

Extraprostatic extension in multiparametric MRI; Is presurgical detection possible?

ABSTRACT

Introduction: Extraprostatic extension (EPE) is one of the important factors affecting the prognosis of prostate cancer (PCa). Therefore, preoperative evaluation of the presence of EPE is essential in multiparametric magnetic resonance imaging (mpMRI) examination. However, for the evaluation of mpMRI, objective criteria are needed to detect EPE, especially microscopic EPE.

Aim: To evaluate the efficacy of 1.5T MRI using lesion length (LL) and tumor-capsule contact length (TCL) in detecting EPE in PCa.

Methods: A total of 110 patients who underwent radical prostatectomy due to PCa were enrolled. Preoperative MR images were evaluated retrospectively by two independent observers who did not know the histopathological results. The observers evaluated LL and TCL. The radiological findings, including lesion location, were verified using histopathological mapping.

Results: Multiparametric MRI examination of the prostate demonstrated low sensitivity (Observer 1; 40.4% and Observer 2; 40.4%) but high specificity (Observer 1; 96.6% and Observer 2; 84.5%), with significant differences for detecting EPE (Observer 1, $P < 0.0001$; Observer 2, $P = 0.003$). The increased PI-RADS score correlated positively with the increased EPE rate ($P < 0.0001$ for both observers). The mean LL and TCL values were statistically significantly higher in patients with EPE than in patients without EPE. The TCL was a significant parameter for EPE, with high sensitivity and low for both observers. For both observers the cutoff value of LL for EPE was 14.5 mm, and the cutoff value of TCL for EPE was 9.5 mm. Histopathological LL value (28 ± 12.3 mm) was higher than radiological LLs (Observer 1; 22.14 ± 10.15 mm and Observer 2; 19.06 ± 8.61).

Conclusion: The results revealed that 1.5T MRI demonstrated low sensitivity and high specificity in detecting EPE. The LL and TCL may be indirectly beneficial in detecting EPE. Considering the radiological underestimation of LL may be helpful before PCa surgery.

KEY WORDS: Capsular invasion, extraprostatic extension, multiparametric prostate MRI, prostate cancer, radical prostatectomy, tumor-capsule contact length

INTRODUCTION

Prostate cancer (PCa) is the most common cancer in the male population.^[1] Multiparametric magnetic resonance imaging (mpMRI), one of the current imaging modalities for prostate glands, has been successful in PCa diagnosis. Therefore, this non-invasive method is now frequently used in the diagnosis and preoperative staging in many healthcare centers. However, the increased use of prostate mpMRI has led to the need for objective criteria. For this purpose, the use of “the “Prostate Imaging Reporting and Data System (PI-RADS),” prepared by the American College of Radiology (ACR) and the European Society of Urogenital Radiology (ESUR), has been suggested in reports. Currently, PI-RADS v2.1 is used for this purpose.

The most critical factors determining prognosis in patients with PCa are the Gleason score and stage.^[2] One of the factors affecting this stage is the presence of extraprostatic extension (EPE). Furthermore, the postoperative prognosis is worse in patients with EPE due to the increased risk of higher positive surgical margin rates and early biochemical recurrence.^[3] For this reason, preoperative evaluation of the existence of EPE in the MRI examination is essential. Recently, the detection of EPE using mpMRI has been based on macroscopic EPE findings. Therefore, objective

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criteria are needed to detect EPE, especially microscopic EPE, while evaluating mpMRI.^[4] Our study aims to evaluate the interobserver agreement in terms of the presence of EPE in the prostate mpMRI obtained using a 1.5T MRI device. Moreover, it aims to assess whether there is a relationship between EPE and capsule-tumor contact length (TCL) and lesion length (LL) in light of histopathological data.

MATERIALS AND METHODS

In this retrospectively designed study, 201 cases that underwent radical prostatectomy performed at our institution between May 2014 and August 2017 were scanned. Of these, 110 patients who met the inclusion criteria were enrolled. The study was conducted after obtaining approval from the ethics committee. The inclusion and exclusion criteria of the study are provided in the following segment.

Inclusion criteria for the included cases utilized in this study were as follows: Underwent radical prostatectomy, prostate malignancy detected by postsurgical histopathologic examination, PI-RADS category 3, 4, or 5 lesions revealed by preoperative mpMRI, and radiologically visible contact between the tumor and capsule.

