Can Extraprostatic Extension Be Predicted by Tumor-Capsule Contact Length in Prostate Cancer? Relationship With International Society of Urological Pathology Grade Groups

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OBJECTIVE. The objective of our study was to evaluate the relationship between the tumor-capsule contact length, defined as tumor contact length (TCL), and extraprostatic extension (EPE) using the MRI-based TCL measurements and the real TCL measurements from pathology and to determine whether the International Society of Urological Pathology (ISUP) grade group of the tumors influenced this relationship.

MATERIALS AND METHODS. In this retrospective study, we reviewed prostate multiparametric MRI (mpMRI) studies performed between 2012 and 2018 of 1576 patients and found that 134 patients also underwent radical prostatectomy (RP) after mpMRI. Finally, 86 patients with index lesions in contact with the prostate capsule in RP specimens were enrolled in the study. ROC analysis was used to evaluate the cutoff values of TCLs measured at pathology and TCLs measured on MRI in terms of EPE according to ISUP grade groups.

RESULTS. There was no statistically significant cutoff value for pathology-based TCL measurements in individual ISUP grade groups and subgroups. Although not statistically significant, pathology-based TCL cutoff values decreased (from 21.0 to 11.0 mm) as ISUP grade group increased in terms of EPE positivity. When the relationship between MRI-based TCL measurements and EPE was considered, statistically significant cutoff values (range, 14.5–16.6 mm) could be determined in many groups and subgroups with low ISUP grades (sensitivity, 66.7–100%; specificity, 52.8–93.0%; $p = 0.006–0.042$). However, no statistically significant cutoff value was found for high ISUP grades.

CONCLUSION. ISUP grade groups may have an effect on the TCL-EPE relationship. When the MRI-based TCL and EPE relationship is evaluated independent of ISUP grade group, a cutoff value around 15–16 mm may be usable to predict EPE.

In the United States prostate cancer is the second leading cause of cancer-related deaths in men [1]. Treatment decisions rely on the accurate staging of prostate cancer. The presence of extraprostatic extension (EPE) is important because it is associated with both higher rates of positive surgical margins and early biochemical recurrence [2]. Patients with EPE have higher tumor recurrence after radical prostatectomy (RP) and worse prognosis than patients with organ-confined disease [2]. Therefore, the ability to predict EPE is important.

Multiparametric MRI (mpMRI) of the prostate is the best imaging tool for local staging [2–4]. However, despite its high specificity, MRI has poor and variable sensitivity for local staging. A recent meta-analysis including 75 studies and a cohort of 9796 patients showed an overall sensitivity of 57% and a specificity of 91% to establish EPE [5]. These results showed the need for improvement, and many studies with the purpose of predicting the presence of EPE with mpMRI have been conducted [2, 6–14].

Currently, the diagnosis of EPE with mpMRI is dependent on subjective visualization of macroscopic EPE and its mechanical effects by the reader, which are relatively late findings [6]. Objective mpMRI parameters with low interobserver variability are needed for predicting disease outcomes. The MRI-determined length of contact between the tumor and prostatic capsule, defined as tumor contact length (TCL), is an emerging mpMRI-based parameter and is considered tto be a predictor of EPE [7, 8].

The TCL thresholds suggested by studies in the literature show a large variability. Three recent studies evaluating TCL as a sign of extracapsular extension suggested

quite different thresholds of 20 mm [6], 6–10 mm [7], and 12.5 mm [8]. This variability in TCL, which is the most important objective parameter for the evaluation of EPE, creates confusion in daily clinical practice.

The broad range of reported TCL thresholds can be explained by differences in study cohorts, patient selection criteria, technical and methodologic variations, or interpretative technique. Also, discrepancies between MRI-based TCL and real TCL at pathology could be a reason for that variation. Studies have reported that dimensions for tumoral lesions on mpMRI are generally smaller than their actual size at pathology [15–19]. This discrepancy could affect the result of the studies that focused on the relationship between MRI-based TCL and EPE. The omission of the aggressiveness of a tumor could be another factor, because a tumor with a high Gleason score and a lower TCL may have a higher probability of EPE than a tumor with a low Gleason score and a higher TCL.

The aim of our study was to evaluate the relationship between TCL and EPE using the real TCLs measured at pathology and to determine whether International Society of Urological Pathology (ISUP) grade groups of tumors influenced this relationship. We also aimed to evaluate the relationship between MRI-based TCL and EPE considering ISUP grade groups reported on biopsies performed before RP and the role of ISUP grade groups in influencing this relationship.

Materials and Methods

Patients

Institutional review board approval and informed consent were obtained for this retrospective study. We searched electronic databases of our institutions (Koc University Hospital, VKF American Hospital, and Instanbul Medical Faculty Hospital) for patients who underwent mpMRI examinations of the prostate between 2012 and 2018 and found that 1576 patients had undergone mpMRI of the prostate during that period. Of those 1576 patients, 134 patients (8.5%) underwent RP after mpMRI of the prostate. The clinical, pathologic, and radiologic records of those 134 patients were reviewed. Finally, 86 patients (mean age, 62.5 ± 6.2 [SD] years) who met the following inclusion criteria were enrolled in this retrospective study: complete pathologic records for both preoperative prostate biopsy samples and postoperative whole-mount RP specimens, index lesions had contact with the prostate capsule in RP specimens, 8 weeks or more between prostate biopsy and mpMRI if biopsy was performed before prostate mpMRI, and 4 months or less between prostate mpMRI and RP. Patients with MRI studies with severe MRI artifacts and patients who underwent preoperative hormonal or radiation therapy were excluded from this study. The mean level of prostate-specific antigen in the 86 patients was 7.52 ng/mL (range, 2.10–40.00 ng/mL).

