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Contents

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Bull Urooncol 2024;23(1):1-5

The Effect of Perineural Invasion on Biochemical Recurrence-free Survival Following Nerve-sparing Radical Prostatectomy

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Abstract

Objective: Perineural invasion (PNI) is a histopathological finding which represents invasion of the nerves and surroundings by cancer cells. Several studies have reported that PNI in prostate cancer (PCa) is a poor prognostic factor. However, there are insufficient data in literature related to the use of PNI status in the biopsy at the stage of making a decision for nerve-sparing surgery. This research aimed to investigate the impact of PNI identified in prostate biopsies on the biochemical recurrence-free survival (RFS) in individuals who underwent nerve-sparing radical prostatectomy (RP) for PCa.

Materials and Methods: The data of 972 patients who underwent nerve-sparing RP due to a clinically localized PCa diagnosis were retrospectively examined. Patients were divided into two groups as PNI (+) and PNI (-) according to PRI status in prostate biopsy pathology.

Results: Evaluation was made of 747 patients with suitable data for analysis. PNI was determined in the prostate biopsy of 162 patients and not in the biopsies of 585 patients. The 5-year biochemical RFS rates were 90% for PNI (+) patients and 89.6% for the PNI (-) group, and the difference between the two groups was not statistically significant. When the PNI positive and negative groups were compared in respect of surgical margin positivity, the surgical margin was determined as positive in 42 (25.9%) of the group with PNI and in 84 (14.4%) of the group without PNI. Surgical margin positivity was determined to be statistically significantly greater in the PNI (+) group. Biochemical RFS rates were compared according to the surgical margin positivity status, and 5-year biochemical RFS was found to be 81.5% in those with surgical margin positivity and 91.6% in those with surgical margin negativity, no statistically meaningful distinction was found between the groups

Conclusions: The findings of this study indicated that PNI determined in prostate biopsy did not affect 5-year RFS following nerve-sparing RP.

Keywords: Prostate, prostate cancer, radical prostatectomy, perineural invasion, prostate spesific antigen, survival, recurrence

Introduction

Prostate cancer (PCa) ranks as the second most commonly diagnosed cancer among males globally and stands as the sixth leading cause of cancer-related fatalities (1).

According to the results of many recent studies based on data series obtained from population-based records, the incidence and mortality rates of PCa seem to have fallen or be stable in several countries. This is thought to be due to prostate-specific antigen (PSA) screening being effective in reducing the incidence of PCa and developments in treatment modalities reducing mortality rates (2). However, despite these developments, some PCa's have a more aggressive course and even if there is early diagnosis and definitive treatment, there is rapid recurrence.

Although there are several treatment alternatives available for localised PCa, biochemical recurrence (BCR) can be determined in approximately 18% of patients after treatment (3,4). Pathological grade, preoperative PSA levels, and Gleason score (GS) are known to be risk factors widely used for BCR (5).

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Perineural invasion (PNI) is a histopathological finding representing the invasion of nerves or the surroundings by cancer cells, and it is seen in 7-43% of needle biopsies in PCa (6,7).

PNI can be seen as a poor prognostic factor in many cancer types other than prostate, such as pancreas, rectum, and gastric cancers (8-10). There are many studies linking this interaction between tumor and nerve cells to separate perineural tumor spread, just as in lymphovascular invasion (11-13).

Although many studies have reported that PNI is a poor prognostic factor in PCa, there are insufficient data in literature about the use of PNI status in the biopsy at the stage of making a decision for nerve-sparing surgery (14-16).

The primary goal of this investigation is to appraise the significance of PNI and discern how it influences the decision-making for nerve-sparing radical prostatectomy (RP). The study aims to investigate the effects of PNI in prostate biopsy samples taken from patients with PCa, specifically examining its impact on BCR-free survival (RFS) after nerve-sparing RP.

Materials and Methods

A retrospective analysis was conducted on the data of 972 patients with clinically localized PCa who underwent nerve-sparing RP without receiving adjuvant or neoadjuvant hormonal treatment or adjuvant radiotherapy, using the Urologic Cancer Database - Prostate of the Urooncology Association of Turkey.

The data for the study were gathered using the REDCap data collection software, a tool developed by Vanderbilt University and licensed by the Urooncology Association in Turkey (17,18).

The patients were subjected to assessment, considering demographic and clinical parameters such as age, body mass index, clinical information (PSA, and clinical T stage). Additionally, pathological data derived from transrectal ultrasound prostate biopsies were taken into account, including GS, International Society of Urological Pathology (ISUP) grade, PNI, and lymphovascular invasion.

Additional factors considered were the type of operation (open, laparoscopic RP, or robot-assisted laparoscopic RP), nerve-sparing RP side (single or bilateral), surgical margin status of the RP specimen, and follow-up BCR rates.

The criteria for BCR were met when two consecutive PSA values of 0.2 ng/mL or higher exhibited an increasing trend post RP. Patients were classified into two groups depending on whether PNI was present or absent, as determined during the pathology examination of the prostate biopsy.

Statistical Analysis

Statistical analysis was carried out using the SPSS software (Version 25.0, SPSS Inc., Chicago, IL, USA). Each continuous variable underwent scrutiny for normality through both the Kolmogorov-Smirnov and Shapiro-Wilk tests. The one-way ANOVA test was implemented for normally distributed data, while the Kruskal-Wallis test was chosen for non-normally distributed data. Given the significance of the analysis of variance (ANOVA), post-hoc tests were conducted. When dealing with non-normally distributed data, the Mann-Whitney U test was utilized for making comparisons.

ROC curves were constructed to evaluate the diagnostic performance of a binary classifier system. Areas under the curve, sensitivity, and specificity were computed.

A significance level of $p<0.05$ was adopted, signifying that results with a p-value below 0.05 were deemed statistically significant.

Results

Evaluation was made of 747 patients who underwent nerve-sparing RP with suitable data for analysis. Of these, PNI was determined in the preoperative prostate biopsy of 162 patients and not in the biopsies of 585 patients.

The comparative analysis of clinical and pathological characteristics between the two groups is presented in Table 1. The mean age of patients in the PNI (+) group was 61.85±6.90 years, while in the PNI (-) group, it was 61.58±6.77 years, with no statistically significant difference observed between the groups (p=0.551). Among the patients, 509 underwent open RP, 70 underwent laparoscopic RP, and 168 underwent robot-assisted RP. There was no statistically significant difference in the distribution of surgical types between the groups (p=0.443).

Table 1. Clinical and pathological characteristics of the PNI negative and positive patients

Parameter	n	PNI (+)	PNI (-)	p-value
Patient	747	162	585	
Age		61.85±6.90	61.58±6.77	0.551
Surgery				
Open	509	127 (78.4%)	382 (65.3%)	0.443
Lap	70	15 (9.3%)	55 (9.4%)	
Rob	168	20 (12.3%)	148 (25.3%)	
NS side				
Single	82	23 (14.2%)	59 (10.1%)	0.155
Bilateral	665	139 (85.8%)	526 (89.9%)	
PSA (median)	6.79	7.37	6.60	0.050
IQR	(1.49-84.00)	(1.84-53.23)	(1.49-84.00)	
Clinical T stage				
T1c	350	82 (50.6%)	268 (45.9%)	0.182
T2a	162	34 (20.9%)	128 (21.9%)	
T2b	126	22 (13.6%)	104 (17.7%)	
T2c	109	24 (14.9%)	85 (14.5%)	
ISUP grade				
Grade 1	380	87 (53.7%)	293 (50.0%)	0.265
Grade 2	248	40 (24.6%)	208 (35.5%)	
Grade 3	69	19 (11.8%)	50 (8.6%)	
Grade 4	39	9 (5.6%)	30 (5.2%)	
Grade 5	11	7 (4.3%)	4 (0.7%)	
Surgical margin				
Negative	514	120 (74.1%)	501 (85.6%)	0.0001
Positive	233	42 (25.9%)	84 (14.4%)	

PNI: Perineural invasion, PSA: Prostate-specific antigen, IQR: Interquartile range, ISUP: International Society of Urological Pathology

Regarding nerve-sparing procedures, unilateral surgery was performed in 82 patients, and bilateral surgery was performed in 665 patients. No significant difference was identified between the groups concerning the choice between unilateral or bilateral nerve-sparing surgery (p=0.155).

The median PSA value was 7.37 (range, 1.84-53.23) in the PNI (+) group and 6.60 (range, 1.49-84.00) in the PNI (-) group, with no significant difference determined between the groups in respect of the preoperative PSA values (p=0.050).

No significant difference was determined between the two groups in respect of the clinical T stages (p=0.182).

When the patients were grouped according to ISUP grades, 380 patients were ISUP grade 1, 248 were grade 2, 69 were grade 3, 39 were grade 4, and 11 were grade 5. No statistically significant difference was determined between the groups with and without PNI in respect of the ISUP grades (p=0.265).

Of the 747 patients who underwent nerve-sparing surgery, the surgical margin was determined as positive in 126 (16.8%) patients. When examining surgical margin positivity between the PNI (+) and PNI (-) groups, the PNI (+) group exhibited a statistically significant higher rate (25.9%) compared to the PNI (-) group (14.4%) with a p-value of 0.001.

The mean follow-up period was 58.6 months and the 5-year biochemical RFS was 89.7%. The 5-year biochemical RFS was 90% in the PNI (+) patients and 89.6% in the PNI (-) group, with no significant difference determined between the groups (p=0.909) (Figure 1).

Biochemical RFS rates were compared according to the surgical margin positivity status, and 5-year biochemical RFS was found to be 81.5% in those with surgical margin positivity and 91.6% in those with surgical margin negativity, with no statistically significant difference determined between the groups (p=0.097) (Figure 2).

Discussion

The relationship between the biopsy finding of PNI in PCa and the pathological characteristics in RP or progression after definitive treatment has been the subject of research in several studies. Lee et al. (14) examined the relationship between PNI in biopsies and the pathological characteristics in RP, and showed that in all risk groups, the biopsy finding of PNI was valuable in predicting surgical margin positivity and pathological grade T3 disease.

Similarly, in a study by Kang et al. (19), PNI in PCa patients applied with RP was shown to be a negative pathological parameter and an independent predictor of BCR (20).

Yu et al. (21) reported that PNI was an independent riak factor associated with an increased risk of biochemicial recurrence in PCa patients applied with radiotherapy.

Although there are also studies reporting the contrary, according to a recent meta-analysis, which included 19 studies and 13,412 patients, of which 4,197 (31.2%) had PNI, the determination of PNI in PCa patients who underwent RP or radiotherapy was associated with a higher risk of BCR (22-25).

Although many studies have shown that PNI in biopsy is a significant risk factor related to adverse events following RP, there is a limited amount of literature related to the role of PNI at the stage of decision-making for nerve-sparing surgery.

In a study published in 2010 by Loeb et al. (25), in which all the operations were performed by P. Walsh, it was reported that PNI positivity increased the rate of biochemical progression approximately 3-fold, but biochemical progression was not affected by PNI positivity in patients who underwent bilateral nerve-sparing surgery. With a mean follow-up period of 2.8 years in that study, which compared 113 PNI-positive patients with 956 PNI-negative patients who underwent bilateral nerve-sparing surgery, it was determined that nerve-sparing surgery reduced the risk of progression in PNI-positive patients (25).

The mean follow-up duration for the participants in this study was 58.6 months, revealing a 5-year biochemical RFS rate of 89.7%. The 5-year biochemical RFS rates were found to be 90% in patients with PNI (+) and 89.6% in those with PNI (-), showing no statistically significant difference between the two groups.

In the above-mentioned study by Loeb et al. (25), no significant difference was determined in respect of surgical margin positivity

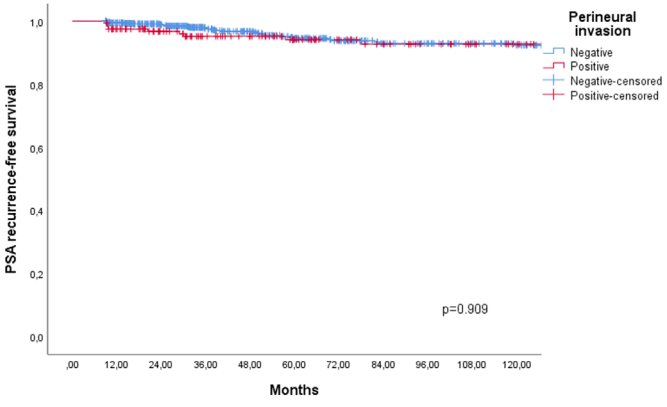

Figure 1. Probability estimates of biochemical RFS in perineural invasion negative and positive patients

RFS: Recurrence-free survival, PSA: Prostate-specific antigen

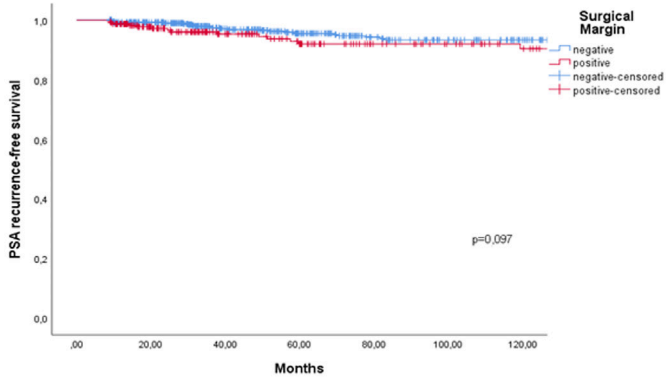

Figure 2. Probability estimates of biochemical RFS in surgical margin negative and positive patients

RFS: Recurrence-free survival, PSA: Prostate-specific antigen

in the patients with PNI who underwent nerve-sparing surgery. However, in the current study, surgical margin positivity was determined as 25% in PNI (+) patients who underwent nerve-sparing RP and 14.4% in the PNI (-) patients, and the difference was statistically significant.

