Original Article

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Prognostic Role of Tumor Percentage in Multiparametric MRI for Upgrade Prediction Before Radical Prostatectomy

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Abstract

Objective: To determine the parameters that can predict upgrade with multiparametric magnetic resonance imaging (mpMRI) findings before radical prostatectomy (RP) in prostate cancer. The development of mpMRI increases the prediction rate of upgrades.

Materials and Methods: The study included 69 patients who were diagnosed with prostate cancer (PCa) between January 2017-December 2020 and subsequently underwent RP. Patients were divided into two groups by comparing prostate biopsies and RP specimens as patients with upgrade (group 1) and patients without upgrade (group 2). Of the 69 patients, 26 were in group 1 and 43 in group 2. The images were evaluated by a single radiologist experienced in mpMRI using the Prostate Imaging Reporting and Data System v2.1 scoring system. Biopsy and RP pathology specimens were evaluated by an experienced neuropathologist.

Results: The median prostate-specific antigen (PSA) levels were higher in patients with upgraded pathology [8.60 (5.90-14.00) ng/dL vs. 7.70 (5.20-10.00) ng/dL, respectively; p=0.040]. The prostate volume [31.88 (23.40-51.48) vs. 48.06 (23.40-87.35); p=0.009] and PSA density [3.72 (2.17-5.62) vs. 5.75 (3.35-9.6), respectively; p=0.007] were lower in patients with upgraded pathology. The tumor percentage on mpMRI was not different between the groups [3.70 (1.80-16.20 vs. 2.50 (1.10-6.60); p=0.076]. The histopathological tumor percentage was significantly higher in patients with upgraded histology (p=0.006).

Conclusions: Although the percentage of tumors on multiparametric mpMRI is an inadequate pattern to predict upgrade in PCa patients, prospective studies designed to evaluate its potential will be of great interest.

Keywords: Multiparametric magnetic resonance imaging, prostate cancer, radical prostatectomy, tumor percentage, upgrade

Introduction

Prostate cancer (PCa) is the most common malignancy and the second most common cause of cancer-related deaths in males (1). Serum prostate-specific antigen (PSA) evaluation has shown that its incidence has increased in the last 2-3 decades and the mortality rate has decreased in recent years due to the progression of imaging methods (2). In a selected group of patients with comorbidities, overtreatment can be performed with a high International Society of Urological Pathology (ISUP) grading instead of active surveillance. Accordingly, surgery-related mortality may increase. However, inadequate treatment decisions due to a low ISUP rating may lead to biochemical recurrences (3,4). Novel studies have shown that the final pathologies of patients diagnosed with low risk based on biopsy in radical prostatectomy (RP) series were upgraded at a rate of 30-50%. When they were regrouped, they were included in the higher risk group (5,6). Thus, causing serious misclassification and deficiencies in the treatment options or planning of management.

Accurate ISUP-grade detection is important for planning the most suitable treatment and predicting prognosis (3). An inconsistency of approximately 50% was reported between

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ISUP grade detected through transrectal prostate biopsy and the grades detected in RP specimens (7,8). The relationship between PSA, PSA density, and tumor percentage in biopsy cores and upgrade was investigated and is not used as an upgrade predictor in clinical practice (6,9). The development of multiparametric magnetic resonance imaging (mpMRI) has increased the estimation rate of upgrades and reduced the mismatch between biopsy and sample histopathology (10,11).

Our primary aim in this study was to detect the parameters that may be useful in the preoperative prediction of upgraded patients by comparing the upgraded and not-upgraded patients on mpMRI characteristics. Our second aim was to present other factors for predicting upgrade in prostate cancer.

Materials and Methods

Patient Selection and Acquisition of Clinicopathological Data

In our retrospective study, the data of 195 patients who had open RP with the same surgical methods due to PCa between January 2017 and December 2020 were scanned, and 69 patients meeting our study criteria were included. PSA values, prostate volume (PV), biopsy results including biopsy ISUP grade, clinical T stage risk group according to the D'amico classification, Prostate Imaging Reporting and Data System (PIRADS) score, tumor volume, PV, and tumor percentage in mpMRI, and RP specimen results including histopathological stage, intraprostatic tumor volume (HP_{TV}), ISUP grade, seminal vesicle invasion presence (SVI), and extracapsular extension presence (ECE) rates detected were recorded. Tumor percentage was calculated by dividing PV by tumor volume. This study was approved by the Ethics Committee of Trakya University Faculty of Medicine (decision no: 08/06, date: 11.04.2022).

Patients who underwent transrectal ultrasonography-guided prostate biopsy, were diagnosed with clinically significant prostate cancer, and underwent mpMRI before RP were included in the study. The following patients were excluded from the study; i) any secondary malignancy, ii) previous transurethral prostate resection, and iii) previous PCa treatment.