MRI Examinations

Prostate MRI examinations were conducted on 3-T MRI scanners (Magnetom Skyra, Siemens Healthcare), and a 16-channel phased-array surface coil was used. Prostate mpMRI studies were performed using the following imaging sequences: triplanar T2-weighted imaging (TR/TE, 3566–3631/100; matrix size, 512 × 352; FOV, 200 mm; slice thickness, 3 mm), T1-weighted imaging, dynamic contrast-enhanced MRI (DCE-MRI), and DWI (b values = 0, 50, 100, 200, 400, 600, and 800 s/mm^2; number of signals acquired, 9). Apparent diffusion coefficient (ADC) mapping and computed high-b-value (b value = 1500 s/mm^2) DW images were derived from acquired DWI. The mean time interval between MRI and RP was 70.42 days (range, 11–117 days).

Standard of Reference and Pathologic Measurements

All whole-mount RP specimens were processed by an experienced genitourinary pathologist according to the standard procedures recommended by the ISUP. The specimens were serially sectioned into 3- to 4-mm slices by standard step-sectioning. Then, the genitourinary pathologist who was blind to MRI findings marked the index lesions on a 16-sector divided standardized prostate diagram. The following criteria were used to describe the index lesion: First, the tumor focus showing EPE was considered to be the index lesion; and, second, if none of the tumor foci showed EPE, the index lesion was considered to be the prostate tumor focus with the highest Gleason score or largest tumor volume. After reviewing all of the RP specimens, the index lesions that came in contact with the prostate capsule were determined, and only these prostate lesions were included in the study. The pathology-based TCL—defined as the length of tumor contact with the adjacent prostate capsule—was measured in accordance with the method previously described by Baco et al. [6]. The tumor volume, ISUP grading score, and EPE status (presence vs absence) of the index lesions were also noted.

Image Analysis and MRI-Determined Tumor Contact Length Measurements

All MR images of the patients enrolled in this study were transferred to prostate software (DynaCAD, version 3.3, Philips Healthcare) and were evaluated independently by two experienced radiologists with 6 and 3 years of experience in prostate cancer imaging, respectively. At the time of image evaluation, the radiologists knew that all patients had undergone RP because of prostate cancer. However, they were blinded to all other patient variables. The radiologists evaluated the images to localize a dominant tumor (index lesion); the index lesion was defined as a masslike lesion that showed low signal intensity on T2-weighted images and ADC maps and high signal intensity on DW images with or without early contrast enhancement on DCE-MRI. Then, the radiologists assessed the images to investigate whether or not there was contact between the dominant tumor and the prostate capsule. If there was, the TCL of the dominant lesion was determined. The TCL of the dominant lesion was defined as the maximum length of prostate lesion contact with the adjacent prostate capsule on axial images. A curved measurement tool was used, as previously reported by Baco et al. [6], to measure the actual contact length between the prostate tumor and adjacent prostate capsule. The TCLs were measured separately on axial T2-weighted imaging and DCE-MRI. The final MRI-based TCL measurements were obtained by dividing the sum of the measurements made by both radiologists who evaluated the images separately. Alterations of prostate shape and size due to preservation of the specimen were considered, and the dominant lesions were evaluated and were matched with histopathologic diagrams as the reference standard. A lesion was considered to be a matched lesion if it was in the same location on both mpMR images and RP specimens.

Prostate Biopsy Techniques

The prostate biopsies were performed with four different approaches: random systematic transrectal ultrasound (TRUS)-guided biopsy in 42 patients, in-bore MRI-guided biopsy in 28 patients, cognitive fusion biopsy in 13 patients, and MRI/TRUS fusion biopsy in three patients.

Assessment of Relationship Between Pathology-Based Tumor Contact Length and Extraprostatic Extension Based on Radical Prostatectomy–Based International Society of Urological Pathology Grade Group

The cutoff values of pathology-based TCLs in terms of EPE were evaluated for all RP-based ISUP grade groups individually. Additional subgroup analyses were also performed. These subgroups were formed by combining ISUP grade groups 1 + 2, ISUP grade groups 3 + 4 + 5, ISUP grade groups 1 + 2 + 3, and ISUP grade groups 4 + 5.