Despite a seemingly shorter RFS in individuals with surgical margin positivity, the analysis showed no statistically significant difference in 5-year biochemical RFS between the groups in this patient cohort.

Study Limitations

Our study has notable limitations, primarily stemming from its retrospective design and analysis.

Additionally, there was no centralized pathological examination. Another significant limitation is the absence of data on pathological examination of patients regarding unilateral or bilateral PNI in the prostatic biopsy specimens.

Conclusion

The findings from this study indicated that the presence of PNI identified in the prostate biopsy did not have an impact on the 5-year biochemical RFS after nerve-sparing RP. Nevertheless, there is a need for further more comprehensive prospective and retrospective studies with longer follow-up periods to confirm these findings.

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Ethics

Ethics Committee Approval: Since this study is designed as a database report ethics committee approval was not obtained.

Informed Consent: Retrospective study.

Authorship Contributions

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

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Original Article

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Can We Predict Recurrence of pT1-2 Renal Cell Carcinoma?

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Abstract

Objective: Some prognostic models have been described for localized and metastatic renal cell carcinoma (RCC). The European Association of Urology guidelines on RCC recommend using these models. However, there is no model for T1 and T2. The study evaluated the risk factors for recurrence in T1 and T2 RCC.
Materials and Methods: Data of 4823 renal tumor patients from the Renal Tumor Database of the Association of Urooncology in Turkey were evaluated. Of 4823 patients, 1845 RCC patients with pathological T1 or T2 were included in this study. The patients were divided into two groups according to the recurrence status. Anatomical, histological, and clinical prognostic factors were statistically compared between the groups. Afterwards, multivariate analysis was performed for the variables that were found to be statistically significant.
Results: The mean follow-up time was 30 (4-180) months. Of 1845 RCC patients, 117 (6.3%) had recurrence. Univariate analysis revealed statistically significant differences between age, preoperative hemoglobin, albumin, neutrophil, alkaline phosphates, platelet and calcium values, histological subtype, Fuhrman grade, surgical technique (radical or partial), and pathological stage in the groups. However, in multivariate analysis, only pathological stage was found to be a risk factor for recurrence (2.17 95%, 1.25-3.77).
Conclusions: The results of our study show that it is difficult to design a prognostic model for the recurrence of pT1 and pT2 RCC. We suggest that patients with a higher tumor diameter should be followed up more frequently.
Keywords: RCC, pT1-2, recurrence, prediction of recurrence

Introduction

Renal cell carcinoma (RCC) is the most frequently occurring renal malignant tumor, accounting for 2-3% of all adult malignant tumors (1). The once classical triad of abdominal mass, pain, and macroscopic hematuria is now recognized to be rare. RCC is incidentally diagnosed at an early stage with the widespread use of ultrasonography and computed tomography in the last two decades. Partial or radical nephrectomy is the standard treatment for cT1-2 RCC. After standard treatment of RCC, the 5-year recurrence rates of T1 and T2 RCC are 9% and 32%, respectively (2). Some prognostic models have been described for predicting recurrence and/or progression in localized and metastatic RCC. The European Association of Urology (EAU) guidelines on RCC recommend using these models (3). However, there is no model for T1 and T2 RCC. The study evaluated risk factors for recurrence in T1 and T2 RCC in Turkey using the Renal Tumor Database of the Turkish Urooncology Association.

Materials and Methods

Data of 4823 patients who underwent partial or radical nephrectomy for RCC from 2000 to 2019 were retrospectively investigated. These data were obtained from the Renal Tumor

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Database of the Turkish Urooncology Association in Turkey. Of 4823 patients, 1845 RCC patients with pathological T1 or T2 stage were included in this study. The pathological stages of the patients were identified according to the TNM 2017 Classification. Exclusion criteria were incomplete data, patients with pathological T3-4 stage and/or metastasis (lymph node and/or distant visceral metastasis), patients aged 18 years, and patients who underwent other procedures without surgical resection, such as microwave or radiofrequency ablation. The Manisa Celal Bayar University Faculty of Medicine Ethics Committee approved the study protocol (decision no: 20.478.486/2044, date: 11.10.2023).

Statistical Analysis

The patients were divided into two groups according to the recurrence status. Anatomical, histological, and clinical prognostic factors were statistically compared between the two groups. Afterwards, multivariate analysis was performed for the variables that were found to be statistically significant. Statistical analysis was performed using the SPSS software package version 22.0 (Statistical Package for Social ScienceTM, Chicago, IL, USA) and $p<0.05$ was considered to be statistically significant.

Results

The mean age of patients (n=1845) was 57.07±12.32. The mean follow-up time was 30 (4-180) months. Of 1845 RCC patients, 117 (6.3%) had recurrence. Univariate analysis revealed statistically significant differences between age, preoperative hemoglobin, albumin, neutrophil, alkaline phosphates, platelet and calcium values, histological subtype, Furhman grade, surgical technique (radical or partial), and pathological stage in the groups. The results of the univariate analysis are presented in Tables 1 and 2. Then, the variables that were found to be statistically significant differences between the two groups were subjected to multivariate analyses. However, in multivariate analysis, only pathological stage was found to be a risk factor for recurrence (2.17 95%, 1.25-3.77).

Discussion

Generally, during the last two decades until recently, there has been an annual increase of approximately 2% in the incidence of RCC both worldwide and in Europe. The higher incidence is hypothesized to be due to a higher prevalence of small renal masses in settings where abdominal imaging is more ubiquitous. In 1993-2004, 54.7%, 10.6%, 16.1%, and 18.6% of clear cell RCC (ccRCC) tumors in the National Cancer Database were classified as stage I, II, III, and IV, respectively (4). In a 2004-2015 Surveillance, Epidemiology, and End Results (SEER) database cohort (77% had ccRCC), the pathologic tumor, node, metastasis (TNM) stage was I (64.3%), II (10.9%), III (16.8%), and IV (8%) (5). Therefore, it is more important to follow-up on local RCC because its incidence has been increasing. The results of this study show that the only prognostic factor in recurrence of local stage RCC (T1 and T2) is the pathological stage of the tumor. This indicates a relationship between tumor size and risk of recurrence. Similar to the results of our study, in a 2004-2015

Table 1. Comparison of demographic data and preoperative laboratory results between the recurrent and non-recurrent groups

		Recurrent group	**Non-recurrent group**	**p-value**
Age (years)	Mean ± SD (n)	61.19±10.62 (145)	56.90±12.40 (1850)	<0.001**
BMI (kg/m^2)	Mean ± SD (n)	28.70±5.33 (28)	28.05±4.86 (534)	0.531
Hospitalization time (days)	Median (n)	5 (77)	4 (1413)	<0.05*
Time (days) from diagnosis to surgery	Median (n)	31 (102)	36 (1628)	0.061
Smoking (pack/year)	Median (n)	5.5 (254)	5 (1850)	0.663
Preoperative laboratory		**Recurrent group**	**Non-recurrent group**	**p-value**
Hemoglobin (g/dL)	Mean ± SD (n)	12.78±2.14 (133)	13.74±1.76 (1755)	<0.001**
White blood count (/µL)	Mean ± SD (n)	8560±2630 (80)	8253±2831 (1452)	0.165
Lymphocyte (/µL)	Mean ± SD (n)	1465±1640 (50)	1177±1265 (1075)	0.205
Neutrophil	Mean ± SD (n)	6191±2599 (51)	5556±1830 (1089)	0.122
Platelet* 1000	Mean ± SD (n)	278.545±94.421 (80)	256.915±77.334 (1446)	<0.05*
Erythrocyte sedimentation rate	Mean ± SD (n)	38.45±38.69 (11)	26.84± 2.87 (111)	0.366
C-reactive protein (mg/L)	Mean ± SD (n)	58.07±89.67 (15)	118.83±239.25 (172)	0.829
Creatinine (mg/dL)	Mean ± SD (n)	0.99±0.36 (136)	0.97±0.68 (1740)	0.100
Aspartate aminotransferase (U/L)	Mean ± SD (n)	21.82±10.69 (66)	22.07±10.55 (1171)	0.070
Alanine transaminase (U/L)	Mean ± SD (n)	22.04±14.95 (65)	23.54±15.39 (1165)	0.344
Alkaline phosphatase (U/L)	Mean ± SD (n)	110.38±77.83 (44)	81.49±32.82 (748)	<0.05*
Lactate dehydrogenase (U/L)	Mean ± SD (n)	196.38±59.74 (47)	213.82±101.49 (587)	0.344
Albumin (g/dL)	Mean ± SD (n)	4.08±0.57 (60)	4.26±0.50 (942)	<0.05*
Calcium (mg/dL)	Mean ± SD (n)	9.30±0.75 (60)	9.44±0.71 (898)	<0.05*

SD: Standard deviation, BMI: Body mass index
*p<0.05 was considered statistically significant,
**p<0.001 was considered statistically significant

SEER database cohort noticed that 5 years survival of T1 and T2 RCC were 97.4% and 89.9%, respectively (5). All of the findings show that tumor size is important for the follow-up of local stage RCC. If the tumor size is larger, we should be more careful in the follow-up of RCC.

Histological subtypes of RCC are another important prognostic factor, and on univariate analysis of some studies, patients with chromophobe RCC vs. papillary RCC vs. ccRCC had a better prognosis (6,7). Univariate analysis of our study showed that the recurrence rate of ccRCC is significantly higher than that of chromophobe and papillary RCC (Table 2). The results of multivariate analyses in our study and previous studies indicated that the histological subtype of RCC is not a prognostic factor for predicting recurrence. EAU Guidelines on RCC noticed that prognostic information provided by the RCC type is lost when stratified according to tumor stage (3).

Sarcomatoid features in RCC have been evaluated as another prognostic factor for predicting recurrence. The findings of our study showed that the recurrence rate of RCC with sarcomatoid differentiations (32.0%) is higher than that of RCC without sarcomatoid features (7.1%) on univariate analysis (Table 2). Trudeau et al. (8) compared 5-year cancer-specific mortality estimates of sarcomatoid RCC (sRCC) and ccRCC. They found that 5-year cancer-specific mortality estimates of sRCC and ccRCC in patients with stage 1-2 RCC were 32% and 6%, respectively. When we analyzed the recurrence rates according to Fuhrman grade, the recurrence rates in RCC patients with Fuhrman grades I, II, III and IV were 1.9%, 6.0%, 14.8% and 32.1%, respectively. This was a statistically significant finding on univariate analysis ($p<0.001$). However, Fuhrman grade, like sarcomatoid features, was not a statistically significant factor in multivariate analysis to predict recurrence in our study.

Preoperative hematological and biochemical parameters in RCC have been investigated as prognostic factors to predict recurrence and create a nomogram or prognostic model. Although some of these parameters are used in prognostic models of Memorial

Table 2. Comparison of gender, preoperative platelet count, surgical technique, postoperative creatinine rise, and pathological features between recurrent and non-recurrent groups

		Recurrent group n (%)	Non-recurrent group n (%)	p-value
Gender	Female	38 (5.4)	667 (94.6)	<0.05*
	Male	107 (8.3)	1183 (91.7)	
Preoperative platelet count *1000	<400	72 (4.9)	1384 (95.1)	<0.05*
	>400	8 (11.4)	62 (88.6)	
Nephrectomy	Partial	23 (2.5)	897 (97.5)	<0.001**
	Radical	120 (11.3)	942 (88.7)	
Postoperative creatinine levels rising	Yes	28 (9.7)	261 (90.3)	<0.05*
	No	43 (4.7)	879 (95.3)	
Pathological features		**Recurrent group n (%)**	**Non-recurrent group n (%)**	**p-value**
T stage	T1a	50 (4.6)	1029 (95.4)	<0.001**
	T1b	54 (8.6)	577 (91.4)	
	T2a	28 (13.8)	175 (86.2)	
	T2b	13 (15.9)	69 (84.1)	
Fuhrman grade	Grade 1	4 (1.9)	209 (98.1)	<0.001**
	Grade 2	55 (6.0)	865 (94.0)	
	Grade 3	53 (14.8)	305 (82.5)	
	Grade 4	17 (32.1)	36 (67.9)	
Surgical margin	Negative	136 (7.3)	1734 (92.7)	0.276
	Positive	3 (3.6)	81 (96.4)	
Pathological necrosis	Yes	17 (9.0)	172 (91.0)	0.450
	No	99 (6.8)	1360 (93.2)	
Sarcomatoid differentiation	Yes	8 (32.0)	17 (68.0)	<0.05*
	No	121 (7.1)	1584 (92.9)	
Microvascular invasion	Yes	7 (16.3)	36 (83.7)	<0.05*
	No	106 (8.0)	1211 (92.0)	
Histological subtypes	Clear cell	125 (8.6)	1323 (91.4)	<0.001**
	Chromophobe	1 (0.4)	223 (99.6)	
	Papillary types 1 and 2	19 (5.9)	304 (94.1)	

*p<0.05 was considered statistically significant,
**p<0.001 was considered statistically significant

Sloan Kettering Cancer Center and International Metastatic Renal-cell Carcinoma Database Consortium Score for metastatic RCC, none of them are used in prognostic models created for localized RCC (3). In our study, some of them were found to be statistically significant prognostic factors for recurrence on univariate analysis in stage 1-2 RCC patients. However, on multivariate analysis, none of them was a statistically significant factor to predict recurrence.

