).

In cases where the Gleason pattern 4 ratio was less than 10%, PSMA PET/MRI exhibited a sensitivity of 65.9% and a specificity of 92.9%. When the Gleason pattern 4 ratio was 10% or higher, the sensitivity was 74.6% and the specificity was 88%. PPV and NPV for cases with a Gleason pattern 4 ratio of less than 10% were 93.5% and 63.4%, respectively, while in cases with a Gleason pattern 4 ratio of 10% or higher, they were 93.6% and 59.5%, respectively (Table 3).

Discussion

Prostate cancer has evolved into a disease with a low mortality rate and an increased rate of early diagnosis, thanks to improved access to healthcare services and effective screening methods. Considering the recent increase in the num-

Table 3. *The values of MpMRI and ^{68}Ga PSMA PET/MRI in local staging and tumoral region detection.*

	MpMRI				^{68}Ga-PSMA PET/MRI			
	Sensitivity	**Specificity**	**PPV**	**NPV**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Seminal vesicle invasion	40	95.24	66.67	86.96	60	95.24	75	90.91
Capsular invasion	33.33	78.57	57.14	57.89	25	100	100	60.87
Detection of tumoral regions								
Low grade (ISUP 1/2)	76.1	92.1	92.1	76.1	63	89.5	87.9	66.7
High grade (ISUP 3/4/5)	73.7	100	100	50	77.2	93.3	97.8	51.9
Gleason pattern 4 <10%	79.5	89.3	92.1	73.5	65.9	92.9	93.5	63.4
Gleason pattern 4 >10%	71.2	100	100	59.5	74.6	88	93.6	59.5

Note: Data were expressed as percentages. Abbreviations: PPV, positive predictive value; NPV, negative predictive value, MpMRI; multiparametric prostate magnetic resonance imaging, ^{68}Ga-PSMA PET/MRI; ^{68}Ga-prostate-specific membrane antigen emission tomography/magnetic resonance imaging.

ber of clinically insignificant prostate cancer diagnoses, it is thought that there is a situation of overdiagnosis, and even a "pseudoepidemic" is created since the increase in disease incidence is not correlated with mortality [6]. As a result, with the developments in the field of novel imaging techniques and the awareness of the comorbidities of radical treatment options, active surveillance and focal treatments have become increasingly effective and widely used, especially in the treatment of low- and intermediate-risk prostate cancer, which is now diagnosed more frequently.

Clinicians have widely used both mpMRI and PSMA PET, which are sophisticated and effective imaging techniques. These two methods are reliably used in active surveillance, preoperative staging, and postoperative oncological monitoring [7]. For this reason, the superiority of these two techniques over each other in capturing which parameter in which situation is a matter of current debate from various perspectives. In a study by Eiber et al. published in 2016 involving 53 patients, they found that the sensitivity of MpMRI was 43% with a specificity of 98%, while the sensitivity of PS MA PET/MRI was 76% with a specificity of 97% [8]. Furthermore, their research indicated that the sensitivity of MpMRI and PSMA PET/MRI was higher in high-risk patients. In our study, however, we did not observe a significant increase in sensitivity as ISUP grade increased or when the Gleason pattern 4 ratio was 10% or higher. In a meta-analysis by Li et al. in 2019, which evaluated 9 studies involving 353 patients, the sensitivity of MpMRI was found to be 60.3% with a specificity of 88.7%, while the sensitivity of PSMA PET/MRI was 78.3% with a specificity of 89.9% [9]. In a study conducted by Hicks et al. in 2018, which included 33 patients, the sensitivity of MpMRI was reported as 50% with a specificity of 90%, while the sensitivity of PSMA PET/MRI was 74% with a specificity of 88% [10]. Drost et al., in a comprehensive meta-analysis published in 2019, analyzed 43 studies and found that MpMRI achieved higher sensitivity and specificity for ISUP grade 2 and above [11]. Our study also supports this observation, as 24 out of the 26 regions not visible on MpMRI had ISUP grade 1 pathology. Also, in a study by Muehlematter et al. published in 2019, the sensitivity of MpMRI for EPE was reported as 46% with a specificity of 75% (12). In our study, we observed a sensitivity of 33.33% and a specificity of 78. 57% for MpMRI in predicting EPE. The sensitivity of PSMA PET/MRI for EPE was reported as 69% with a specificity of 67% in their study, while in our study, these figures were 25% and 100%, respectively. The difference between the results is believed to be due to the low number of patients in both groups in both studies. Muehlematter et al. (2019) had 8 patients with T3a and 5 patients with T3b, while in our study, there were 12 patients with T3a and 5 patients with T3b.

Multi-parametric MRI is a highly valuable tool in the evaluation of suspected PCa cases due to its high sensitivity and specificity for predicting cancer-suspicious areas, particularly in fusion biopsies. However, it has the disadvantage of potentially missing low-grade and small tumor areas. Additionally, patients who are not suitable for MRI (e.g., due to MRI-incompatible prostheses or claustrophobia) may not be able to undergo this examination. Despite the small number of patients in our study, the high soft tissue resolution of MRI showed promising results and indicates that future large-volume studies may yield more significant findings, particularly in local staging, assessing extraprostatic extension, seminal vesicle invasion, and periprostatic lymph node involvement.

Prostate-specific membrane antigen PET/MRI can be used in medium- and high-risk PCa cases. In selected cases, it can also be considered for low-risk PCa. With both the high soft tissue resolution of MRI and the metabolic activity detection capability of PSMA PET, we believe that this imaging method could be more effectively used in the future for fusion biopsies or focal treatments. Positron emission tomography/MRI fusion biopsy studies have also gained attention in recent times [13]. In our study, although PSMA PET/MR showed relatively lower sensitivity and specificity compared to MpMRI, the limited number of patients may have influenced the results. Larger population studies are certainly needed. The most significant disadvantages of PSMA PET/MRI are its high cost and long examination time. Furthermore, this method may have some limitations in detecting low-grade and small PCa foci.

In the last couple of decades, clinicians have been prompted to explore various avenues to address potential morbidities arising from definitive treatment options, such as erectile dysfunction and urinary incontinence. Current guidelines emphasize focal treatment options and active surveillance for low-risk patients, while definitive treatment options are recommended for intermediate and high-risk groups [7]. For this reason, patient stratification, choosing the right course of treatment for the right patient, and using reliable diagnostic techniques are now essential in this field.

In recent times, there has been a growing interest in studies where patients with localized PCa, identified through MpMRI and PSMA/PET, undergo RP without the need for a biopsy [16]. It's possible that in the future, with the increasing use of methods like MpMRI and PSMA/PET, we may enter an era where patients are actively monitored without the need for a biopsy or where they are directed towards either focal or radical treatment options based on imaging findings alone.

Although we anticipate that this study will make an significant contribution to the literature by providing a lesion-based analysis with interdisciplinary standardization, our study has some significant drawbacks. The retrospective nature is the major limitation of the study. Even though the number of lesions assessed was adequate, the power of the study might have been increased by recruiting more participants and increasing the number of lesions assessed.

In conclusion, MpMRI and PSMA PET/MRI are reliable methods for the local staging of PCa and the prediction of tumor localization. No statistically significant advantage of either method was discerned in the course of our study.

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