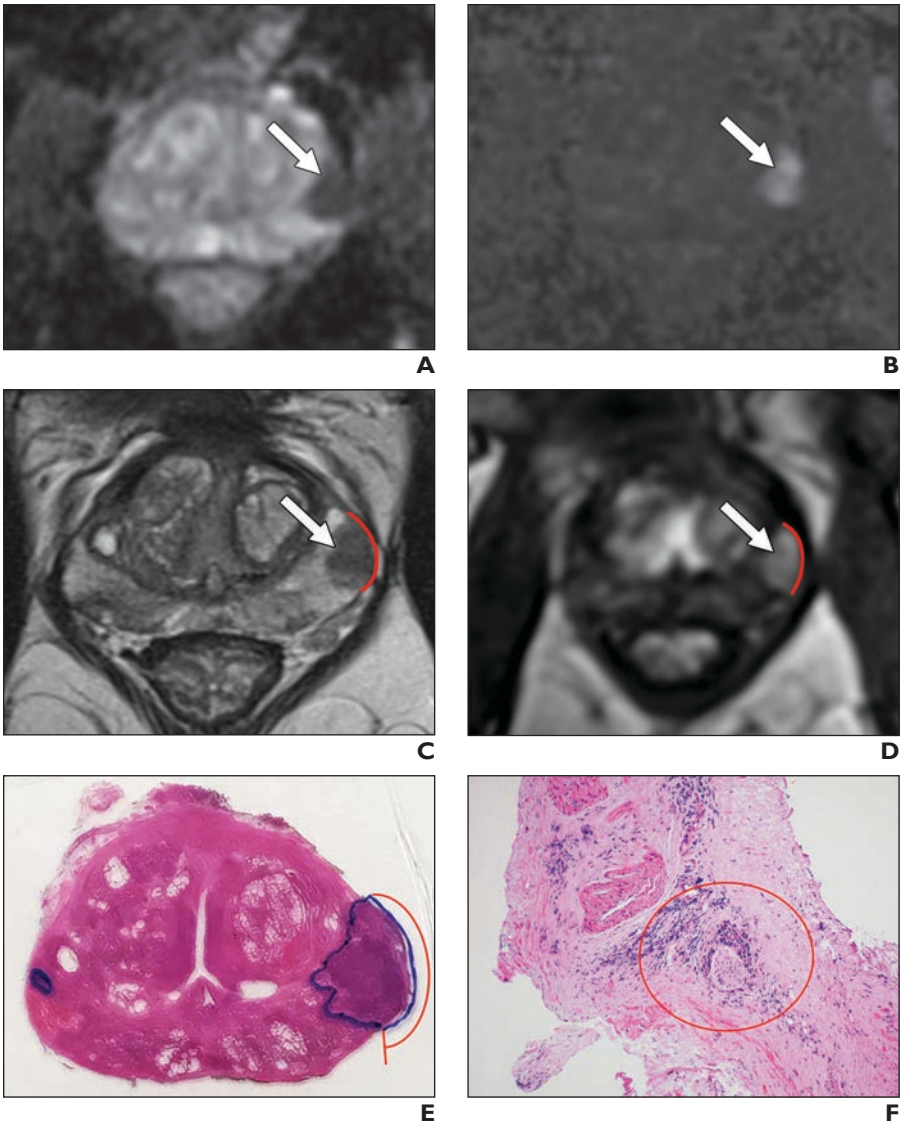

Fig. 1—MR images and photomicrographs of Gleason score 4 + 4 prostate cancer (index lesion) in left peripheral zone of prostate in 68-year-old man.
A–D, Apparent diffusion coefficient map (**A**), DW image (**B**), T2-weighted image (**C**), and T1-weighted dynamic contrast-enhanced (DCE) image (**D**) shows tumor (*arrow*). Length of tumor-capsule contact (*curved lines*, **C** and **D**) on T2-weighted image and T1-weighted DCE image is shown by digitalized curvilinear ruler tool.
E, Photomicrograph of whole-mount pathologic slice. Index lesion (*large area outlined in blue*) is in left peripheral zone, and another tumor focus (*small area outlined in blue*) is in right peripheral zone. Length of tumor-capsule contact (pathology-based tumor contact length) is shown by red curved line. Straight red line shows end of tumor-capsule contact length.
F, Photomicrograph (H and E, ×100) shows extraprostatic extension (*circle*).

Assessment of Relationship Between MRI-Based Tumor Contact Length and Extraprostatic Extension Based on Biopsy-Based International Society of Urological Pathology Grade Group

The cutoff values of MRI-based TCLs in terms of EPE were evaluated for all prostate biopsy–based ISUP grade groups individually. Analyses of additional subgroups, which are listed in the previous section, were also performed.

Assessment of Relationship Between MRI-Based Tumor Contact Length and Extraprostatic Extension Based on Radical Prostatectomy–Based International Society of Urological Pathology Grade Group

In this assessment, we assumed that we could reach the true ISUP scores in all patients and we evaluated our data according to that scenario. We used RP-based ISUP grade group results for the evaluation of the relationship between MRI-based TCL and EPE. The cutoff values of MRI-based TCLs in terms of EPE were evaluated for all RP-based ISUP grade groups individually. Analyses of additional subgroups, as mentioned earlier, were also performed.

Assessment of Positive and Negative Extraprostatic Extension Subgroups for Differences in Pathology-Based Tumor Contact Length

We compared both EPE-positive and EPE-negative subgroups in relation to ISUP grade groups 1 + 2 and ISUP grade groups 3 + 4 + 5 subgroups for differences in pathology-based TCLs. We also compared both EPE-positive and EPE-negative subgroups in relation to the ISUP grade groups 1 + 2 + 3 and ISUP grade groups 4 + 5 subgroups for the same purpose.

Assessment of the Influence of International Society of Urological Pathology Grade Group on Measurement Differences Between MRI-Based and Pathology-Based Tumor Contact Lengths

The measurement differences between MRI-based TCLs and pathology-based TCLs were evaluated for all RP-based ISUP grade groups individually. Analyses of additional subgroups, as mentioned earlier, were also performed.

Statistical Analysis

Statistical analysis was performed using SPSS software (version 21.0, IBM) for Microsoft Windows. The ROC analysis was used to evaluate the cutoff values of TCLs in terms of EPE in the groups and subgroups formed according to ISUP grade groups. The Shapiro-Wilk test was used to evaluate the normal distribution in groups and subgroups. The Kruskal-Wallis test was used to compare EPE-positive and EPE-negative subgroups. The Pearson correlation test was used to evaluate the correlation between the MRI-based TCL and pathology-based TCL measurements in the groups that had normal distribution, and the Spearman correlation test was used to evaluate the correlation between the MRI-based TCL and pathology-based TCL measurements in groups that did not have normal distribution.