Study Limitations

The limitation of our study is that the rate of recurrence was small because the patients had local stage RCC. Therefore, it was difficult to perform multivariate and subgroup analyses.

Conclusion

The results of our study show that there are some prognostic factors to predict recurrence in patients with T1-2 RCC on univariate analysis. However, on multivariate analysis, only tumor stage was found to be a statistically significant prognostic factor. Therefore, it is difficult to create a prognostic model for T1-2 RCC recurrence. On the other hand, we found that tumor stage in T1-2 RCC is a prognostic factor for recurrence. In summary, the risk of recurrence may increase as the tumor size increases in patients with T1-2 RCC. We suggest that patients with larger RCC should be followed up more carefully.

Ethics

Ethics Committee Approval: The Manisa Celal Bayar University Faculty of Medicine Ethics Committee approved the study protocol (decision no: 20.478.486/2044, date: 11.10.2023).

Informed Consent: Retrospective study.

Authorship Contributions

Concept: O.Ü., T.M., Design: O.Ü., Data Collection or Processing: S.B., V.İ., E.Ö., B.A., S.Y., E.C.B., N.A., S.S., Analysis or Interpretation: G.A., Literature Search: E.S., Writing: O.Ü.

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Original Article

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Do Subgroup Evaluations Provide Additional Contributions to Biochemical Recurrence in Grade Group 4 and 5 Patients? A Multicenter Study by the Turkish Urooncology Association Prostate Cancer Working Group

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Abstract

Objective: To investigate the effect of the International Society of Urological Pathology (ISUP) grade group 4 (GG4) and ISUP GG5 subgroups according to prostate biopsy on biochemical recurrence (BCR).

Materials and Methods: Patients who underwent radical prostatectomy (RP) after being diagnosed with GG4 and GG5 prostate cancer according to prostate biopsy and who had follow-up data were retrospectively evaluated. Patient data were obtained from the Urologic Cancer Database-Prostate of the Turkish Urooncology Association. GG4 and GG5 pathologies were evaluated using Gleason subgroups. The effect of clinicopathological parameters on BCR after RP was investigated separately in the GG4 and GG5 patient groups.

Results: In GG4, 73 of 188 patients developed BCR. When GG4 patients were evaluated for BCR, only lymphovascular invasion was significant for BCR (p=0.004). In addition, seminal vesicle invasion (SVI) and high ISUP grade according to RP pathology were significant in patients with BCR (p=0.004 and p=0.005). In the follow-up of 145 patients with GG5, 80 patients developed BCR. When GG5 patients were evaluated for BCR, no predictive factor was found for developing BCR. However, surgical margin positivity, extraprostatic extension, and SVI after RP were found to be significant in patients with BCR (p=0.031, p=0.011 and p=0.007).

Conclusion: According to our results, the ISUP GG system, which does not include Gleason subgroups, is an appropriate classification system for GG4 and GG5 patients for the prediction of BCR in the Turkish patient population, in parallel with the current literature.

Keywords: Prostate cancer, Gleason score, biochemical recurrence, ISUP grade group

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Introduction

Prostate cancer (PC) is the most common solid organ malignancy in men and the second most common cause of cancer-related death (1). Many studies have reported that a high Gleason score (GS) is a prognostic factor for survival (2,3). For better management of the disease by the clinician, Gleason patterns are combined as primary and secondary patterns to increase their prognostic value (4,5). Tumor grading using grade groups (GG) was first described by Epstein et al. (6) and was validated in a multicenter study (2). This grading was finally approved by the International Society of Urological Pathology (ISUP) in 2014. However, there are studies suggesting that it may be difficult to evaluate these patients under a single group because of the heterogeneity in GG4 and GG5 patients. In this context, there are different biological and oncological outcomes between the subgroups according to these studies (6-9). In addition, another limitation is that cribriform and intraductal tumor variants do not have clear ISUP grading.

The aim of the study was to investigate the effect of Gleason subgroups on biochemical recurrence (BCR) in ISUP GG4 and ISUP GG5 patients according to prostate biopsy and to simultaneously evaluate the possible predictive factors for BCR after radical prostatectomy (RP) in each GG.

Materials and Methods

Patients with data entry completed in the Urological Cancer Database-Prostate of the Turkish Urooncology Association (TUOA) and who underwent RP due to PC and had follow-up data were retrospectively reviewed for this study (TUO-PR-21-04). Among them, patients diagnosed with GG4 and GG5 PC according to prostate biopsy and other clinicopathological parameters were investigated in the study. All parameters obtained from the database, clinical findings (digital rectal examination, preoperative PSA, BMI, prostate volume), multiparametric prostate magnetic resonance imaging findings [PIRADS score, lesion number, lesion size, extracapsular extension (ECE), seminal vesicle invasion (SVI)], prostate biopsy findings [type of biopsy and MR fusion biopsy technique (cognitive or MR fusion and transperineal or transrectal), GS, ISUP GG, total number and percentage of positive cores on biopsy, percentage of cores removed from the lesion and presence of perineural invasion, lymphovascular invasion (LVI), and high-grade prostatic intraepithelial neoplasia] and RP pathological findings [ISUP GG, surgical margin positivity (pSM), ECE, SVI, lymph node status] were evaluated. In addition, according to the follow-up data, the BCR status of the patients was investigated. In parallel with the literature, BCR was considered an increase above 0.2 ng/mL of PSA after falling to undetectable levels (PSA nadir) in the postoperative period (10). All patients and GG patients were assessed according to the BCR status after RP.

Patients who had GG4 on prostate biopsy were divided into three subgroups according to the GS as 4+4, 3+5, and 5+3 subgroups. Similarly, GG5 patients were also divided into three subgroups as GS subgroups of 4+5, 5+4, and 5+5. The effects of these Gleason subgroups and other clinicopathological findings on BCR were separately investigated for each GG.

Statistical Analysis

The study data were obtained from Research Electronic Data Capture (REDCap) electronic data tools hosted by TUOA (11,12). REDCap is a secure, web-based software platform designed to support data capture for research studies. In the statistical analysis, the t-test, Mann-Whitney U test and χ^2 test were used to analyze continuous and categorical variables according to BCR status. Values of $p<0.05$ were considered statistically significant.

Results

In this study, 188 and 145 patients with GG4 and GG5 were investigated, respectively. In the follow-up of the GG4 patients, 73 (38.8%), 13 (6.9%), and 21 (11.1%) patients developed BCR, castration-resistant prostate cancer (CRPC), and metastasis, respectively. In the follow-up of GG5, 80 (55.2%), 31 (21.4%), and 27 (18.6%) patients developed BCR, CRPC, and metastasis, respectively. Lymph node dissection (LND) was performed in 155 patients (82.4%) and 130 patients (89.7%) in GG4 and GG5. None of the patients received neoadjuvant androgen deprivation therapy (ADT). Among GG4 and GG5 patients, 76 (40.4%) and 79 (54.5%) received additional treatment because of the development of BCR after RP ± LND, respectively. In GG4, 38 (20.2%), 15 (8%) and 6 (3.2%) patients received only radiotherapy (RT), RT + ADT and only ADT, respectively. In GG5, 42 (29%), 24 (16.5%), and 3 (2.1%) patients received only RT, RT + ADT and only ADT, respectively.

For evaluating GG4 patients, clinicopathological data and comparison results according to BCR status are given in Table 1 and 2. According to the results, only the presence of LVI on biopsy was found to be significantly higher in the BCR group (p=0.004). For RP pathological findings, while pSM (p=0.054), ECE (p=0.078) and LND status (p=0.35) were similar, SVI and high ISUP grade were significantly higher in the BCR group (p=0.004 vs p=0.005 respectively).

For evaluating GG5 patients, clinicopathological data and comparison results according to BCR status are given in Table 3 and 4. In this cohort, pSM (p=0.031), ECE (p=0.011) and SVI (p=0.007) on RP pathology were found to be higher in the BCR0-positive group.

For each GG4 and GG5 group, the Gleason subgroup according to biopsy pathology did not affect BCR after RP.

Discussion

In this study, the effect of Gleason subgroups on BCR was investigated separately in GG4 and GG5 patients according to prostate biopsy. Although the hypothesis of our study was that Gleason subgroups have a possible effect on BCR in GG4 and GG5 patients, it could not be demonstrated for the GG groups in our cohort. However, in GG4 patients in our cohort, only one factor (LVI) on prostate biopsy and two factors (SVI and high GG) on RP pathology were associated with BCR after RP. For GG5 patients in our cohort, no factor was found on prostate biopsy, and three factors (pSM, ECE, and SVI) on RP pathology were related to BCR after RP.

Validation studies for PC grading combine a GS of 8 into a single prognostic group (13). However, according to previous

Table 1. Grade group 4 patient's clinical and demographical features				
GG 4		**No BCR (n=115)**	**BCR (n=73)**	**p-value**
Digital rectal examination	Benign	96 (88.1%)	53 (79.1%)	0.084
	Malign	13 (11.9%)	14 (20.9%)	
Extracapsular extention on MRI	Positive	4 (28.6%)	0 (0%)	0.258
	Negative	10 (71.4%)	5 (100%)	
Seminal vesicle invasion on mpMRI	Positive	1 (7.2%)	1 (16.7%)	0.521
	Negative	13 (92.8%)	5 (83.3%)	
Targeted lesion side on mpMRI	Right	19 (90.5)	7 (77.8%)	0.547
	Left	2 (9.5%)	2 (22.2%)	
Targeted lesion location on mpMRI	Anterior	11 (84.6%)	4 (80%)	0.868
	Posterior	2 (15.4%)	1 (20%)	
Targeted lesion area on mpMRI	Apex	16 (80%)	9 (90%)	0.413
	Mid	3 (15%)	0 (0%)	
	Base	1 (5%)	1 (10%)	
Prostate biopsy technique	Transperineal	2 (16.7%)	1 (16.7%)	0.730
	Transrectal	10 (83.3%)	5 (83.3%)	
PIRADS	3	0 (0%)	1 (11.1%)	0.130
	4	11 (52.4%)	2 (22.2%)	
	5	10 (47.6%)	6 (66.7%)	
PSA (ng/mL)		13.1±16.6	16.2±19.4	0.273
BMI		28.6±3.3	28.7±1.4	0.317
Prostate volume		40.9±19.3	37.9±17.9	0.460
Targeted lesion length (mm)		17.1±7.2	19.0±7.0	0.509
Positive core number		4.5±2.9	5.6±3.4	0.083
Positive core ratio (%)		65.4±30.2	73.6±29.5	0.141
Biopsy technique	Conventional	103 (88.6%)	67 (91.8%)	0.408
	MRI directed	12 (11.4%)	6 (8.2%)	
Number of targeted lesion		2.1±1.2	1±0	0.060

BCR: Biochemical recurrence, GG: Grade groups, mpMRI: Multiparametric prostate magnetic resonance imaging, PSA: Prostate-specific antigen, BMI: Body mass index

Table 2. Grade group 4 patient's biopsy and radical prostatectomy pathology results				
GG 4		**No BCR (n=115)**	**BCR (n=73)**	**p-value**
Biopsy ISUP subgroups	3+5	19 (16.5%)	9 (12.3%)	0.289
	4+4	94 (81.7%)	60 (82.2%)	
	5+3	2 (1.8%)	4 (5.4%)	
Biopsy PNI positivity	Positive	25 (28.7%)	21 (41.2%)	0.096
	Negative	62 (71.3%)	30 (58.8%)	
Biopsy LVI positivity	Positive	1 (1.2%)	7 (14%)	0.004
	Negative	85 (98.8%)	43 (86%)	
Biopsy HGPIN	Positive	13 (15.6%)	10 (20.4%)	0.320
	Negative	70 (84.4%)	39 (79.6%)	
RP PSM	Positive	53 (46.4%)	43 (59.7%)	0.054
	Negative	61 (53.6%)	29 (40.3%)	
RP ECE positivity	Positive	52 (46.8%)	39 (59.1%)	0.078
	Negative	59 (53.2%)	27 (40.9%)	
RP SVI	Positive	28 (24.6%)	32 (44.4%)	0.004
	Negative	86 (75.4%)	40 (55.6%)	
Lymph node invasion	Positive	93 (89.4%)	62 (84.9%)	0.35
	Negative	21 (10.6%)	11 (15.1%)	
RP grade group	1	6 (5.3%)	3 (4.1%)	0.005
	2	31 (26.9%)	7 (9.6%)	
	3	29 (25.2%)	16 (21.9%)	
	4	30 (26.1%)	20 (27.4%)	
	5	19 (16.5%)	27 (37.0%)	