The exclusion criteria for cases were as follows: No preoperative MRI examination performed at our institution (20 patients), no findings except PI-RADS 1 or 2 category on preoperative mpMRI (17 patients), hemorrhagic foci on MRI performed in the early post-biopsy period (18 patients), PI-RADS 4–5 lesions that had no visible contact with capsule (20 patients) and lesions that could not be verified by pathological mapping (16 patients).

Images were obtained using a 1.5T MRI scanner (General Electric Optima 450W, 1.5T, GE Medical Healthcare, USA). A 16-channel body coil was used. While performing perfusion imaging, a gadobutrol-based contrast agent (Gadovist®, BAYER) was administered intravenously at 0.1 mmol/kg [Table 1]. The demographic characteristics of the cases, their PI-RADS scores, and the TCL of the lesions were recorded. Moreover, the LL and EPE presence was recorded separately, both radiologically and pathologically. Two independent observers evaluated the MR images with 4 and 3 years of experience in prostate mpMRI. The assessments were made with the observers blinded to the pathology results.

First, observers assessed the MR images of 110 patients independently and categorized them according to PI-RADS v2.1. In cases where there was suspicion of multifocal PCA, only the index lesion, which is considered the largest among the lesions having the highest PI-RADS score, was evaluated. An assessment was made regarding the radiological presence of EPE. Afterward, the LL and the TCL were measured. LL was measured on the plane where the lesion had the longest axis. However, TCL was digitally measured on the T2W images for

Table 1: MRI Acquisition Parameters

Sequences	T1 DCE Perfusion (3D/FSPGR)	T2 Fast Recovery Fast Spin Echo (FRFSE Propeller)	DWI (SE/ EPI)
Plane	Axial	Axial, Sagittal and Coronal	Axial
Fat Suppression	-	-	-
Time to echo (ms)	1.9	121.9	72.3
Flip angle (°)	12	160	90
Section	4	3	3
Thickness (mm)			
Slice Gap	0	0	0
FOV (mm x mm)	240×192	200×200	240×240
Matrix	160×160	320×320	96×96
NEX	0.78	2.5	2
b value (sec/mm ²)	-	-	50, 800, 1000, 1500

which contact with the capsule was the most visible [Figure 1]. Moreover, the lesions that were not in contact with the capsule were recorded in a separate group. The distance between the lesion and capsule was measured in this group of lesions, and the histopathological presence or absence of EPE was recorded.

Radiological EPE was assessed by considering the criteria previously described in the literature. Criteria that suggest radiologic investigation for EPE are: capsular irregularity, bulging in the capsule, capsular retraction, rectoprostatic angle obliteration, extracapsular tumor, extracapsular tumor enhancement, asymmetry or direct involvement in neurovascular bundles, asymmetric enhancement of the neurovascular bundles and pathological signal change in seminal vesicles.

The relation between the lesion and the capsule was assessed using T1 weighted (T1W) dynamic, diffusion-weighted (DW), apparent diffusion coefficient (ADC), and T2W images. After radiological evaluations, histopathological data were evaluated in LL, Gleason score, and EPE presence. The data were also classified according to the International Society of Urological Pathology (ISUP) grade groups, along with the Gleason score. In addition to these evaluations, mapping was performed for all cases to confirm the lesion detected radiologically. This was done to assess the interobserver agreement in terms of radiological findings and to compare them with histopathological data.

Statistical analysis

Categorical data were expressed as values and percentages. The numerical data were described as mean, standard deviation, minimum, and maximum values. The Chi-square test was used to compare the categorical data. The independent-sample t-test was used to assess the difference between the mean values of the parametric data distributed between groups. Furthermore, the Mann-Whitney U test was used for nonparametric data. In cases with significant differences between the groups, the optimum cutoff point was calculated by performing ROC analysis, and the area under the curve,

sensitivity, and specificity values were calculated. Spearman correlation analysis was conducted to evaluate correlations between nonparametric numerical data. In the assessment of the interobserver agreement, weighted Kappa for PI-RADS, Cohen's kappa for binomial categorical variables, and intraclass correlation coefficient for numerical data were calculated. SPSS 21.0 (IBM Corp., New York, USA) was used in statistical analyses. Cases where $P < 0.05$ were considered statistically significant.

RESULTS

All included cases had histopathologically proven PCa. The mean age was 65.25 ± 6.45 (minimum = 48, maximum = 79) years.