Results

The mean and median tumor volumes based on RP specimens of the index lesions were 2.3 and 2.0 cm^3 (range, 0.4–15.9 cm^3). The mean and median pathology-based TCLs determined from RP specimens were 17 and 15 mm (SD, 9 mm; range, 1–48 mm), respectively. Contact with the prostate capsule was present for all lesions on MRI examination (Fig. 1). The ISUP grade groups of the index

TABLE 1: Comparison of Tumor Contact Length (TCL) by Radical Prostatectomy (RP)-Based International Society of Urological Pathologists (ISUP) Subgroup and Extraprostatic Extension (EPE) Status

RP-Based ISUP Grade Subgroups	No. of Patients	Pathologic TCL (mm)					Kruskal-Wallis	
		Mean	SD	Median	Percentile 25	Percentile 75	χ^2	*p*
1 + 2							4.178	0.243
EPE-negative	45	15.38	9.12	15.00	10.00	17.00		
EPE-positive	6	20.50	10.95	22.00	15.00	30.00		
3 + 4 + 5								
EPE-negative	17	16.29	6.63	15.00	11.00	20.00		
EPE-positive	18	18.50	9.23	17.00	13.00	24.00		
1 + 2 + 3							3.983	0.263
EPE-negative	55	15.73	8.78	15.00	10.00	20.00		
EPE-positive	15	19.93	9.59	20.00	13.00	24.00		
4 + 5								
EPE-negative	7	14.86	5.93	13.00	10.00	22.00		
EPE-positive	9	17.44	9.65	15.00	14.00	22.00		

lesions on RP specimens and on prostate biopsies are shown in Tables 1 and 2; 24 of 86 patients (27.9%) had evidence of EPE on RP specimens (Table 2). When the biopsy and RP results were compared for the agreement of ISUP grade groups, their agreement was poor ($\kappa = 0.454$, $p = 0.001$). Biopsy results did not change in 53 of 86 patients (61.6%) after RP pathologic evaluation. Upgrade of ISUP grade was detected in 25 patients (29.1%) and downgrade was detected in eight patients (9.3%) according to the RP results. The highest upgrade rate was in ISUP grade group 1 cases; ISUP grade in 15 of 18 patients (83.3%) was upgraded in this group.

Analysis of Relationship Between Pathology-Based Tumor Contact Length and Extraprostatic Extension Based on Radical Prostatectomy–Based International Society of Urological Pathology Grade Group

There were not enough patients in ISUP grade group 1 ($n = 3$ patients) and ISUP grade group 4 ($n = 5$ patients) to perform statistical analysis. Pathology-based TCLs of the three patients in ISUP grade group 1 were 6, 7, and 8 mm. In these three patients, EPE was negative. Pathology-based TCLs of the five patients in ISUP grade group 4 were 13, 15, 22, 22, and 24 mm. EPE was positive in two patients with pathology-based TCLs of 15 and 22 mm and negative in the other three patients.

For lesions in ISUP grade groups 2, 3, and 5, no statistically significant cutoff values were detected (Table 3). Despite this statistical insignificance, we observed that an increase in ISUP grade group was associated with a decrease in pathology-based TCL thresholds in terms of EPE (Table 3).

When considering ISUP grade group 1 + 2, where the predominant pattern is Gleason grade 3, as a single group (low ISUP grade groups) and ISUP grade group 3 + 4 + 5 (high ISUP grade groups), we found that there was also no statistically significant cutoff value (Table 3). We could not detect statistically significant cutoff values even when more aggressive groups (ISUP grade group 4 + 5, high ISUP grade groups) were considered as a single group (Table 3). However, we again observed that an increase in ISUP grade group in these groups, although statistically insignificant, was associated with a decrease in pathology-based TCL thresholds in terms of EPE (Table 3).

There was no statistically significant difference between EPE-positive and EPE-negative groups in relation to ISUP grade group 1 + 2 and ISUP grade group 3 + 4 + 5 compared with pathology-based TCL values ($\chi^2 = 4.178$, $p = 0.243$) (Table 1). Similarly, the comparison of EPE-positive and EPE-negative ISUP grade group 1 + 2 + 3 and ISUP grade group 4 + 5 for pathology-based TCL values could not show a statistically significant difference ($\chi^2 = 3.983$, $p = 0.263$) (Table 1). However, the rates of EPE-positive disease were significantly higher in patients in the high ISUP grade groups than in patients in the low ISUP grade groups. Although six of 51 patients (11.7%) had EPE-positive disease in ISUP grade group 1 + 2, 18 of 35 patients (51.4%) in ISUP grade group 3 + 4 + 5 had EPE-positive disease.

When ISUP grade group was ignored (i.e., ISUP grade group 1 + 2 + 3 + 4 + 5), no statistically significant cutoff values were detected for the relationship between pathology-based TCL and EPE (Table 3). However, when a TCL cutoff value of 15.5 mm was chosen, sensitivity was 58.3% and specificity was 62.9% (AUC, 0.630; $p = 0.063$) (Table 3).

TABLE 2: Comparison of Radical Prostatectomy (RP)-Based and Biopsy-Based International Society of Urological Pathologists (ISUP) Groups With and Without Extraprostatic Extension (EPE)

ISUP Grade Group	RP-Based ISUP Grade Group ($n = 86$)	Biopsy-Based ISUP Grade Group ($n = 86$)	EPE-Positive	EPE-Negative
1	3	18	0	3
2	48	36	6	42
3	19	15	9	10
4	5	10	2	3
5	11	7	7	4

Note—Data are reported as numbers of patients.