BCR: Biochemical recurrence, GG: Grade groups, ISUP: International Society of Urological Pathology, PNI: Perineural invasion, LVI: Lymphovascular invasion, HGPIN: High-grade prostatic intraepithelial neoplasia, RP: Radical prostatectomy, PSM: Surgical margin positivity, ECE: Extracapsular extension, SVI: Seminal vesicle invasion

Table 3. Grade group 5 patient's clinical and demographical features				
GG 5		No BCR (n=65)	BCR (n=80)	p-value
Digital rectal examination	Benign	49 (82.1%)	58 (81.7%)	0.513
	Malign	10 (16.9%)	13 (18.3%)	
Extracapsular extention on MRI	Positive	3 (42.9%)	5 (71.4%)	0.296
	Negative	4 (57.1%)	2 (28.6%)	
Seminal vesicle invasion on mpMRI	Positive	1 (12.5%)	5 (62.5%)	0.059
	Negative	7 (87.5%)	3 (37.5%)	
Targeted lesion side on mpMRI	Right	10 (90.9%)	8 (72.7%)	0.500
	Left	1 (9.1%)	3 (27.3%)	
Targeted lesion location on mpMRI	Anterior	7 (100%)	7 (77.8%)	0.248
	Posterior	0 (0%)	2 (22.2%)	
Targeted lesion area on mpMRI	Apex	10 (90.9%)	7 (70%)	0.609
	Mid	1 (9.1%)	2 (20%)	
	Base	0 (0%)	1 (10%)	
Prostate biopsy technique	Transperineal	2 (25%)	1 (12.5%)	0.500
	Transrectal	6 (75%)	7 (87.5%)	
PIRADS	3	1 (8.3%)	0 (0%)	0.280
	4	3 (25.0%)	1 (9.1%)	
	5	8 (66.7%)	9 (81.8%)	
PSA (ng/mL)		18.2±24.9	35.8±139.6	0.074
BMI		26.8±2.6	27.8±4.5	0.352
Prostate volume		58.6±36.0	43.5±30.3	0.104
Targeted lesion length (mm)		17.1±6.8	21.7±5.8	0.131
Positive core number		6.4±3.6	7.0±3.6	0.514
Positive core ratio (%)		72.5±30.5	80.2±26.9	0.215
Biopsy technique	Conventional	57 (87.7%)	72 (90%)	0.428
	MRI directed	8 (12.3%)	8 (10%)	
Number of targeted lesion		1.88±1.8	1.75±1.2	0.749

BCR: Biochemical recurrence, GG: Grade groups, mpMRI: Multiparametric prostate magnetic resonance imaging, PSA: Prostate-specific antigen, BMI: Body mass index

studies, in both 3+5 and 5+3 subgroups of GG4 patients, the proportional excess of the Gleason 3 pattern is considered protective in terms of oncologic outcomes. In addition, it was suggested that 3+5 has the same results as GG2, whereas tumors with 5+3 should be grouped together with GG5 (14). The presence of GS 5 was the strongest pathologic predictor of BCR, metastasis, and cancer-specific mortality (CSM). In this context, the presence of GS 5 may play an important role in oncologic outcomes within GG4 and classifying these patients into a single category (GG4) may be insufficient to assess the subgroups of patients (GSs of 3+5, 4+4 and 5+3) (6,15). In parallel, another study reported that the mortality in the subgroup of GS 5+3 patients was almost doubled compared with GS 4+4 patients. A difference in mortality was not detected between patients with GSs of 3+5 and 4+4. This situation shows that different oncologic results may be obtained for the GG4 subgroups (8). However, our results do not support the importance of a primary GS 5 in GG4 patients for BCR after RP. In conclusion, our results are consistent with the validation studies.

For GG5 patients, there was a similar discussion that the presence of GS 5 and primary GS 5 indicated worse oncologic outcomes. In a study, for CSM, GSs 5+4 or 5+5 were detected to be disadvantageous compared with GSs of 4+5. It was also stated that the rarest subtype was Gleason 5+5 (9.9%), whereas Gleason 5+4 was found in 19.1% of cases. The 10-year CSM was found to be highest in the 5+5 subgroup (39.1%), followed by 5+4 (28%) and 4+5 (18.2%) subgroups (16).

In another study, the authors suggested that biopsy GSs 4+5, 5+4, and 5+5 should be evaluated separately in pretreatment risk stratification because of differences in CSM (17), contrary to Epstein et al. (13). However, the patient distribution and scarcity of subgroups of GG5 make it difficult to evaluate this group. As such, the Cancer of the Prostate Strategic Urologic Research Endeavor - based study evaluated 225, 81 and 48 patients treated with both RP and EBRT in the GS 4+5, 5+4 and 5+5 subgroups according to biopsy, respectively (17). Similar results were obtained in other studies due to the sample size (18,19). Although the discussion in this field is ongoing, our results obtained from 145 patients show that there is no difference in BCR after RP between the subgroups of GG5 patients.

Study Limitations

First, because of its multicenter nature, patient selection and evaluation of adjuvant and salvage therapies may be heterogeneous. Second, only the effect on BCR was investigated

Table 4. Grade group 5 patient's biopsy and radical prostatectomy pathology results				
GG 5		**No BCR (n=65)**	**BCR (n=80)**	**p-value**
Biopsy ISUP subgroups	4+5	48 (73.8%)	52 (65%)	0.375
	5+4	14 (21.5%)	20 (25%)	
	5+5	3 (4.7%)	8 (10%)	
Biopsy PNI	Positive	22 (40.7%)	36 (53.7%)	0.108
	Negative	32 (59.3%)	31 (42.3%)	
Biopsy LVI	Positive	7 (13.5%)	11 (16.7%)	0.415
	Negative	45 (86.5%)	55 (83.3%)	
Biopsy HGPIN	Positive	10 (20%)	8 (12.3%)	0.320
	Negative	40 (80%)	57 (87.7%)	
RP PSM	Positive	39 (60%)	60 (75.9%)	0.031
	Negative	26 (40%)	19 (24.0%)	
RP ECE	Positive	32 (53.3%)	56 (73.7%)	0.011
	Negative	28 (46.7%)	20 (26.3%)	
RP SVI	Positive	27 (41.5%)	50 (63.3%)	0.007
	Negative	38 (58.5%)	29 (36.7%)	
Lymph node invasion	Positive	61 (93.8%)	69 (87.3%)	0.152
	Negative	4 (6.2%)	10 (12.7%)	
RP grade group	1	0 (0%)	1 (1.25%)	0.091
	2	2 (3.1%)	2 (2.5%)	
	3	13 (20%)	5 (6.25%)	
	4	7 (10.8%)	6 (7.5%)	
	5	43 (66.1%)	66 (82.5%)	

BCR: Biochemical recurrence, GG: Grade groups, ISUP: International Society of Urological Pathology, PNI: Perineural invasion, LVI: Lymphovascular invasion, HGPIN: High-grade prostatic intraepithelial neoplasia, RP: Radical prostatectomy, PSM: Surgical margin positivity, ECE: Extracapsular extension, SVI: Seminal vesicle invasion

because of the difficulty in obtaining survival data. Third, pathology was not evaluated in a single center, and patients were dependent on their own pathologists for identification and reporting of GSs. All these limitations raise concerns about the generalizability of the study. However, our results reflect real-world data in a limited patient population.

Conclusion

In conclusion, evaluations of GG4 and GG5 patients according to GS subgroups (GG4: 4+4, 3+5 and 5+3; GG5: 4+5, 5+4 and 5+5) found no significant differences in terms of BCR after RP. Accordingly, the ISUP GG system that does not include Gleason subgroups for GG4 and GG5 patients is an appropriate classification system for the prediction of BCR after RP in the Turkish patient population. Prospective studies with homogeneous patient distribution will provide stronger evidence in the future.

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Ethics

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Authorship Contributions

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Original Article

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Prognostic Values of Inflammatory Markers in Patients with High-grade Lamina Propria-invasive Bladder Cancer

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Abstract

Objective: In this study, we investigated the prognostic values of various pathological and inflammatory parameters in patients with high-grade lamina propria-invasive (T1G3) bladder cancer (BC).

Materials and Methods: Between 2006 and 2018, patients with pathological evaluation of T1G3 bladder urothelial carcinoma in our institution who did not meet the exclusion criteria were included in the study. Parameters such as gender, tumor diameter, tumor number, lamina propria invasion depth, presence of carcinoma *in situ*, presence of lymphovascular invasion (LVI), presence of variant histology, lymphocyte monocyte ratio (LMR), platelet lymphocyte ratio (PLR), neutrophil lymphocyte ratio (NLR), and systemic inflammatory markers (SIM) were statistically analyzed.

Results: After the exclusion criteria were evaluated, 76 patients were included in the study from 157 patients. Recurrence was observed in 37 (48.68%) patients, and progression was observed in 21 (27.63%) patients. A significant relationship was discovered between LMR (p<0,001), PLR (p<0.004), NLR (p<0.002), tumor diameter (p<0.002), number of tumors (p<0,007), and SIM score (p<0,001) with the probability of recurrence. The probability of progression was associated with NLR (p<0.023), LVI (p<0.005), tumor diameter (p<0.012) and tumor number (p<0.001). A significant relationship was found between SIM (p<0.041) and recurrence-free survival. We found a significant relationship between LVI (p<0.022) and progression-free survival.

Conclusions: In this study, we found positive correlations between some inflammatory markers and recurrence/progression in patients with T1G3 BC. According to our study, inflammatory parameters such as NLR, PLR, LMR, and SIM score should be evaluated while investigating the possibility of recurrence/progression in patients with T1G3 BC.

Keywords: Non-muscle invasive bladder cancer, high-risk bladder cancer, neutrophil-lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, progression, recurrence-free survival

Introduction

Bladder cancer (BC) is the tenth most frequent cancer in the world and the seventh most prevalent cancer among men. The global incidence for men is 9.5 per 100,000 population/year, whereas for women it is 2.4 (1). At the time of diagnosis, 75% of BCs are non-muscle invasive (NMIBC) (2). Progression occurs in approximately 1 in every 5 individuals with lamina propria-invasive high-grade (T1G3) BC (3,4). The European Organization for Research on Treatment of Cancer (EORTC) and the Spanish Urology Association for Oncological Treatment (CUETO) nomograms use a variety of clinical and pathological variables to predict recurrence and progression in NMIBC patients (5,6). Individuals with diverse pathologic data were classified as very high-risk according to the European Association of Urology (EAU) CIOMC 2014 recommendation. For patients in the very high-risk group, the guidelines suggest an early cystectomy (7). In BCG-refractory tumors, early cystectomy is also advised. Delayed early cystectomy is associated with lower cancer-specific survival (8). However, the presence of lymphovascular invasion (LVI) and the presence of some variant histology (VH), which are suggested for early cystectomy in the EAU NMIBC guidelines, were not validated in the nomograms. Among the inflammatory parameters in the literature, neutrophil lymphocyte ratio (NLR) (9), platelet lymphocyte ratio (PLR) (10) and systemic inflammatory markers (SIM) score (11) were associated with recurrence, and NLR (9), lymphocyte monocyte ratio (LMR) (12) and SIM score (11) were associated with progression.

Therefore, in this study, the prognostic value of pathological parameters such as depth of lamina propria invasion, VH, and

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LVI, as well as inflammatory parameters such as NLR, PLR, LMR, and SIM score were evaluated in patients with T1G3 BC.

Materials and Methods

Before starting the study, the approval of the Çukurova University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (decision no: 77, date: 04.05.2023) was obtained.

Inclusion and Exclusion Criteria

This study included patients with T1G3 bladder urothelial carcinoma who underwent pathologic examinations at our institution department of pathology between 2006 and 2018. The patients' data were reviewed retrospectively. Patients who met any of the following criteria were excluded:

- Patients with a history of upper urinary tract urothelial carcinoma before bladder transurethral resection (TURB).

- Patients who underwent incomplete TURB due to tumor load, followed by an early cystectomy and/or chemotherapy and/or radiation.

- Patients with any clinical, pathologic, or prognostic data that were unknown.

- Patients with recurrent T1G3 BC whose included specimens were not the first T1G3 specimens.

- Patients who underwent early cystectomy for various reasons.

- Patients who underwent part of their diagnosis and treatment at an outside facility and did not fulfill any of the study exclusion criteria were included in the trial.