According to histopathological results, there were 17 (15.5%) ISUP grade 1, 40 (36.3%) ISUP grade 2, 18 (16.4%) ISUP grade 3, 19 (17.3%) ISUP grade 4, and 16 (14.5%) ISUP grade 5 tumors. The Gleason score-based numbers were as follows: 17 (15.5%) Gleason 6, 58 (52.7%) Gleason 7, 19 (17.3%) Gleason 8, 14 (12.7%) Gleason 9, and 2 (1.8%) Gleason 10 tumors. The stage was T2 in 58 cases (52.7%) and T3 in 52 cases (47.3%). The histopathological evaluation revealed 52 cases (47.3%) with EPE and 58 cases (52.7%) without EPE [Table 2].

The prostate mpMRI findings for the cases were categorized as PI-RADS 3, 4, and 5. For Observer 1, 20% of the cases had PI-RADS 3 lesions, 35.5% had PI-RADS 4, and 44.5% had PI-RADS 5 lesions. Similarly, the values were 21%, 35.5%, and 45.5% respectively for Observer 2. Furthermore, interobserver agreement was good for PI-RADS, LL, and the TCL, whereas it was moderate for the presence of EPE [Table 3].

For Observer 1, sensitivity was 40.4%, specificity was 96.6%, positive predictive value was 91.3%, and negative predictive value was 64.3% for EPE detection. For Observer 2, sensitivity, specificity, positive predictive value, and negative predictive

value were 40.4%, 84.5%, 70%, and 61.3%, respectively. Prostate mpMRI demonstrated low sensitivity but high specificity in EPE detection, with a significant value ($p < 0.0001$ for Observer 1 and $P = 0.003$ for Observer 2).

EPE was present in 9% of PI-RADS 3, in 36% of PI-RADS 4, and 73% of PI-RADS 5 cases for Observer 1, whereas these rates were 10%, 36%, and 72%, respectively, for Observer 2. In addition, the incidence of EPE increased as the PI-RADS score increased for both observers ($p < 0.0001$ for both observers).

There was a significant positive correlation between LLs measured on MRI examination for both observers. Rho correlation coefficient values were 0.72 for Observer 1 and 0.57 for Observer 2 ($p < 0.0001$).

The TCL demonstrated a significant difference in cases with and without EPE [Table 4]. The TCL is a considerable parameter for EPE, with relatively high sensitivity and low specificity for both observers. Furthermore, the LL had significant results, with moderate sensitivity and specificity for measurements on the radiological assessment of both observers and measures made from the pathology specimen [Table 5].

A cutoff value of 22 mm was observed for the LL concerning EPE in the histopathological examination, with a sensitivity of 63% and a specificity of 75%. Moreover, the mean value determined for Observer 1 for TCL was 18 mm, while it was 14.5 mm for Observer 2. Therefore, the cutoff value, which had the highest sensitivity according to the Youden index, was 9.5 mm. The mean values of LL were 22 and 19 mm, respectively. Therefore, the cutoff value for high sensitivity was determined as 14.5 mm for both observers.

DISCUSSION

PCa accounts for 25% of malignancies newly diagnosed every year in Europe.^[5] The multiparametric approach is essential for detecting and characterizing PCa. Furthermore, PCa prognosis is closely related to the cancer stage. In this context, MRI

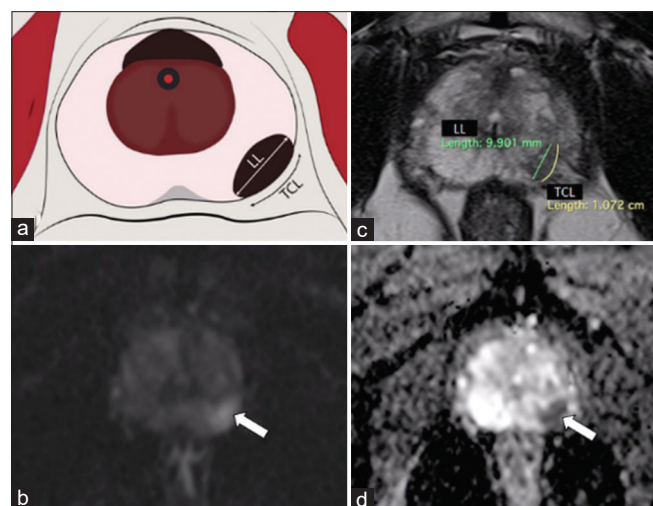


Figure 1: The measurement of lesion length and tumor contact length on illustration (a) and T2W axial image of a PI-RADS 5 lesion (b). The lesion was demonstrated by the arrow on DWI (c) and ADC mapping (d)