TABLE 3: Results of ROC Curve Analysis for Pathology-Based Tumor Contact Length (TCL) in Determining Extraprostatic Extension (EPE) Stratified by Radical Prostatectomy (RP)-Based International Society of Urological Pathologists (ISUP) Grade Groups and Subgroups

ISUP Grade Groups and Subgroups (No. of Patients)	Pathology-Based TCL Cutoff Value (mm)	AUC (95% CI)	Sensitivity (%)	Specificity (%)	*p*
ISUP 1 (*n* = 3)	—	—	—	—	—
ISUP 2 (*n* = 48)	21.0	0.688 (0.413–0.964)	66.6	85.7	0.139
ISUP 3 (*n* = 19)	15.0	0.572 (0.306–0.838)	66.6	50.0	0.596
ISUP 4 (*n* = 5)	—	—	—	—	—
ISUP 5 (*n* = 11)	11.0	0.661 (0.324–0.997)	71.4	75	0.395
ISUP 1 + 2 (*n* = 51)	21.0	0.698 (0.424–0.973)	66.6	86.6	0.118
ISUP 1 + 2 + 3 (*n* = 70)	17.5	0.659 (0.494–0.825)	60.0	72.7	0.06
ISUP 3 + 4 + 5 (*n* = 35)	16.0	0.582 (0.389–0.774)	50.0	64.7	0.409
ISUP 4 + 5 (*n* = 16)	13.5	0.595 (0.302–0.888)	77.8	57.1	0.525
ISUP 1 + 2 + 3 + 4 + 5 (*n* = 86)	15.5	0.630 (0.491–0.769)	58.3	62.9	0.063

Note—Dash (—) indicates that there were not enough patients in the ISUP group for statistical analysis.

Analysis of Relationship Between MRI-Based Tumor Contact Length and Extraprostatic Extension Based on Biopsy-Based International Society of Urological Pathology Grade Group

No statistically significant threshold could be detected, except for a few subgroups that consisted of low ISUP grade groups, in both T2-weighted and DCE-MRI sequences. The results are shown in the Table 4. In T2-weighted imaging–based TCL evaluation, when a TCL cutoff value of 14.6 mm was chosen, the sensitivity was 85.7% (p = 0.029) and 73.3% (p = 0.042) in ISUP grade group 1 + 2 and ISUP grade group 1 + 2 + 3, respectively (Table 4). In DCE-MRI–based TCL evaluation, the sensitivity was 71.4% (p = 0.057) and 66.7% (p = 0.051) when the TCL cutoff value of 16.1 mm was chosen in these subgroups (Table 4). However, statistically significant cutoff values were not detected in the individual ISUP grade groups and high ISUP grade subgroups.

Analysis of Relationship Between MRI-Based Tumor Contact Length and Extraprostatic Extension Based on Radical Prostatectomy–Based International Society of Urological Pathology Grade Group

When we assumed that we could reach the true ISUP scores in all patients, there was a statistically significant relationship between MRI-based TCL (T2-weighted imaging–based TCL and DCE-MRI–based TCL) and EPE with all low ISUP grade groups as ISUP grade group 2, ISUP grade group 1 + 2, and ISUP grade group 1 + 2 + 3 (Table 4). The statistically significant cutoff values in these groups ranged from 14.5 to 16.6 mm (Table 4). However, there were no statistically significant cutoff values in individual high ISUP grade groups and high ISUP grade subgroups (Table 4).

Analysis of the Influence of International Society of Urological Pathology Grade Group on Measurement Differences Between MRI-Based and Pathology-Based Tumor Contact Lengths

When we evaluated our findings to determine if there was a difference between pathology-based TCL and MRI-based TCL measurements according to ISUP grade group, we found that they were highly correlated in all groups; however, this correlation was much stronger in high ISUP grade groups than in low ISUP grade groups (Table 5).

Discussion

The MRI-based TCL has been reported to be a useful [6–8, 13, 20] or moderately useful [9, 10] parameter for EPE prediction in almost all studies in the literature. However, the thresholds suggested by studies show a large variability [6–8]. This variability in TCL measurement leads to disagreement on the selection of the proper threshold to use in clinical practice. In our study, we evaluated the real TCLs determined at pathology to find the optimal thresholds for EPE prediction. One of our aims was to reduce the MRI-based TCL measurement errors. However, in our study, contrary to the literature, we did not observe that pathology-based TCL (which is the final measurement) was as useful as MRI-based TCL for predicting EPE. Our results did not indicate a statistically significant threshold when all the ISUP grade groups were evaluated in one group (i.e., omitting tumor aggressiveness as in other studies) (Table 3). Considering tumor aggressiveness of the tumor, which is likely to affect EPE, we also did not find statistically significant thresholds in all individual ISUP grade groups and subgroups (Table 3). However, although there was no statistically significant difference, the decrease of pathology-based TCL cutoff values in terms of EPE positivity as RP-based ISUP grade groups increased indicates that ISUP grade group may have an effect on the TCL-EPE relationship.

One of the main reasons no statistically significant differences could be detected in most subgroups (particularly in pathology-based TCL evaluation groups) may be related to the number of patients. The number of patients in our study was low. It was further reduced when divided into subgroups. Another reason was the high overlap rate between the EPE-positive and EPE-negative groups. Tumor heterogeneity may be responsible for this overlap. Because we classified tumors according to ISUP grade groups, we have considered all the tumors with the same ISUP grade group as a homogeneous group. However, the focal Gleason grade at the junction of the tumor and the capsule may differ despite representing the same ISUP grade group.