Patient Follow-up

Every three months, cystoscopy and urine cytology were performed in accordance with the EAU NMIBC guidelines (7). The same urologist conducted a re-TURB within 2 to 6 weeks of the original TURB (5). The re-TURB treatment involved removal of the bladder's hyperemic patch-like lesions and the tumor scar and baseline. According to the EAU guidelines, each patient underwent adjuvant and 1-3 years of maintenance intravesical BCG treatment (7).

Pathological Evaluation

All specimens were analyzed using standard pathologic methods and staged using the tumor, node, metastasis classification from 2009. Tumor grade was determined using the World Health Organization's 1973 methodology. The presence of tumor cells in an endothelium-covered area without a submuscular layer is termed as LVI (13). If micropapillary, neuroendocrine, sarcomatoid, nested, microcystic, or plasmacytoid variants were found, the histology was marked as VH (14).

The pathology materials of the patients included in the study were re-examined by a single uropathologist, and the depth of lamina-propria, existence of concurrent LVI, presence of concurrent carcinoma *in situ* (CIS), and presence of VH were all re-examined and included in the study.

The depth of the lamina-propria was evaluated by the invasion of the muscularis mucosa (MM) and vascular plexus (VP). Patients without MM-VP invasion were focally invaded, whereas those who did have MM-VP invasion were termed diffusely invaded.

Laboratory Evaluation

Blood samples taken one month before TURB were used to determine the patients' inflammatory parameters. Because the receiver operating characteristic (ROC) analysis was not significant, the NLR, PLR, and LMR threshold values in the reference publications were used. NLR, PLR, and LMR were divided into 2.5, 150, and 3.41, respectively, based on previously used thresholds in the literature (10,15,16). The SIM score was determined based on positive responses to these thresholds, with 1 point awarded for any value over the set threshold, and these values were then combined to yield a final score between 0 and 3.

Prognose Definition

The emergence of tumors at any time after TURB was classified as recurrence, and advancement was defined as the development of invasion to the muscle layer or clinical T3,4 and/or clinical N1,2 and/or clinical M1 disease in TURB performed after TURB.

The statistical impact of pathologic and clinical factors on the probability of recurrence, probability of progression, recurrence-free survival (RFS), and progression-free survival (PFS) were investigated. RFS was determined as the time to recurrence, whereas PFS was determined as the time to progression.

Statistical Analysis

SPSS version 17.0 software was used for statistical analysis. Histogram plots and the Kolmogorov-Smirnov test were used to assess the variables' conformance to the normal distribution. Descriptive analyses are presented using mean, standard deviation, and median values. The Pearson chi-square test was used to compare categorical variables. The Mann-Whitney U test was used to compare two groups of variables that were not normally distributed (non-parametric). Because the ROC analysis for LMR, PLR, and NLR cut off values were not significant, meta-analysis cut-off values were used as a basis (11). The variables influencing recurrence and progression were determined using Kaplan-Meier analysis, and the effect coefficients were discovered using Cox regression analysis for significant variables. P-values less than 0.05 were considered statistically significant.

Results

Seventy-six patients with T1G3 BC were included in the study between 2006 and 2018. Eleven (14.47%) patients were female and 65 (85.53%) were male. The mean age of patients was 66.28±9.58. The median duration of follow-up was 43.89±31.54 months, the median RFS was 10.16±14.18 months, and the median PFS was 16.10±12.28 months. Recurrence occurred in 37 individuals (48.68%) and progression occurred in 21 patients (27.63%) (Table 1).

A significant relationship was discovered between LMR ($p<0.001$), PLR ($p<0.004$), NLR ($p<0.002$), tumor diameter ($p<0.002$), number of tumors ($p<0.007$), and SIM score ($p<0.001$) with the probability of recurrence. Patients with LMR <3.41, PLR ≥150, NLR ≥2.5, tumor diameter ≥3, tumor number

≥8, and SIM score 3 had a greater recurrence rate (Table 2). When the probability of progression was compared, NLR (p<0.023), LVI (p<0.005), tumor diameter (p<0.012), and tumor number (p<0.001) were all substantially linked with progression. Patients with NLR ≥2.5, presence of LVI, tumor diameter ≥3, and tumor number ≥8 had a greater rate of progression (Table 2). Factors influencing PFS were investigated. Accordingly, a significant relationship was found between the SIM score (p<0.041) and RFS. The recurrence rate was also found to be high in patients with high SIM scores (Table 3). The factors that influence PFS were investigated, and a significant relationship between LVI (p<0.041) and PFS was found (Table 3). It was determined that the presence of LVI adversely affected progression. The presence of LVI increased progression by 0.288 times (95% confidence interval: 0.090-0.915).

Table 1. Demographics and characteristics of the study population

		n	%
LMR	<3.41	35	(46.05)
	≥3.41	41	(53.95)
PLR	<150	51	(67.11)
	≥150	25	(32.89)
NLR	<2.5	34	(44.74)
	≥2.5	42	(55.26)
Focal/deep submucosal invasion	Focal	31	(40.79)
	Deep	45	(59.21)
Presence of the CIS	Yes	37	(48.68)
	No	39	(51.32)
Presence of lymphovascular invasion	Yes	9	(11.84)
	No	67	(88.16)
Gender	Man	65	(85.53)
	Woman	11	(14.47)
Age	<60	15	(19.74)
	60-70	32	(42.11)
	>70	29	(38.16)
Tumour diameter (cm)	<3	43	(56.58)
	≥3	33	(43.42)
Tumour number	1	34	(44.74)
	2-7	31	(40.79)
	≥8	11	(14.47)
SIM score	0.00	26	(34.21)
	1.00	15	(19.74)
	2.00	18	(23.68)
	3.00	17	(22.37)
Presence of variant histology	Yes	9	(11.84)
	No	67	(88.16)
Relapse	Yes	37	(48.68)
	No	39	(51.32)
Progression	Yes	21	(27.63)
	No	55	(72.37)
Follow-up time (month)		43.89±31.54	36.00 (3.00-150.00)
Recurrence time (month)		10.16±14.18	6.00 (1.00-84.00)
Progression time (month)		16.10±12.28	12.00 (2.00-45.00)

LMR: Lymphocyte monocyte ratio, PLR: Platelet lymphocyte ratio, NLR: Neutrophil lymphocyte ratio, CIS: Carcinoma *in situ*, SIM: Systemic inflammatory markers

Discussion

In contrast to the meta-analysis of data from 15,123 T1G3 patients (17), T1 subgrouping was performed using the T1 a, b, c system, and prognostic factors in NMIBC patients were investigated. Deep lamina propria invasion was found to be ineffective on progression probability and PFS. T1 subgrouping was performed in the present study based on MM-VP invasion. In one study, T1 subgrouping was performed based on T1a, b, c, and MM-VP invasion, and diffuse invasion was found to be associated with progression in the T1a, b, c system, whereas extensive invasion was found to be unrelated to progression in MM-VP invasion subgrouping (18). If the patient group of the present study had been subdivided according to the T1a, b, and c system, a relationship between the possibility of progression with deep invasion and PFS may have been uncovered.

LVI was found to be a risk factor for progression in a meta-analysis of 3,905 patients in 2014 (19). Similar to this meta-analysis, LVI was found to be effective on PFS in both univariate and multivariate analyses. In the current research, as in a previous study involving 1,289 T1G3 patients, no correlation was found between the presence of LVI and relapse (20). The EAU Guideline emphasizes that patients with LVI have a very high-risk of developing the disease and that early cystectomy should be performed in these patients (7). From this perspective, the presence of LVI in the patient group of the current study is associated with PFS, which is also consistent with the guidelines.

According to the CUETO study, 34% of T1G3 patients had CIS (5). In the current study, CIS ratio was 48.68% (37 patients) of T1G3 patients. The probability of progression was higher in the T1G3 + CIS group than in the T1G3 group, the probability of relapse was similar in the EORTC study, and the probability of both relapse and progression was higher in the T1G3 + CIS group than in the T1G3 group in the CUETO study (4-6). Unlike the EORTC and CUETO studies, the presence of CIS in T1G3 disease had no effect on the likelihood of relapse, progression, RFS, or PFS. This could be because of the small number of patients included in the study.

The presence of VH was found to be effective on both relapse and progression in a study involving 1,289 T1G3 patients (20). Furthermore, the EAU Guideline emphasizes that the presence of VH indicates very high-risk disease and that early cystectomy should be performed in these patients (7). There are only 9 patients with VH in our data. The lack of association between VH and progression may be due to the small number of patients with VH.

In the present study, NLR was found to have an effect on the probability of relapse and progression, similar to a meta-analysis involving 1,046 T1G3 patients (9). In a study examining the factors that influence muscle invasion, the PLR cut-off value was determined to be 218 in TURB patients, and similar to the current

Table 2. Probability of recurrence and progression

		Recurrence				p-value	Exp (B) 95% CI	p-value	Progression				p-value	Exp (B) 95% CI	p-value
		Yes		No					Yes		No				
		n	%	n	%				n	%	n	%			
Age	<60	8	53.33	7	46.67	0.917			6	40	9	60	0.276		
	60-70	15	46.88	17	53.13				6	1,875	26	81.25			
	>70	14	48.28	15	51.72				9	31.03	20	68.97			
Gender	Man	30	46.15	35	53.85	0.283			17	26.15	48	73.85	0.484		
	Woman	7	63.64	4	36.36				4	36.36	7	63.64			
Tumour diameter (cm)	<3	16	37.21	27	62.79	0.002	0.392 (0.119-1,286)	0.122	7	16.28	36	83.72	0.012	2,373 (0.796-7,077)	0.121
	≥3	21	63.64	12	36.36				14	42.42	19	57.58			
Tumour number	1	16	47.06	18	52.94	0.007	1.938 (0.569-6,601)	0.140	8	23.53	26	76.47	0.001	0.596 (0.196-1,814)	0.240
	2-7	11	35.48	20	64.52				5	16.13	26	83.87			
	≥8	10	90.91	1	9.09				8	72.73	3	27.27			
Focal/deep Submucosal invasion	Focal	14	45.16	17	54.84	0.610			6	19.35	25	80.65	0.180		
	Deep	23	51.11	22	48.89				15	33.33	30	66.67			
Presence of the CIS	Yes	18	48.65	19	51.35	0.995			13	35.14	24	64.86	0.154		
	No	19	48.72	20	51.28				8	20.51	31	79.49			
Presence of lymphovascular invasion	Yes	7	77.78	2	22.22	0.063			6	66.67	3	33.33	0.005	0.351 (0.054-2,270)	0.271
	No	30	44.78	37	55.22				15	22.39	52	77.61			
Presence of variant histology	Yes	5	13.51	4	10.26	0.660			3	14.29	6	10.91	0.684		
	No	32	86.49	35	89.74				18	85.71	49	89.09			
LMR	<3.41	25	71.43	10	28.57	<0.001	4.636 (0.905-23,748)	0.066	12	34.29	23	65.71	0.231		
	≥3.41	12	29.27	29	70.73				9	21.95	32	78.05			
PLR	<150	19	37.25	32	62.75	0.004	0.399 (0.108-1,472)	0.168	13	25.49	38	74.51	0.551		
	≥150	18	72.00	7	28.00				8	32.00	17	68.00			
NLR	<2.5	10	29.41	24	70.59	0.002	1.251 (0.250-6,265)	0.786	5	14.71	29	85.29	0.023	2,846 (0.974-8,313)	0.056
	≥2.5	27	64.29	15	35.71				16	38.10	26	61.90			
SIM score	0	6	23.08	20	76.92	0.001	1.088 (0.256-4,628)	0.993	4	15.38	22	84.62	0.289		
	1	6	40.00	9	60.00				5	33.33	10	66.67			
	2	11	61.11	7	38.89				5	27.78	13	72.22			
	3	14	82.35	3	17.65				7	41.18	10	58.82			

Chi-square test binary logistic regression, CI: Confidence interval, LMR: Lymphocyte monocyte ratio, PLR: Platelet lymphocyte ratio, NLR: Neutrophil lymphocyte ratio, SIM: Systemic inflammatory markers, CIS: Carcinoma *in situ*