Evaluation of mpMRI and Data Acquisition

Multiparametric MRI included T1-weighted diffusion-weighted images and dynamic contrasted series in all cases and were taken through 1.5T MR (MAGNETOM Aera, Siemens Medical Systems). A single-blinded radiologist experienced in mpMR evaluated all histopathological results using the PIRADS v2.1 scoring system. Pelvic phase sequential coil was used in all cases, and endorectal coil was not used. b-values were taken as 200, 1000, and 1500 in diffusion weighted images, and ADC mappings were calculated. In T1 weighted images; TR 433 ms, TE: 10 ms, FOV: 200 mm, matrix: 512 x 512, in T2 weighted fast spin echo images; TR: 5310 ms, FOV: 200 mm, matrix: 320 x 320, Post-contrasted T1-weighted images in VIBE sequence: TR 4,18 ms, TE: 1,58 ms, Flip angle:12°, FOV: 259 mm matrix: 192 x 192. The slice thickness was 3.5 mm in all series, and the slice gap was 0 mm. Contrast matter was (Gadobutrol, Gd-BT-DO3A, Gadovist, Schering, Berlin) in early and dynamic contrasted series at a dose of 0.1 mmol/kg. As suggested in PIRADS v2.1, prostate gland measurements were calculated using the ellipsoid formula [(maximum anteroposterior (AP) diameter) x (maximum transverse diameter) x (maximum longitudinal diameter) x $\pi/6$]. Measurements were made as the maximum AP diameter and longitudinal diameter in midsagittal T2-weighted images and the longest diameter measurement in axial T2-weighted images. In addition, while collecting study data, radiologists and urologists agreed on the lesions and finalized them.

Histopathological Evaluation

Post-RP pathology specimens of all patients included in the study were evaluated by an experienced neuropathology expert blinded to mpMRI results. The apex and bladder neck surgical borders of all RP specimens were sampled, and the surgical borders of the prostate were stained. All tumoral areas in the quadrants agreed with ISUP 2014, and grade groups were determined. Histopathological phase HP_{TV}, ISUP grade, ECE, and SVI rates were recorded.

Statistical Analysis

Statistical analyses were performed using SPSS 20.0 (licence no: 10240642) package program. The categorical data were expressed as number and frequency, and the continuous data were expressed as median and interquartile range. The Mann-Whitney U test was used for the comparison of quantitative values between variables. Chi-square tests were used for the comparison of categorical data. P value <0.05 was regarded as the statistical significance limit. Spearman correlation analysis was used to examine the relationships between preoperative mpMRI and histopathological data. Receiver operating characteristic (ROC) analysis was used to show the sensitivity and specificity of tumor rate in mpMRI in predicting upgrade.

Results

The median age of patients was 65 years and similar between groups. There were 26 patients in group 1 and 43 patients in group 2, and the distribution and comparison of their radiological and histopathological characteristics are detailed in Tables 1 and 2. The PSA level was statistically higher and PSA density was lower in patients with upgraded pathology (p=0.040, and p=0.007, respectively). PVs in both mpMRI and histopathological examination were significantly lower in patients with upgraded histology (p=0.012, and p=0.009 respectively). However, the tumor volumes in both mpMRI and histopathological examination were similar between groups (p=0.480, and p=0.140, respectively).

The tumor percentage on mpMRI did not differ between the groups [3.70 (1.80-16.20 vs. 2.50 (1.10-6.60); p=0.076]. Histopathological tumor percentage was significantly higher in patients with upgraded histology (p=0.006). Additionally, extra prostatic extension was only significantly higher in patients with upgrade (p=0.015) and mpMRI only predicted 25% of patients.

When we regard 1.75 as the cut-off value for tumor rate in MR based on the ROC analysis, the upgrade was predicted with 80% sensitivity and 45% specificity (Figure 1). While the upgrade rate was 20.8% in patients with a tumor percentage less than 1.75, the cut-off value was 46.7% in those with an upgrade rate above the cut-off value (Table 3).