Some studies evaluated the effect of ISUP grade group on the presence of EPE independent of TCL [12, 14]. Nyarangi-Dix et al. [12] and Mehralivand et al. [14] stated that as the ISUP grade group increased, the odds ratio also increased in terms of EPE presence. Similarly, in our study, EPE positivity

was higher in patients in the high ISUP grade group than in those in the low ISUP grade group (Table 1). However, none of the studies in the literature have investigated the direct effect of ISUP grade group on the TCL-EPE relationship. Differences in ISUP grade group of lesions in study cohorts may have an effect on the reporting of very different thresholds for MRI-based TCLs in the literature. In fact, although there was no statistically significant difference in our study, pathology-based TCL cutoff values were decreased in terms of EPE positivity as ISUP grade group increased (Table 3).

A recent study by Matsumoto et al. [21] focused on the impact of the zonal origin (anterior or posterior tumor) of the tumors on the TCL-EPE relationship. In their study, among patients with TCL of 10–20 mm, nine of 32 patients (28%) with an anterior tumor had EPE compared with 24 of 45 patients (53%) with a posterior tumor ($p = 0.036$) [21]. They concluded that anterior tumors have more favorable pathologic characteristics than posterior tumors with the same TCL measured on MRI. However, they also indicated that the anterior group had a lower pathologic Gleason score than the posterior group (Gleason score $\leq 3 + 4$, 58% vs 35%; $p < 0.001$) in their study cohort, and the difference was statistically significant. This difference in the Gleason scores might have affected the results. The group with the lower Gleason score (anterior lesions in their cohort) had a low ratio of positive EPE. In fact, they also stated in their study that a high Gleason score is an independent risk factor for EPE. Even the index tumor size was significantly larger in the anterior group than in the posterior group (mean size, 15.7 vs 13.8 mm; $p = 0.022$); the ratio of positive EPE was low in the anterior group when compared with that in the posterior group. The results might be related to the lower Gleason scores of the anterior lesions instead of localization. The results also might be related to the localization of the lesions or other factors such as genetics and anatomic factors. In fact, the findings of their research are consistent with our results. In the group with lower Gleason scores, there was a low ratio of positive EPE and vice versa, in both studies. Studies that focus on these details may clarify the most important factors for predicting EPE in the future.

In routine clinical practice the relationship between TCL and EPE is evaluated with the help of the data measured on MRI. In our study, we also have evaluated the relationship between TCL values measured on MRI and EPE. Because the data about the aggres-

TABLE 4: Results of ROC Curve Analysis for T2-Weighted Imaging–Based Tumor Contact Length (TCL) and Dynamic Contrast-Enhanced MRI (DCE-MRI)–Based TCL in Determining Extraprostatic Extension (EPE) Stratified by Biopsy-Based and Radical Prostatectomy (RP)-Based International Society of Urological Pathologists (ISUP) Grade Groups and Subgroups

ISUP Grade Groups and Subgroups (No. of Patients)	TCL Cutoff Value (mm)	AUC (95% CI)	Sensitivity (%)	Specificity (%)	*p*
Determining EPE stratified by biopsy-based ISUP grade groups and subgroups					
T2-weighted imaging–based TCL					
ISUP 1 ($n = 18$)	15.1	0.844 (0.586–1)	100	68.7	0.122
ISUP 2 ($n = 36$)	14.6	0.690 (0.471–0.908)	80.0	58.6	0.181
ISUP 3 ($n = 15$)	19.0	0.536 (0.216–0.855)	62.5	57.1	0.817
ISUP 4 ($n = 10$)	17.8	0.500 (0.088–0.912)	50.0	66.7	1
ISUP 5 ($n = 7$)	14.5	0.950 (0.777–1)	80.0	100	0.081
ISUP 1 + 2 ($n = 54$)	14.6	0.759 (0.595–0.923)	85.7	62.2	0.029[a]
ISUP 1 + 2 + 3 ($n = 69$)	14.6	0.674 (0.497–0.851)	73.3	55.8	0.042[a]
ISUP 3 + 4 + 5 ($n = 32$)	15.2	0.573 (0.368–0.777)	70.6	40.0	0.485
ISUP 4 + 5 ($n = 17$)	14.5	0.611 (0.328–0.894)	77.8	50.0	0.441
ISUP 1 + 2 + 3 + 4 + 5 ($n = 86$)	15.2	0.673 (0.534–0.812)	70.8	60.0	0.013[a]
DCE-MRI–based TCL					
ISUP 1 ($n = 18$)	20.7	0.969 (0.884–1)	100	93.7	0.035[a]
ISUP 2 ($n = 36$)	13.8	0.614 (0.300–0.927)	80.0	51.7	0.422
ISUP 3 ($n = 15$)	16.2	0.571 (0.258–0.885)	62.5	57.1	0.643
ISUP 4 ($n = 10$)	16.3	0.750 (0.418–1)	75.0	83.3	0.201
ISUP 5 ($n = 7$)	10.7	0.600 (0.145–1)	80.0	50.0	0.699
ISUP 1 + 2 ($n = 54$)	16.1	0.725 (0.486–0.965)	71.4	73.3	0.057
ISUP 1 + 2 + 3 ($n = 69$)	16.1	0.667 (0.479–0.855)	66.7	71.2	0.051
ISUP 3 + 4 + 5 ($n = 32$)	14.9	0.604 (0.400–0.808)	64.7	46.7	0.317
ISUP 4 + 5 ($n = 17$)	14.8	0.653 (0.381–0.924)	66.7	50.0	0.290
ISUP 1 + 2 + 3 + 4 + 5 ($n = 86$)	16.1	0.672 (0.526–0.818)	62.5	73.3	0.014[a]

(Table 4 continues on next page)