Table 3. Recurrence free survival and progression free survival statistics

		Recurrence free-survival						Progression free-survival					
		Estimate	95% CI		p-value	Exp (B) 95% CI	p-value	Estimate	95% CI		p-value	Exp (B) 95% CI	p-value
			Lower bound	Upper bound					Lower bound	Upper bound			
Age	<60	12,750	8,887	16,613	0.382			20,667	10,238	31,095	0.416		
	60-70	10,933	0,245	21,622				11,667	5,496	17,837			
	>70	7,857	4,177	11,538				16,000	6,691	25,309			
Gender	Man	11,433	5,883	16,984	0.071			15,765	9,852	21,677	0.994		
	Woman	4,714	3,890	5,539				17,500	4,487	30,513			
Tumour diameter (cm)	<3	7,250	4,853	9,647	0.276			17,429	7,318	27,540	0.536		
	≥3	12,381	4,586	20,176				15,429	9,133	21,724			
Tumour number	1	8,750	5,246	12,254	0.614			18,875	10,130	27,620	0.614		
	1-7	14,909	0,575	29,243				19,800	4,997	34,603			
	≥8	7,200	4,111	10,289				11,000	5,632	16,368			
Focal/deep submucosal invasion	Focal	14,786	3,736	25,835	0.149			15,000	9,297	20,703	0.829		
	Deep	7,348	4,627	10,069				16,533	9,441	23,626			
Presence of CIS	Yes	6,278	4,358	8,198	0.051			13,692	8,552	18,832	0.174		
	No	13,842	5,351	22,333				20,000	9,062	30,938			
Presence of lymphovascular invasion	Yes	5,286	2,730	7,842	0.153			8,833	4,867	12,799	0.022	0.288 (0.090-0.915)	0.035
	No	11,300	5,755	16,845				19,000	12,308	25,692			
Presence of variant histology	Yes	8,400	2,091	14,709	0.776			22,667	0.000	45,421	0.268		
	No	10,438	5,225	15,650				15,000	9,922	20,078			
LMR	<3.41	12,160	5,596	18,724	0.095			18,167	9,614	26,720	0.456		
	≥3.41	6,000	3,563	8,437				13,333	8,831	17,836			
PLR	<150	8,158	4,719	11,596	0.538			18,077	12,178	23,976	0.509		
	≥150	12,278	3,576	20,980				12,875	2,844	22,906			
NLR	<2.5	6,700	3,074	10,326	0.250			13,800	7,559	20,041	0.670		
	≥2.5	11,444	5,358	17,531				16,813	10,146	23,479			
SIM score	0	3,667	2,462	4,871	0.041	0.754 (0.527-1,080)	0.124	13,000	5,201	20,799	0.605		
	1	8,500	4,621	12,379				13,600	7,572	19,628			
	2	11,455	5,883	17,026				26,400	16,746	36,054			
	3	12,643	1,531	23,754				12,286	0.780	23,792			

Chi-square Test Binary Logistic Regression, CI: Confidence interval, CIS: Carcinoma *in situ*, LMR: Lymphocyte monocyte ratio, PLR: Platelet lymphocyte ratio, NLR: Neutrophil lymphocyte ratio, SIM: Systemic inflammatory markers

study, no correlation was found with PLR progression (12). PLR was found to be effective on the probability of recurrence, similar to a meta-analysis (10). There have been few studies in the literature examining the relationship between muscle invasion and LMR in T1G3 patients. Similar to study (12), LMR was not found to be effective on the probability of progression. One study of 1,151 high-risk patients with NMIBC discovered that a high SIM score correlated with recurrence and progression. We found a positive correlation between a high SIM score and the probability of recurrence, but in contrast to that study, the current study determined that a high SIM score was not associated with progression. The lack of a correlation between a high SIM score and progression in the current study could be attributed to the small sample size and the heterogeneity of the groups with and without progression (11).

Similar to the EORTC study, there was no correlation between the probability of relapse and progression in T1G3 patients or between gender or age, but there was a correlation between tumor size and tumor number (6).

Study Limitations

Small number of patients and retrospective nature are limitations of our study.

Conclusion

In the literature, there are studies investigating the prognostic values of inflammatory markers in T1G3 patients. We examined 4 parameters together in our study (NLR, PLR, LMR, SIM). All parameters were associated with the probability of recurrence. NLR was associated with the probability of progression. SIM was assessed with RFS. We found that inflammatory parameters must be considered when evaluating T1G3 patients. Despite having some patients, the prognostic significance of pathological and clinical parameters that were not included in the nomogram but had been shown to affect progression in other studies were investigated together. Clinical, pathological, and molecular data that have been shown to be accurate in multiple studies but are not included in nomograms should be evaluated with EORTC and CUETO-like studies, and significant data should be validated for nomograms.

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Ethics

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Authorship Contributions

Concept: İ.Ö.Y., Design: İ.Ö.Y., Data Collection or Processing: İ.Ö.Y., Analysis or Interpretation: İ.Ö.Y., Literature Search: İ.Ö.Y., Writing: İ.Ö.Y., M.D., N.A., İ.A.A., Y.B., V.İ.

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Original Article

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Survival Outcomes of Treatment Modalities in Patients with Variant Histopathology of Bladder Cancer in First Transurethral Resection of the Bladder

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Abstract

Objective: Diagnoses of variant histopathology (VH) in bladder cancer (BC) are increasing, and although there is a standard treatment algorithm for BC, the guidelines lack a standardized approach for treating VH in BC. We aimed to compare the survival results of the treatment algorithm applied to patients with BC with VH in the first transurethral resection of the bladder (TUR-B) procedure.

Materials and Methods: We retrospectively assessed data on patients with VH of BC in the first TUR-B between January 2000 and January 2021. After the first TUR-B, we determined TUR-B+/- BCG, radical cystectomy (RC), and trimodal therapy (TMT) as the three potential treatments for patients according to the initial plans applied by the clinics.

Results: A total of 289 patients with VH of BC in the first TUR-B were included in the study. Their mean age was 66.7±10.1 years, and most (246, 85.1%) were male. We found that TMT was associated with lower survival, and BCG administration offered no advantage in terms of overall survival (OS) or cancer specific survival (CSS) among patients with non-muscle-invasive bladder cancer (NMIBC). In patients with MIBC, immediate RC provided a significant advantage over other treatment methods in terms of both OS and CSS.

Conclusions: There is still no standard treatment for patients with VH of BC. Patients are less likely to survive TMT than other treatment modalities.

Keywords: Bladder cancer, variant histopathology, transurethral resection of bladder, radical cystectomy, trimodal therapy

Introduction

Bladder cancer (BC) is the seventh most frequently diagnosed cancer in the male population, although it ranks eleventh worldwide when considering both genders; its incidence rates (per 100,000 person/years) are 9.0 for men and 2.2 for women (1). Although 90% of BC is urothelial carcinoma, and mostly pure urothelial carcinoma, several variant histopathology (VH) may arise, some of which are urothelial and others that are non-urothelial (2,3). Currently, the diagnosis of VH in BC is common for transurethral resection of the bladder (TUR-B) or radical cystectomy (RC) specimens (4). Patients are diagnosed with VH when there is >50% of this component in the tumor specimen, and they usually exhibit an aggressive clinical course (5). Over the past decade, VH in BC has become increasingly noted, and several

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studies have been conducted, particularly on patients treated with RC, to evaluate its effect in muscle-invasive BC (MIBC) patients. All of these studies found VH to be associated with poor survival outcomes (6). There are few cases of VH in non-muscle-invasive BC (NMIBC) reported in the literature; however, understanding the role of VH in BC for this patient group is also important so that we can develop effective treatments that prevent cancer progression.

Although the guidelines set out a treatment algorithm for patients with BC, regardless of whether they have NMIBC or MIBC, they do not offer a clear recommendation for BC with VH. This means that urologists follow no specific method when VH is identified in the first TUR-B in BC, instead basing their approach on their expertise and experience. In this context, we compared the survival results of the treatment algorithm when applied to patients with VH identified in the first TUR-B procedure.

Materials and Methods

We retrospectively assessed data on patients with VH of BC identified in the first TUR-B recorded in the BC database of the Urooncology Association of Turkey, involving 11 urology centers, between January 2000 and January 2021.

Patients with pure urothelial carcinoma, urachal carcinoma, or a mesenchymal tumor whose histopathology excluded VH in the first TUR-B (even those who later had VH at the follow-up), whose data could not be obtained, who underwent partial cystectomy, or whose follow-up period was less than 1 year were excluded from the study.

The VH of BC was defined according to the World Health Organization (WHO) classification (3). Several data items-demographic characteristics such as age, gender, body mass index, presence of diabetes, hypertension, glomerular filtration rate, American Society of Anesthesiology score, and Eastern Cooperative Oncology Group performance status score were recorded and analyzed.

After the first TUR-B, we determined TUR-B +/- BCG, immediate RC, and trimodal therapy (TMT) as the three potential treatments according to the initial plans applied by the clinics. Patients who underwent immediate RC with LND within 3 months after the first TUR-B were included in the immediate RC group, whereas those who underwent RC after 3 months of the first TUR-B were grouped based on the first planned treatment. TMT, systemic chemotherapy (CT), radiotherapy (RT), and maximum-applied TUR-B as bladder-sparing therapy were considered.

Pathological specimens were evaluated at each institution's pathology department using the tumor node metastasis classification for staging and the 2004 WHO classification for grading.

Overall survival (OS) was defined as freedom from death from any cause. Deaths attributable to BC were coded as cancer-specific death events, and cancer specific survival (CSS) was calculated accordingly. The duration of follow-up was the time from surgery to the date of death or the last date of admission to the outpatient clinic. Patient survival was confirmed by hospital or national health system data.

The ethics committee approval of the study was obtained from the Ethics Committee of the University of Çukurova (decision no: 28, date: 05.03.2021).

Statistical Analysis

Categorical variables are expressed as numbers and percentages, and continuous variables are summarized as means and standard deviations or as medians and minimum-maximum, where appropriate. For univariate analysis, OS and CSS were calculated using the Kaplan-Meier method, and the log-rank test was performed to test the differences between survival curves. Cox proportional hazard regressions were performed to determine significant predictors of OS and CSS. In univariate analysis, variables significant at the $p<0.25$ level were entered into multiple Cox regression analyses (backward procedure, LR method). All analyses were performed using IBM SPSS Statistics version 20.0 software. The statistical level of significance for all tests was considered to be 0.05.

Results

The study included 289 patients with VH of BC identified in the first TUR-B between January 2000 and January 2021. Their mean age was 66.7±10.1 years. Among them, 246 (85.1%) were male and 43 (14.9%) were female. The demographic and clinical characteristics of the study population are summarized in Table 1. In terms of cancer, 34.6% of the patients had NMIBC and 65.4% had MIBC, and 94.8% of the patients had a high grade (HG). The most common variant was squamous differentiation (34.9%), followed by micropapillary differentiation (15.6%). The VH types are summarized in Table 2. Of the patients, 77 (26.6%) received only recurrent TUR-B, 36 (12.5%) received TUR-B + BCG, 146 (50.5%) received immediate RC, and 30 (10.4%) received TMT. RC with LND was later performed in 62 patients who were first treated with TURB +/- BCG, after a mean of 14.96±23.62 months.

The mean follow-up was 30.9±33.3 months, the median OS for all patients was 33.7 months, and the 5-year OS was 37.7%. The results of the survival analyses according to the clinical factors of the 289 patients are shown in Table 3. When we assessed their demographic parameters, we found that neither OS nor CSS significantly differed by gender (p=0.658 and p=0.997, respectively), but OS was shorter in cases where patients were aged ≥65 years (p=0.034). The median OS and CSS were found to be shorter in MIBC cases than in NMIBC cases (p=0.003). Figures 1 and 2 show the corresponding Kaplan-Meier curves. Although the median OS and CSS were shorter in cases with an HG, these differences were not statistically significant (p=0.386 and p=0.653), potentially due to the small number of low grade patients in the study. There was no significant difference between the VH types in terms of OS and CSS (p=0.087 and p=0.557, respectively), but when it came to treatment, the OS and CSS were shorter for those undergoing trimodal treatment (both p=0.001).

The results of the survival analyses performed according to the tumor stage are shown in Tables 4 and 5. Although the treatment method did not affect the OS or CSS of patients with NMIBC, both the median OS and CSS of patients with MIBC

who underwent TMT were shorter than those of the other two methods. In contrast, the median OS and CSS of T2-stage patients who underwent RC were the longest (p=0.022 and p=0.005, respectively).