Table 1. Comparison of demographic, radiological, and histopathological data			
	Group 1 **Patients with upgrade (n=26)**	**Group 2** **Patients without upgrade (n=43)**	**p***
Age (years)	64.00 (60.00-69.00)	60.00 (60.00-69.00)	0.600
PSA (ng/mL)	8.60 (5.90-14.00)	7.70 (5.20-10.00)	**0.040**
mpMRI prostate volume (mm^3)	32.60 (23.30-41.80)	46.50 (26.20-79.50)	**0.012**
Histopathology of prostate volume (mm^3)	31.88 (23.40-51.48)	48.06 (23.40-87.35)	**0.009**
mpMRI total tumor volume (mm^3)	2.15 (0.49-4.82)	1.01 (0.46-4.36)	0.480
Histopathological tumor volume (mm^3)	6.10 (2.30-11.50)	3.10 (1.60-8.60)	0.140
Histopathological tumor percentage (%)	17.56 (10.00-30.00)	10.50 (4.60-18.00)	**0.006**
mpMRI tumor percentage (%)	3.70 (1.80-16.20)	2.50 (1.10-6.60)	**0.076**
PSA density	3.72 (2.17-5.62)	5.75 (3.35-9.61)	0.007
PSA: Prostate-specific antigen, mpMRI: Multiparametric magnetic resonance. All variables are presented as median and interquartile range			

Table 2. Comparison of the two groups according to clinical and histopathological data			
	Group 1 **Patients with upgrade (n=26)**	**Group 2** **Patients without upgrade (n=43)**	**p-value**
Biopsy ISUP **Grade 1** **Grade 2** **Grade 3** **Grade 4** **Grade 5**	 15 (57.7%) 8 (30.8%) 1 (3.8%) 2 (7.7%) 0 (0%)	 21 (48.8%) 11 (25.6%) 3 (7%) 4 (9.3%) 4 (9.3%)	0.651*
Histopathology ISUP **Grade 1** **Grade 2** **Grade 3** **Grade 4** **Grade 5**	 0 (0%) 15 (57.7%) 3 (11.5%) 4 (15.4%) 4 (15.4%)	 20 (46.5%) 15 (34.9%) 1 (2.3%) 4 (9.3%) 3 (7%)	**0.000***
Clinical T stage **1** **2**	 22 (84.6%) 4 (15.4%)	 32 (74.4%) 11 (25.6%)	0.320#
Histopathological T stage **1** **2** **3**	 0 16 (61.5%) 10 (38.5%)	 1 (2.4%) 31 (72.1%) 11 (25.5%)	0.410#
D'amico **Low** **Moderate** **High**	 13 (50%) 8 (30.8%) 5 (19.2%)	 19 (44.2%) 15 (34.9%) 9 (20.9%)	0.890#
mpMRI PIRADS score **2** **3** **4** **5**	 4 (15.4%) 4 (15.4%) 11 (42.3%) 7 (26.9%)	 4 (9.3%) 10 (23.3%) 14 (32.6%) 15 (34.9%)	0.620#
mpMRI extraprostatic extension **Yes** **No**	 3 (11.5%) 23 (88.5%)	 6 (14%) 37 (86%)	0.990*
mpMRI seminal vesicle invasion **Yes** **No**	 1 (3.8%) 25 (96.2%)	 5 (11.6%) 38 (88.4%)	0.380*
mpMRI lymph node positivity **Yes** **No**	 7 (26.9%) 19 (73.1%)	 12 (27.9%) 31 (72.1%)	0.92#

Table 2. Continued			
	Group 1 **Patients with upgrade (n=26)**	**Group 2** **Patients without upgrade (n=43)**	**p-value**
Histopathology of extraprostatic extension **Yes** **No**	 12 (46.2%) 14 (53.8%)	 8 (18.6%) 35 (81.4%)	**0.015#**
Histopathology seminal vesicle invasion **Yes** **No**	 4 (15.4%) 22 (84.6%)	 5 (11.6%) 38 (88.4%)	0.720*
ISUP: International Society of Urological Pathology, mpMRI: Multiparametric magnetic resonance imagining, PIRADS: Prostate Imaging Reporting and Data System *Fisher's exact test was used. #Chi-square test was used.			

Table 3. Comparison of upgrade rates based on tumor percentage (cut-off 1.75)				
		Tumor percentage		**Total**
		<1.75	**>1.75**	
Upgrade	**Absent**	19	24	43
		79.2%	53.3%	62.3%
	Present	5	21	26
		20.8%	46.7%	37.7%

Discussion

Upgrade was detected in 37.6% of the patients in this study, and the intraprostatic tumor percentage acquired through histopathological examination was associated with upgrade pathology. The second endpoint is the inadequacy of mpMRI in EPE detection, which is the most important component of local staging.