TABLE 4: Results of ROC Curve Analysis for T2-Weighted Imaging–Based Tumor Contact Length (TCL) and Dynamic Contrast-Enhanced MRI (DCE-MRI)–Based TCL in Determining Extraprostatic Extension (EPE) Stratified by Biopsy-Based and Radical Prostatectomy (RP)-Based International Society of Urological Pathologists (ISUP) Grade Groups and Subgroups (continued)

ISUP Grade Groups and Subgroups (No. of Patients)	TCL Cutoff Value (mm)	AUC (95% CI)	Sensitivity (%)	Specificity (%)	*p*
Determining EPE stratified by RP-based ISUP grade groups and subgroups					
T2-weighted imaging–based TCL					
ISUP 1 (*n* = 3)	—	—	—	—	—
ISUP 2 (*n* = 48)	15.7	0.807 (0.655–0.959)	83.3	65.9	0.016[a]
ISUP 3 (*n* = 19)	20.2	0.519 (0.205–0.832)	55.6	88.9	0.895
ISUP 4 (*n* = 5)	—	—	—	—	—
ISUP 5 (*n* = 11)	15.0	0.804 (0.527–1)	71.4	100	0.108
ISUP 1 + 2 (*n* = 51)	16.6	0.809 (0.658–0.959)	66.7	68.2	0.015[a]
ISUP 1 + 2 + 3 (*n* = 70)	14.5	0.680 (0.500–0.860)	73.3	52.8	0.034[a]
ISUP 3 + 4 + 5 (*n* = 35)	15.2	0.559 (0.361–0.757)	66.7	50.0	0.558
ISUP 4 + 5 (*n* = 16)	15.0	0.651 (0.350–0.952)	77.8	71.4	0.315
ISUP 1 + 2 + 3 + 4 + 5 (*n* = 86)	15.2	0.673 (0.534–0.812)	70.8	60.0	0.013[a]
DCE-MRI–based TCL					
ISUP 1 (*n* = 3)	—	—	—	—	—
ISUP 2 (*n* = 48)	16.1	0.835 (0.685–0.986)	83.3	73.2	0.009[a]
ISUP 3 (*n* = 19)	16.3	0.506 (0.211–0.801)	55.6	66.7	0.965
ISUP 4 (*n* = 5)	—	—	—	—	—
ISUP 5 (*n* = 11)	12.3	0.625 (0.285–0.965)	71.4	50.0	0.508
ISUP 1 + 2 (*n* = 51)	16.1	0.847 (0.706–0.988)	83.3	75.0	0.006[a]
ISUP 1 + 2 + 3 (*n* = 70)	16.1	0.701 (0.528–0.874)	66.7	73.6	0.018[a]
ISUP 3 + 4 + 5 (*n* = 35)	14.8	0.552 (0.352–0.752)	61.1	50.0	0.605
ISUP 4 + 5 (*n* = 16)	14.3	0.603 (0.315–0.891)	66.7	57.1	0.491
ISUP 1 + 2 + 3 + 4 + 5 (*n* = 86)	16.1	0.672 (0.526–0.818)	62.5	73.3	0.014[a]

Note—Dash (—) indicates that there were not enough patients in the ISUP group for statistical analysis.
[a]Indicates statistically significant result.

siveness of a tumor is routinely provided by ISUP grade group values determined using biopsy results, we analyzed our data to determine if an MRI-based TCL threshold could be used to predict the presence of EPE while also considering biopsy-based ISUP grade group. However, no statistically significant threshold could be detected, except for a few subgroups, in either T2-weighted imaging or DCE-MRI sequences. These subgroups consisted of low ISUP grade groups. To summarize, our study did not provide statistically significant TCL thresholds in almost all ISUP grade groups for the relationship between TCL and EPE using routine data collected in clinical practice (i.e., MRI-based TCLs and biopsy-based ISUP grade groups).

In clinical practice, there can be a discordance between ISUP grade group results obtained from biopsies and those obtained from RP. In fact, when we compared the biopsy and RP results in our study, their agreement was poor ($\kappa = 0.454$, $p = 0.001$). However, the biopsy method was not standardized in our study cohort. The group also included blind systemic biopsies. Studies in the literature have shown that targeted biopsies are more accurate for correct stratification [22]. Theoretically, more accurate ISUP scores could be obtained with a homogeneous group including only targeted biopsies. Targeted biopsy rates are increasing in clinical practice. For this reason, we also evaluated what the relationship between MRI-based TCL and EPE would be if we had access to more realistic ISUP scores. So, we used RP-based ISUP grade group results for the evaluation of the MRI-based TCL-EPE relationship (Table 4). Our results suggest that, in the future, with widespread use of targeted biopsy methods providing more accurate biopsy results, a threshold around 16 mm could be used in low biopsy-based ISUP grade groups (Table 4). However, although no statistically significant value was determined in our study for high biopsy-based ISUP grade groups, this threshold may decrease with an increase in biopsy-based ISUP grade group.