Potential predictors of OS and CSS were evaluated separately using Cox's proportional hazards model. Multivariate models for NMIBC patients included their age, treatment, and variant type when modeling OS, and their CSS, variant type, and treatment method when modeling CSS. In neither case were significant factors found to have affected OS or CSS. Multivariate models

Table 1. Demographical and clinical characteristics

	n=289
Age (years)	66.7±10.1
	68.0 (29.0-92.0)
Gender, n (%)	
Male	246 (85.1)
Female	43 (14.9)
BMI kg/m^2	25.8±4.3
	25.3 (15.9-39.1)
Smoking n (%)	222 (76.8)
Diabetes mellitus, n (%)	67 (23.2)
Hypertension, n (%)	110 (38.1)
ECOG, n (%)	
<3	164 (56.7)
≥3	8 (2.8)
Missing information	117 (40.5)
ASA, n (%)	
<3	103 (35.6)
≥3	53 (18.3)
Missing information	133 (46.0)
eGFR	88.7±12.9
	89.5 (13.6-124.7)
Histology, n (%)	
Ta	14 (4.8)
T1	86 (29.8)
T2	189 (65.4)
Grading, n (%)	
Low grade	15 (5.2)
High grade	274 (94.8)
Carcinoma *in situ*, n (%)	57 (19.7)
Treatment method, n (%)	
TUR-B +/- BCG	113 (39.1)
Radical cystectomy	146 (50.5)
Trimodal therapy	30 (10.4)
Neoadjuvant chemotherapy, n (%)	27 (9.3)

Unless otherwise expressed, data are expressed as mean ± standard deviation, median (minimum-maximum), BMI: Body mass index, ECOG: Eastern Cooperative Oncology Group, ASA: American Society of Anesthesiology, eGFR: Estimated glomerular filtration rate, TUR-B: Transurethral resection of bladder, BCG: Bacillus Calmette-Guerin

Table 2. Variant histopathology

Subgroups	**n (%)**
Squamous differentiation	101 (34.9)
Micropapillary	45 (15.6)
Nested	38 (13.1)
Sarcomatoid differentiation	30 (10.4)
Glandular differentiation	27 (9.3)
Small cell	10 (3.4)
Plasmacytoid	18 (6.2)
Trophoblastic	8 (2.8)
Microcystic	9 (3.1)
Lymphoepithelioma-like	3 (1)

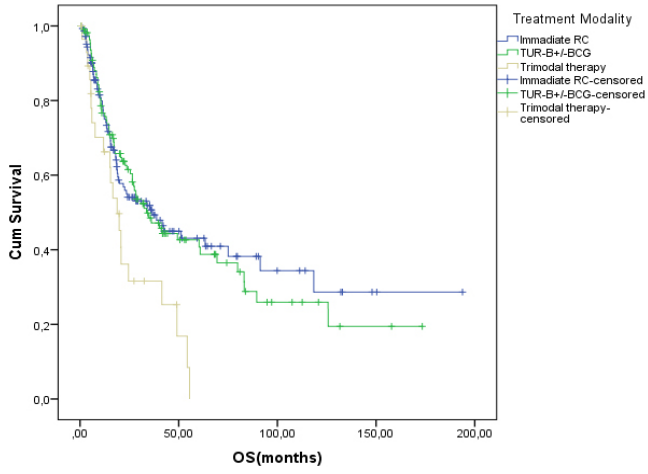

Figure 1. Kaplan-Meier plots of overall survival according to treatment modality

BCG: Bacillus Calmette-Guerin, RC: Radical cystectomy, TUR-B: Transurethral resection of bladder, OS: Overall survival

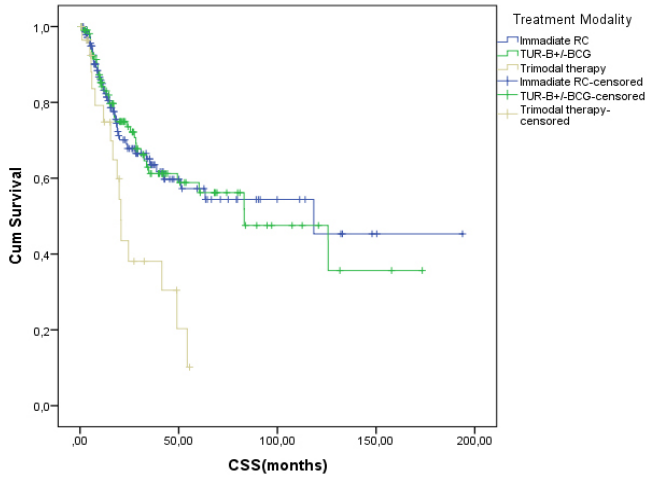

Figure 2. Kaplan-Meier plots of CSS according to the treatment modality

BCG: Bacillus Calmette-Guerin, RC: Radical cystectomy, TUR-B: Transurethral resection of bladder, CSS: Cancer specific survival

for T2-stage patients then included their age, diabetes mellitus, variant type, and treatment method when modeling their OS, and their age, variant type, and treatment method when modeling their CSS. Having undergone TMT was associated with a significantly higher risk of death and cancer-specific death than immediate RC treatment [hazard ratio (HR) =2.22, 95% confidence interval (CI): 1.23-4.01, p=0.008 vs. HR=2.87, 95% CI: 1.49-5.54, p=0.002]; no other factor was associated with OS or CSS in T2-stage patients.

Discussion

Diagnoses of VH in BC are increasing nowadays, and although there is a standard treatment algorithm for BC, the guidelines lack a standardized approach for treating VH in BC. In this context, we compared the survival results of treatment methods applied to patients from 11 urology centers diagnosed with VH of BC in the first TUR-B procedure. We found that TMT was associated with lower survival, and BCG administration offered no advantage in terms of OS or CSS among patients with NMIBC. In patients with MIBC, immediate RC provided a significant advantage over other treatment methods in terms of both OS and CSS.

Three-quarters of patients with newly diagnosed BC have NMIBC, which is associated with recurrence in 60-80% and progression in 10-30% (7-9). The standard initial therapy is complete tumor removal via transurethral resection. Based on the risks of recurrence and progression, the European guidelines (determined by the European Organization for Cancer Research and Treatment scoring system) strongly recommend adding BCG to transurethral resection for patients with NMIBC intermediate- and high-risk tumors (10).

When NMIBC is accompanied by VH, a more aggressive disease occurs, and the progression rate is approximately 40% (11). There is no clear treatment algorithm for such patients. Previous studies have presented conflicting data on the use of BCG in NMIBC with VH (11-14). Shapur et al. (12) compared

Table 3. Results of survival analyses based on clinical and prognostic factors

	OS			CSS		
	Total N/N of events	**OS (months) mean/median**	**p-value**	**Total N/N of events**	**CSS (months) mean/median**	**p-value**
Age						
<65	122/60	84.6/41.6	0.034	120/40	113.6/-	0.169
≥65	167/93	49.5/26.5		166/58	70.2/60.3	
Gender						
Male	246/132	67.6/30.9	0.658	245/84	97.6/83.1	0.997
Female	43/21	60.1/38.8		41/14	75.5/63.4	
Variant type						
Nested	38/19	72.5/42.3	0.087	36/15	82.5/63.4	0.557
Squamous	101/50	66.2/41.5		101/31	92.5/-	
Sarcomatous	30/20	60.7/14.38		30/13	96.9/23.5	
Glandular	27/10	77.9/60.9		26/7	98.9/118.4	
Micropapillary	45/30	33.1/21.0		45/16	49.3/34.8	
Others	48/24	55.5/35.4		48/16	74.4/49.1	
Tumor stage						
Ta+T1	100/41	82.8/83.1	0.003	99/23	112.6/118.4	0.003
T2	189/112	59.1/23.7		187/75	84.9/42.3	
Tumor grade						
LG	15/7	82.6/83.1	0.386	15/5	104.6/83.1	0.653
HG	274/146	68.9/30.9		271/93	97.2/63.4	
Carcinoma *in situ*						
No	232/120	73.3/33.7	0.437	231/74	105.1/83.2	0.118
Yes	57/33	50.3/33.7		55/24	64.7/38.8	
Treatment modality						
TUR-B+/-BCG	113/63	65.3/33.7	0.011	110/38	93.4/83.2	0.005
Immediate RC	146/69	79.1/36.7		146/44	108.6/118.4	
Trimodal therapy	30/21	24.5/18.8		30/16	28.1/30.7	
Total	289/153	69.1/33.7		286/98	98.3/83.1	

OS: Overall survival, CSS: Cancer specific survival, LG: Low grade, HG: High grade, TUR-B: Transurethral resection of bladder, BCG: Bacillus Calmette-Guerin, RC: Radical cystectomy

data from 22 patients with VH of NMIBC who received BCG immunotherapy with data from 144 patients with HG urothelial carcinoma. They concluded that patients with VH of NMIBC could be treated with intravesical immunotherapy if the tumor was non-bulky (>4 cm), and although progression was more common, their life expectancy was similar to that of patients with HG urothelial carcinoma (12). However, in some variant subgroups (small-cell carcinoma, pure sarcomatoid, plasmacytoid, and micropapillary), intravesical treatments such as BCG immunotherapy are ineffective and, therefore, not recommended (11-13). Suh et al. (14) retrospectively evaluated the results of BCG instillation and RC (group 1) versus observation alone (group 2) in patients with high-risk NMIBC squamous or glandular variants. Both the 5-year OS and CSS rates in the BCG instillation and RC groups reflected a survival advantage over the observation group. They concluded that intravesical BCG and RC led to increased survival in high-risk patients diagnosed with NMIBC with squamous or glandular histological variants (14).

VH increases BC risk even if it is not muscle-invasive; therefore, early, aggressive intervention using RC is often recommended for patients with VH (15). In a study by Dursun et al. (16)

Table 4. Results of Ta+T1 patients Cox proportional-hazards regression analysis of the effect of potential prognostic factors on OS and CSS

	Total N/N of events	OS (months) mean/median	p-value	Total N/N of events	CSS (months) mean/median	p-value
Ta+T1						
BCG						
No	65/29	76.5/60.9	0.104	65/18	97.5/118.4	0.043
Yes	34/11	79.7/69.4		33/4	114.1/-	
Treatment modality						
TUR-B+/-BCG	57/23	90.7/83.1	0.088	56/13	121.4/-	0.254
Immediate RC	32/11	78.6/118.4		32/6	95.6/118.4	
Trimodal therapy	11/7	30.7/41.5		11/4	36.8/41.5	
Variant type						
Nested	16/6	104.9/83.2	0.112	15/4	119.9/-	0.471
Squamous	36/16	59.8/14.7		36/8	84.3/-	
Sarcomatous	9/5	48.0/2.4		9/4	60.9/-	
Glandular	10/2	89.7/-		10/1	118.4/118.4	
Micropapillary	15/9	43.2/14.3		15/3	63.8/-	
Others	14/3	116.8/-		14/3	116.8/-	

OS: Overall survival, CSS: Cancer specific survival, BCG: Bacillus Calmette-Guerin, RC: Radical cystectomy, TUR-B: Transurethral resection of bladder

Table 5. Results of T2 Patients Cox proportional hazards regression analysis of the effect of potential prognostic factors on OS and CSS

	Total N/N of events	OS (months) mean/median	p-value	Total N/N of events	CSS (months) mean/median	p-value
T2						
BCG						
No	180/109	58.0/22.9	0.397	179/73	84.8/38.8	0.731
Yes	6/3	55.6/41.3		5/2	60.4/60.3	
Treatment modality						
TUR-B +/- BCG	56/40	40.5/26.5	0.022	54/25	58.1/32.4	0.005
Immediate RC	114/58	75.7/33.7		114/38	106.5/63.4	
Trimodal therapy	19/14	20.6/18.8		19/12	22.7/19.8	
Variant type						
Nested	22/13	31.5/19.4	0.353	21/11	33.5/19.4	0.440
Squamous	65/34	62.9/33.7		65/23	84.2/60.3	
Sarcomatous	21/15	53.6/15.5		21/9	97.5/23.5	
Glandular	17/8	76.1/36.1		16/6	91.1/-	
Micropapillary	30/21	28.4/20.5		30/13	38.2/30.9	
Others	34/21	38.9/27.6		34/13	54.9/49.1	

OS: Overall survival, CSS: Cancer specific survival, BCG: Bacillus Calmette-Guerin, RC: Radical cystectomy, TUR-B: Transurethral resection of bladder

comparing the results of bladder preservation therapy and RC OS for NMIBC patients, based on a total sample of 8920, the researchers concluded that RC led to a better OS for sarcomatoid, squamous, glandular, and neuroendocrine variants compared with bladder preservation therapy, but this result was not observed in patients with micropapillary VH. In a further study of 119 patients with T1 HG micropapillary BC, the authors evaluated survival outcomes after immediate RC versus conservative management with BCG and found that CSM and OM did not differ significantly between the two groups (17). Using the Surveillance Epidemiology, and End Results database, Deuker et al. (18) evaluated CSS in VH of BC patients treated with or without RC and found that RC was performed in 7.4-10% of VH of BC patients vs. 5.1% of HG urothelial BC patients. They revealed that RC was associated with higher CSS rates than other treatments in T1 VH of BC patients, whereas no differences were recorded for adenocarcinoma or other VH of BC types. Therefore, they concluded that RC, for stage T1N0M0 VH of BC, appears to provide a protective effect with respect to squamous or neuroendocrine carcinoma, thereby improving the patients' CSS, but not in adenocarcinoma or other VH of BC types (18). In our study, most of our NMIBC patients were HGs. Although intravesical BCG was administered to 34 patients with NMIBC, we did not observe a positive effect on survival. While immediate RC produced similar OS and CSS rates to TUR-B +/ BCG, TMT led to worse survival results than the other two treatments. The difference we found was not statistically significant, but it may become meaningful when a greater number of patients are studied.

Nearly 30% of new BC diagnoses are MIBC, including cancer in stages T2-T4 (19). MIBC treatment is based on multidisciplinary collaboration involving surgical, RT, and medical oncology teams (20). RC with lymph node dissection, with or without neoadjuvant treatment, has become accepted as the standard treatment approach in MIBC. With an overall complication rate of 27-64%, RC is an aggressive surgical procedure associated with high perioperative mortality, and the 5-year OS of patients who have undergone RC remains below 60% (21,22). Many patients are unsuitable for surgery; therefore, bladder-sparing strategies are performed as their treatment instead (20). Bladder-sparing chemoradiotherapy avoids the morbidity and mortality of radical surgery and allows for the preservation of the natural bladder, which is why it is preferred by some patients (23). However, RC with LND, with or without neoadjuvant CT, remains the primary treatment for patients with VH of BC presenting with localized MIBC (24). In a meta-analysis study of VH by Mori et al. (22) that evaluated the prognoses of BC patients undergoing RC, VH was associated with worse cancer-specific, overall, and relapse-free survival rates. Subgroup analyses demonstrated that micropapillary, plasmacytoid, and small-cell VH were associated with worse OS (22).