Table 2: The evaluation of MRI findings for both observers according to the presence of EPE

Histopathological EPE	Observer 1		Observer 2	
	EPE (+)	EPE (-)	EPE (+)	EPE (-)
(+)	21	31	21	31
(-)	2	56	9	49

Table 3: Data obtained in the assessment of interobserver agreement

	Agreement value	Statistical Test
PI-RADS	0.8	Weighted Kappa
Presence of EPE	0.48	Cohen's Kappa
LL	0.77	ICC
TCL	0.72	ICC

plays a critical role in staging, vital in PCa management. The presence of EPE impacts TNM staging by increasing the T-stage from 2 to 3 and significantly increases the risk of biochemical recurrence in postoperative follow-up.^[6]

In the literature, several studies evaluate the effectiveness of MRI in detecting EPE. According to the results obtained in these studies, MRI sensitivity in detecting EPE fluctuated in a wide range (40%–84%), but its specificity was as high as 97%. Furthermore, a few recent publications on TCL^[4,7-10] have emerged. In these studies, no consensus was established on the threshold value for TCL, which varied in a wide range of 6–20 mm. However, PI-RADS v2, published by ACR in 2015 and used to prepare prostate MRI reports in many healthcare centers, recommends accepting a threshold value of 10 mm for TCL when evaluating EPE.^[7] Even though ACR revised it as PI-RADS v2.1, there are no new recommendations for TCL^[11] [Table 6].

Rosenkrantz *et al.*^[4] assessed preoperative 3T MRI images of 90 patients who underwent radical prostatectomy. The evaluation was made on T2W and ADC images. The threshold values for TCL were determined as 6 mm for T2W and 7 mm for ADC [Table 6].

Woo *et al.*^[9] performed a study regarding EPE on 3T MRI images with one observer in 2016. T2W, ADC, and DCE images were evaluated, and the threshold values of TCL were 14, 13, and 12 mm, respectively. No statistically significant difference was found between the sequences. The statistical workup, in which all sequences were evaluated together, yielded a threshold value of 14 mm. Furthermore, the clinical stage, PSA, and

Gleason score were significantly correlated with the presence of EPE [Table 6].

In a study conducted by Costa *et al.* in 2018,^[12] the efficiency of 3T MRI using an endorectal coil in detecting EPE was examined. It was observed that a TCL higher than 10 mm increased the probability of EPE by 2.4 times^[12] [Table 6]. Rooij *et al.*^[13] evaluated a total of 75 studies (9796 patients) in a meta-analysis investigating the accuracy of MRI in local staging of PCa. Pooled data for overall stage T3 detection (38 studies, 4001 patients) showed sensitivity and specificity of 0.61 (95% CI 0.54–0.67) and 0.88 (95% CI 0.85–0.91), respectively. Functional imaging in addition to T2-weighted imaging and use of higher field strengths (3 T) improved sensitivity for extracapsular extension (ECE) and seminal vesicle invasion. ECE sensitivity was not improved by endorectal coil use^[13] [Table 6].

Bakır *et al.*^[10] performed one of the most recent studies on this topic in 2020. The T MRIs of 86 patients were evaluated, and the relationship between TCL and EPE using the MRI-based TCL measurements and the actual TCL measurements from pathology were assessed. A cutoff value of 15–16 mm was obtained according to the MR-based TCL measurements. However, there was no significant relationship between pathology-based TCL measurements and EPE. Therefore, it was concluded that MRI-based TCL measurements might be beneficial in predicting EPE.

A limited number of studies use 1.5T MR for evaluation.^[8,14,15] The threshold values for TCL were mentioned as 14 and 20 mm in these publications [Table 6].

In our study, it was observed that the increased PI-RADS score was significantly correlated with the presence of EPE, as well as increased Gleason score and ISUP grade. On the other hand, LL and TCL were significantly associated with the presence of EPE. Moreover, a cutoff value was observed in the histopathological and radiological examinations for LL. Likewise, a cutoff value for the radiological TCL was observed concerning EPE. Considering these data, it is thought that the LL and the TCL may be used as auxiliary in detecting EPE while evaluating MRI images.