An unexpected finding in our study was the fact that no statistically significant cutoff value for pathology-based TCL could be determined for the TCL-EPE relationship in both low and high ISUP grade groups, whereas a significant cutoff value could be found for low ISUP grade groups in many MRI-based TCL subgroups. This finding raises the question whether there was

TABLE 5: Correlation of Measurements Between MRI-Based Tumor Contact Length (TCL) and Pathology-Based TCL Stratified by Radical Prostatectomy (RP)-Based International Society of Urological Pathologists (ISUP) Grade Groups and Subgroups

RP-Based ISUP Grade Groups and Subgroups (No. of Patients)	Correlation With Pathology-Based TCL		*p*
	T2-Weighted Imaging–Based TCL	DCE-MRI–Based TCL	
1 (*n* = 3)	—	—	—
2 (*n* = 48)	0.67	0.68	< 0.001[a]
3 (*n* = 19)	0.62	0.64	< 0.005[a]
4 (*n* = 5)	—	—	—
5 (*n* = 11)	0.85	0.76	< 0.001[a]
1 + 2 (*n* = 51)	0.66	0.70	< 0.001[a]
1 + 2 + 3 (*n* = 70)	0.64	0.67	< 0.001[a]
3 + 4 + 5 (*n* = 35)	0.74	0.71	< 0.001[a]
4 + 5 (*n* = 16)	0.89	0.82	< 0.001[a]

Note—Dash (—) indicates that there were not enough patients in the ISUP group for statistical analysis.
[a]Indicates statistically significant result.

a significant difference between both TCL measurements. MRI-based TCL measurements were reported to be highly correlated with pathology-based TCL measurements in two recent studies in the literature [6, 23]; however, in one of those studies, investigators stated that as the TCLs increase, the MRI-based TCL likely underestimated the pathology-based TCL [6]. When we evaluated our findings to determine if there was a difference between pathology-based TCL and MRI-based TCL measurements according to ISUP grade group, we found that they were highly correlated in all groups similar to the previous studies; however, this correlation was much stronger in high ISUP grade groups than in low ISUP grade groups (Table 5). This finding could explain the similar statistical results between pathology-based TCL-EPE and MRI-based TCL-EPE relationship in high ISUP grade groups (i.e., no statistically significant cutoff value was determined in both groups). In low ISUP grade groups, the pathology-based TCL and MRI-based TCL values were less concordant and statistical results involving the TCL-EPE relationship for pathology-based TCL and MRI-based TCL were diverging; that is, statistically significant thresholds were detected in many ISUP subgroups in MRI-based TCL groups but not in pathology-based TCL groups. The analysis of our data shows that the discordant results between MRI-based TCL and pathology-based TCL in low ISUP grade groups were caused by both overestimating and underestimating MRI-based TCL compared with pathology-based TCL. It is difficult to find a meaningful explanation for why statistically significant thresholds existed for MRI-based TCL-EPE relationship in the low ISUP grade groups. The Gleason pattern in the area in contact with the capsule could play a role in explaining this finding. MRI-based TCL measurements may show factors that increase the risk of EPE, such as a more aggressive component in contact with the capsule, more easily in low ISUP grade groups than in high ISUP grade groups. This theory needs to be confirmed with further studies including a greater number of patients.

When the MRI-based TCL-EPE relationship was evaluated independent of ISUP grade groups (similar to other studies in the literature), a cutoff value of 15.2 mm for T2-weighted imaging–based TCL measurements yielded sensitivity of 70.8% and specificity was 60.0% ($p = 0.013$) and a cutoff value of 16.1 mm for DCE-MRI–based TCL yielded a sensitivity and specificity of 62.5% and 73.3% ($p = 0.014$) (Table 4). For the evaluation of pathology-based TCL, when a cutoff value of 15.5 mm was chosen, sensitivity was 58.3% and specificity was 62.9% ($p = 0.06$); despite being insignificant, a p value of 0.06 is very close to the statistically significant p value threshold ($p < 0.05$) (Table 3). In fact, this value was very close to the values measured by MRI-based TCL. Considering these findings, a cutoff MRI-based TCL value around 15–16 mm may be usable to predict EPE independent of ISUP grade group in clinical practice. Mehralivand et al. [14] also used a threshold of 15 mm for TCL in their grading system proposed for the assessment of EPE risk in their study. They reported the sensitivity and specificity of this threshold to be 70% and 72%, respectively [14]. However, according to our study results, these MRI-based TCL cutoff values are more reliable statistically for low ISUP grade groups and the thresholds have a probability to decrease for high ISUP grade groups.

Our study had some limitations. First, the number of patients was low. ISUP grade groups 1 and 4 did not have enough patients for statistical analysis. The number of patients was especially low in ISUP grade group 1. Another limitation of our study was the lack of evaluation on which Gleason grade pattern was dominant at the points where the tumor touched the capsule. The lack of evaluation of this dominant pattern may have an effect on outcomes. In our study, the prostate biopsy procedures consisted of a mixed group of targeting and systematic biopsy techniques. It was not a homogeneous group. The results of our biopsy groups were affected by the heterogeneity of techniques.

Conclusion

When we evaluated the relationship between pathology-based TCL and EPE, we observed that pathology-based TCL did not have statistically significant cutoff values for predicting EPE in individual ISUP grade groups and subgroups. Although there was no statistically significant difference, we observed that pathology-based TCL cutoff values decreased as ISUP grade group increased in terms of EPE positivity. When the relationship between MRI-based TCL and EPE was considered, a statistically significant cutoff value could be determined in many groups and subgroups with low ISUP grade groups; however, no statistically significant cutoff was found for high ISUP grade groups. When the MRI-based TCL-EPE relationship was evaluated independent of ISUP grade group, a cutoff value around 15–16 mm may be usable to predict EPE. Our results showed that these MRI-based TCL cutoff values are more reliable statistically for low ISUP grade groups and that the thresholds may have a tendency to decrease for high ISUP grade groups. Also, we observed that the MRI-based TCL and pathology-based TCL measurements are highly correlated in all ISUP groups; however, this correlation was much stronger in

high ISUP grade groups than in low ISUP grade groups. The results obtained from our study should be validated in larger studies. In a study involving a larger number of subjects, statistical significance might be achieved regarding thresholds.

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