Final Gleason score (GS) following RP is a strong marker of disease prognosis and is related to recurrence, metastasis, and mortality (12). Gleason grading is commonly used to decide on different treatment options in addition to prognosis prediction (12). Upgrade in final histopathological GS compared with biopsy GS was reported as 20-60% (8,9). Thus, the prediction of cases with high possibility is essential for GS upgrade. Parameters such as PSA and tumor percentage in biopsy cores were reported as effective in the prediction of upgrade (6,9). With the addition of diffusion imaging to mpMRI,, intraprostatic tumor localization and detection have become more precise (11). mpMRI for detecting upgrades and the PIRADS score was primarily used for the prediction of these upgrades in general (11,13). Tumor volume has been reported as a possible prognostic marker of PCa in the literature (14). Turkbey et al. (15) showed a correlation between intraprostatic tumor volume in mpMRI and final histopathological tumor volume. However, this correlation was not detected in our study. Although this difference may be caused by not using an endorectal coil in volume measurements in our study, prostate gland volume was calculated using the ellipsoid formula because of its practicality, applicability, and low difference between observers, as mentioned in PIRADS v2.1. However, the prostate glandular shape is not completely ellipsoid and may cause measurement errors, especially in very large or negligible prostates or transitional zone hyperplasia cases. Although some studies in the literature suggested a lead volume (cylinder + semi - ellipsoid) formula (AP diameter x transverse diameter x $5\pi/24$), it was not suggested in the current studies due to a volume measurement higher than the reality and was not mentioned in PIRADS v2.1 (16-19). Our study also did not present any relationship between tumor volume and upgrade, and the study by Ullrich et al. (20) using the same methodology for volume measurement supports the results of our study. However, these results showed that tumor volume is not the only factor for upgrading. The tumor percentage in which tumor volume and prostate size are calculated together is associated with the upgrade of histology.

In addition to PSA and GS, which are the major factors in PCa primary staging, tumor volume and location are also important in risk classification and treatment planning (21). A relationship was also observed between the tumor involvement percentage of biopsy cores and upgrade risk of low-risk prostate cancers (6). Considering that standard 12-core biopsy represents the whole prostate, tumor percentage in cores can be regarded as a reflection of global tumor percentage. Because of this hypothesis, our study is, to the best of our knowledge, the first to investigate the relationship between tumor percentage in mpMRI and postoperative upgrade. A study reported the tumor percentage of the specimen after RP as an independent predictor of biochemical recurrence, and the efficiency of tumor percentage to be acquired from mpMRI gains significance (22). Imaging in patients with low risk and some patients with average risk according to the D'amico Risk Classification were stated at low suggestion levels in the guidelines (3). However, the fact that they can be upgraded and their treatment plans may change go unnoticed. However, the fact that these can be upgraded and treatment plans changed is overlooked. Although it can be calculated more easily and faster with mpMRI and does not require additional cost, the percentage of tumors was not found to be significant in estimating upgrade. We believe that this indicator will gain significance with more comprehensive and broader prospective studies.

Although the use of mpMRI in PCa local staging quickly increases, there are conflicting results on EPE prediction in the literature, and its availability in clinical practice is uncertain (23,24). Thus, when the mpMRI were compared with the final pathology in the study by Boesen et al. (25), they were found to be useful in EPE prediction. Contrary to the literature, in our study, mpMRI could not identify EPE in most patients with upgraded pathology. As a result, mpMRI may be inadequate for local staging in upgrade pathology. However, it may be useful

to develop new methods, such as tumor percentage calculation, through a review of mpMRI criteria.

Study Limitations

The current study has several limitations that warrant discussion. First, the study design was retrospective, which introduces inherent biases. For instance, there may be selection bias due to the exclusion and inclusion criteria. In addition, the lack of randomization could affect the generalizability of the findings.

Second, the sample size of our study was relatively small, and all patients were recruited from a single institution, which could limit the external validity of the findings. More comprehensive studies with a larger and more diverse patient population would be useful to verify our results and make them more widely applicable.

Finally, while collecting study data, radiologists and urologists agreed and finalized the lesions. However, because it is thought that urologists do not have sufficient experience in mpMRI, the fact that two radiologists did not evaluate the images can be considered as a limitation.

Overall, despite these limitations, our study provides a significant contribution to the growing body of literature suggesting the potential benefits of mpMRI in the management of prostate cancer. We believe that our findings provide a foundation for future research to further explore and develop this important field.

Conclusion

Although the percentage of tumors on mpMRI is an inadequate pattern to predict upgrade in PCa patients, prospective studies designed to evaluate its potential will be of great interest.

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Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Trakya University Faculty of Medicine (decision no: 08/06, date: 11.04.2022).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: M.G.A., E.A., C.M.Y., Concept: M.G.A., E.A., C.M.Y., B.A., Design: M.G.A., E.A., B.A., Data Collection or Processing: G.E., M.F.Ş., Ş.H., Analysis or Interpretation: G.E., M.F.Ş., F.G., Literature Search: M.G.A., F.G., E.A., Writing: M.G.A., G.E., M.F.Ş., F.G., E.A., C.M.Y., B.A.

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