Unlike in the other studies, we evaluated both radiologic and histopathologic LL and TCL to detect EPE. Furthermore, we used the most recent version of the PI-RADS (v2.1) while

Table 4: The evaluation of numerical data according to the presence of EPE*

Numerical Data	EPE Mean±standart deviation		P
	(+)	(-)	
Observer 1			
Lesion Length (mm)	22.14±10.15	15.47±7.36	<0.0001
Tumor Contact Length (mm)	18.35±10.72	11.7±8.07	<0.0001
Observer 2			
Lesion Length (mm)	19.06±8.61	15.05±7.56	0.02
Tumor Contact Length (mm)	14.56±7.59	10.91±7.51	0.001
Lesion Length measured pathologically	28±12.3	18.68±8.85	<0.0001

*Since numerical data do not show normal distribution, the analysis was carried out using Mann-Whitney U Test

Table 5: Data from Receiver Operating Characteristic (ROC) analysis

	Area under the curve (%)	P	Cut off value (mm)	Sensitivity	Specificity	Youden index
Observer 1						
Lesion Length	72.2%	<0.0001	14.5	73.1%	60.3%	0.334
Tumor Contact Length	71.7%	<0.0001	9.5	84.3%	50%	0.343
Observer 2						
Lesion Length	67.3%	0.002	14.5	69.2%	70.7%	0.399
Tumor Contact Length	68.7%	0.001	9.5	80.8%	46.8%	0.276
Lesion Length measured pathologically	71.8%	<0.0001	21.5	63.5%	75.9%	0.393

Table 6: Recent publications evaluating EPE and TCL on MRI

Publication	Number of Cases	Scanner	Number of Observers Evaluating MRI	Endorectal Coil Usage	MR sensitivity for EPE (%)	MR specificity for EPE (%)	Evaluation of LL	Evaluation of TCL	Threshold for TCL (mm)
Rosenkrantz <i>et al.</i> (2016) ^[4]	90	3T	2	-	-	-	-	+	6 (focal EPE) 10 (non-focal EPE)
Baco <i>et al.</i> (2015) ^[8]	111	1.5T	1	-	40	83	-	+	20
Woo <i>et al.</i> (2017) ^[9]	185	3T	1	-	-	-	-	+	14
Bakir <i>et al.</i> (2020) ^[10]	86	3T	2	-	-	-	-	+	15-16
Costa <i>et al.</i> (2018) ^[12]	80	3T	2	+	-	-	+	+	10
Rooij <i>et al.</i> (2015) ^[13]	Meta-analysis	1.5T and 3T	-	+/-	61	88	-	-	-
Van Holsbeeck <i>et al.</i> (2016) ^[14]	123	1.5T	-	-	57	91	-	+	20
Rud <i>et al.</i> (2018) ^[15]	183	1.5T	1	-	-	-	-	+	14

evaluating mpMRI. On the other hand, most of these studies were performed using 3T MRI scanners. Endorectal coils were also utilized in some cases. Our study evaluated the effectiveness of the mpMRI obtained with a 1.5T MR device without an endorectal coil, which is a commonly used method in many centers for EPE detection. Furthermore, pathological capsule invasion was not observed in 20 lesions without capsule contact, which was mentioned in the exclusion criteria. Therefore, studies evaluating the distance between the capsule's distance and pathological EPE in such lesions may yield more reliable results.

In addition, it is seen that histopathological LL is higher than radiological LL. Our literature knowledge suggests that this may be due to the difficulty of detecting low-grade tumor areas on MRI.^[16,17] This possible radiological underestimation should be considered, especially before focal treatments.

There were some limitations to the study design. The number of patients was limited since only patients who underwent radical prostatectomy were enrolled. Although we could not compare 1.5T and 3T methods in detecting EPE, no studies in the literature provide such comparisons. The evaluation of TCL was made only radiologically, and this fact might be accepted as another limiting factor. Histopathological assessment of TCL may shed more light on this topic.

CONCLUSIONS

The prostate mpMRI obtained using a 1.5T MRI scanner has low sensitivity and high specificity in detecting EPE. The low sensitivity is likely due to the difficulty of detecting microscopic EPE. It would be helpful to consider the indirect role of LL over 1.5 cm and TCL greater than 1 cm, especially in detecting microscopic EPE. Future studies evaluating LL and TCL with more cases may provide more reliable findings in EPE detection.

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Conflicts of interest

There are no conflicts of interest.

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