To date, there have been no randomized prospective studies on the strongest treatment method to choose for patients with variant MIBC. Krasnow et al. (25), in a study in which they administered TMT to 303 patients, 66 of whom had a variant, found 5- and 10-year disease specific survival rates of 75% and 67%, respectively, in papillary urothelial BC, versus 64% and 64% in VH of BC. The 5- and 10-year OS rates, meanwhile, were 61% and 42% in papillary urothelial BC versus 52% and 42% in the VH of BC. They concluded that the VH of BC responded to TMT, and there was no significant difference in oncological results compared with papillary urothelial BC (25). In a study using the National Cancer Database, Janopaul-Naylor et al. (23) reported the results of different treatments applied to patients with VH of MIBC, with TMT applied to 356 patients and RC applied to 2093 patients. They found that in a multivariate analysis, there was a trend toward worse OS with TMT compared with surgery (HR 1.15, 95% CI 1.00-1.33, p=0.052). Although there was a trend toward better OS with TMT in the first year of follow-up, there was worse OS with TMT after 1 year (23). In our study, we found that patients with MIBC who underwent TMT had worse survival rates than those who underwent immediate RC. We conclude that immediate RC should be recommended if applicable to these patients.

Study Limitations

We must note that our study had some limitations. One of the most important aspects was its retrospective and multicenter nature. Although the number of patients was high overall, there were not enough for specific subgroups. We also failed to perform survival analyses for the VH subgroups.

Conclusion

Although VH is one of the most important factors affecting survival in BC, urological centers still lack a standard treatment approach for affected patients, to be applied regardless of whether they have NMIBC or MIBC. Currently, the survival outcome of TMT is worse than those of other treatment modalities, which is concerning and calls for immediate research efforts to address this issue. Accordingly, prospective, randomized, multicenter studies on this subject are urgently needed.

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Authorship Contributions

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Original Article

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Correlation Between PSA Density and Multiparametric Prostate MRI in the Diagnosis of Prostate Cancer

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Abstract

Objective: In the diagnosis of prostate cancer, only digital rectal examination and prostate-specific antigen (PSA) testing cause unnecessary prostate biopsies, excessive cost, and treatment burden. Therefore, PSA density (PSAD) and multiparametric magnetic resonance imaging (mp-MRI) of the prostate are becoming common. In this study, we aimed to investigate the predictiveness of PSAD and mp-MRI of the prostate in the diagnosis of prostate cancer, which are non-invasive diagnostic methods.

Materials and Methods: The files of 193 patients who applied to the urology outpatient clinic for approximately 5 years were reviewed and evaluated retrospectively. Serum PSAD values and prostate imaging reporting and data system (PIRADS) scores were recorded. Prostate biopsies were performed. The cut-off value for PSAD was 0.15 ng/mL/cc. Patients with <0.15 were divided into group 1, and those with ≥0.15 were divided into group 2. Patients with a PIRADS score of 3 were divided into the suspicious group, and patients with a PIRADS score of 4 or 5 were divided into the risky group.

Results: Prostate volume, PSA, and PSAD were significantly different between the benign and malignant groups. PSAD was positively correlated with the PIRADS score. Of the 123 patients with a PIRADS score of 3, 82.9% had benign prostatic enlargement (BPE) and 17.1% had prostate cancer. Of the 70 patients with a PIRADS score of 4 or 5, 45.7% had BPE and 54.3% had prostate cancer (p<0.001). Clinically significant prostate cancer rates were significantly different between the PSA score groups and were also different for PIRADS (p<0.001). The sensitivity and specificity of PSAD in the diagnosis of prostate cancer were 67.8% and 64.9%, respectively. The sensitivity and specificity of the PIRADS score in the diagnosis of prostate cancer were 64.4% and 76.1%, respectively. When these two parameters were used in combination, the specificity was 87.3% and the sensitivity was 81.4% in the presence of at least one.

Conclusion: According to the data of the study, it was concluded that PSAD and PRIDAS scores are complementary diagnostic methods in the diagnosis of prostate cancer and are indispensable elements in the diagnosis. PSAD and PRIDAS scores are important diagnostic parameters in making the biopsy decision in the diagnosis of prostate cancer and help to prevent unnecessary prostate biopsies.

Keywords: PI-RADS, prostate cancer, prostate MRI, prostate needle biopsy, PSA density

Introduction

Prostate cancer is the second most common cancer in men worldwide (1). It is the most common solid organ tumor in elderly men (2). Adenocarcinomas constitute more than 95% of prostate cancers and develop from acinar or ductal epithelial cells of the prostate glands (3). Age, genetic predisposition, metabolic and hormonal factors, diet, and infection-related factors are risk factors for prostate cancer. However, the underlying causes of its onset and progression have not been fully elucidated (4-6).

Prostate-specific antigen (PSA) has been used in addition to digital rectal examination (DRE) for prostate cancer screening since the late 1980s (7). However, serum PSA level is an organ-specific marker. It may differ not only in malignancy but also in healthy individuals depending on variables such as age, ethnicity, and prostate volume. It may also increase in benign diseases, such as prostatitis and benign prostatic enlargement (BPE), trauma, and transurethral interventions (8). High serum PSA levels in such cases lead to unnecessary prostate biopsy decisions (9). Cancer is detected in only 34% of patients undergoing biopsy because of high PSA levels (10). From another point of view, 66% of

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biopsies performed are unnecessary. Complications related to biopsy may be observed in a certain proportion of these patients (11).

The determinants used in the biopsy decision are serum PSA levels and DRE findings. Even if these two data are used together, they cannot provide sufficient sensitivity and specificity for biopsy. Therefore, the use of PSA density (PSAD), free/total PSA ratio, PSA velocity, and multiparametric magnetic resonance imaging (mp-MRI) of the prostate to make a biopsy decision are discussed.

Prostate biopsy is performed according to the PSA, PSAD, and PRM data. In addition, mp-MRI of the prostate has been used since the 1980s as a non-invasive imaging method for the evaluation of the prostate gland and surrounding organs (12). In recent years, the use and diagnostic accuracy of mp-MRI in the detection of prostate cancer has been increasing with the development of MRI techniques (13).

The ratio of PSA to prostate volume is PSAD. With the PSAD value, it is aimed to distinguish between cancer and BPE in PSA values between 4 and 10 ng/mL. PSAD has higher sensitivity and specificity than PSA. It has a greater diagnostic potential than serum PSA alone (14).

The use of MRI has become widespread in the last 40 years. With the development of the T2-weighted mp-MRI protocol, which includes dynamic contrast imaging sequences that provide functional and anatomical imaging, its use worldwide has been increasing rapidly, especially in the last 10 years (15).

In this study, we aimed to determine the sensitivity and specificity of PSAD and mp-MRI in the diagnosis of prostate cancer and to determine the efficacy in preventing unnecessary prostate biopsies with their combined use.

Materials and Methods

The study was approved by the Sivas Cumhuriyet University Ethics Committee (decision number: 2022-03/07, date: 23.03.2022). The files of 193 patients who had a PSA value higher than 2.5 ng/mL and had histopathological data after multiparametric prostate MRI and prostate biopsy between January 2017 and December 2021 were reviewed and evaluated retrospectively. PSAD values were calculated by the ratio of serum PSA value at the time of biopsy and prostate volume measured by transrectal ultrasound during biopsy. Due to the possibility of deviation from the normal distribution and possible undocumented infectious conditions, the upper limit of PSA was determined to be 25 ng/mL. The cut-off value for PSAD was determined to be 0.15. Patients with PSAD 0.15 were divided into group 1 and patients above 0.15 were divided into group 2.

The mp-MRIs of the patients were interpreted by the Radiology Department of Cumhuriyet University using the Prostate Imaging Reporting and Data System (PIRADS) version 2 classification. According to prostate cancer risk, patients with a PIRADS score of 1 or 2 were classified as the low-risk group, patients with 3 as the intermediate-risk group, and patients with 4 or 5 as the high-risk group.

Prostate biopsies were conventionally performed with 12- and/or 16-quadrant tru-cut transrectal ultrasonography (TRUS). Patients with an International Society of Urological Pathology (ISUP) score ≥2 in the pathology result of their biopsy were diagnosed with clinically significant prostate cancer.

Patients having an active infection (acute or chronic prostatitis, urinary tract infection, etc.), taking a drug that may affect the serum PSA value, having a condition that may affect the serum PSA value (such as acute urinary retention), and undergoing interventions that may affect the serum PSA value (cystourethroscopy, transurethral resection, etc.) were excluded from the study. Patients whose pathology did not result in benign prostatic tissue or prostate cancer (atypical small acinar proliferation or high-grade prostatic intraepithelial neoplasia) were excluded from the study. TRUS prostate biopsy is not applied to patients in the low-risk group with a PIRADS score of 1 or 2 in our clinic; therefore, these patients were excluded from the study.

Statistical Analysis

The data of the study were uploaded to the SPSS 8 (ver: 22.00) program. When the parametric test assumptions were fulfilled in the evaluation of the data, the significance test of the difference between the two means was used in the independent groups when comparing the measurements obtained from two independent groups, the analysis of variance was used when comparing the measurements obtained from more than two groups, the Spearman rank correlation test was used to determine the relationships between the variables, the predictive values for the variables receiver operating characteristic (ROC) analysis was used to determine the data obtained by counting, and the chi-square test was applied to evaluate the data obtained by counting, and the error level was taken as 0.05.

Results

One hundred and 93 patients included in the study were separated according to their PSAD values. The patients were between the ages of 48 and 82 years. Group 1 (PSAD <0.15) comprised 55.9% and group 2 (PSAD >0.15) comprised 45.1% of the patients. According to mp-MRI, 63.7% of the patients had PIRADS 3, 26.4% had PIRADS 4, and 9.9% had PIRADS 5. PIRADS scores were divided into intermediate risk group (score 3) and high risk group (score 4-5), and their rates were 63.7% and 36.3%, respectively. In the biopsy pathology data, 69.4% of the patients had BPE and 30.6% had prostate cancer. Clinically significant prostate cancer (ISUP ≥2) was 17.6% of patients (Table 1).

The mean values of biopsy results of patients with BPE and prostate cancer included in the study were 65.29 and 66.95 for age, 80.84 and 57.17 for prostate volume, 8.84 and 12.29 for PSA, 0.12 and 0.24 for PSA. Prostate volume, PSA, and PSAD were significantly different between the BPE and prostate cancer groups. It was observed that the mean values of PSAD increased with the increase in PIRADS scores. These values are 0.13 for PIRADS 3, 0.18 for PIRADS 4, and 0.3 for PIRADS 5 (Table 2).

Age, PSA, PSAD, and prostate volumes of patients with prostate cancer were analyzed using the ROC analysis method. The areas under the curve were 0.609, 0.685, 0.809, and 0.257, respectively (Figure 1). These data indicate that PSAD is more

valuable and significant than other parameters in the diagnosis of prostate cancer. However, it should be noted that there is no PIRADS score, which is a categorical variable, in this ROC analysis.

PSAD groups and pathology data were compared. Biopsy results of 106 patients in group 1 (PSAD <0.15) were reported as BPE in 82.1% and prostate cancer in 17.9%. Biopsy results of 87 patients with PSAD group 2 (PSAD >0.15) were reported as BPE in 54% and prostate cancer in 46%. PIRADS scores and pathology data were compared. Biopsy results of 123 patients with PIRADS 3 were reported as BPE in 82.9% and prostate cancer in 17.1%. Of 51 patients with PIRADS 4, 52.9% were reported as BPE and 47.1% as prostate cancer. Of 19 patients with PIRADS 5, 26.3% were reported as BPE and 73.7% as prostate cancer. In the examination performed by dividing the PIRADS scores into 3 (intermediate risk) and 4-5 (high risk) groups, 82.9% of the 123 patients in the intermediate risk group had BPE and 17.1% had prostate cancer. In the high-risk group, 45.7% of 70 patients had BPE and 54.3% had prostate cancer (Table 3).

In the study, clinically significant prostate cancer rates were 4.7% in PSAD group 1 patients and 33.3% in group 2 patients. In PIRADS scores, it was 8.2% in PIRADS score 3, 29.3% in PIRADS score 4, and 47.4% in PIRADS score 5. In the PIRADS scores, clinically significant prostate cancer was observed in 8.2% of the patients in the intermediate-risk group and 34.3% of the patients in the high-risk group (Table 4). The matching of PSAD groups and PIRADS scores according to pathology data in the study is given in Table 5.

The relationship between the PSAD and PIRADS groups was evaluated according to pathology data. A statistically significant difference was found between PSAD and PIRADS in patients with biopsy results of BPE (p=0.036). 35.1% of patients with high risk according to PSAD had malignancy. According to PIRADS, 23.9% of patients with high risk had malignancy. There was no statistically significant difference between PSAD and PIRADS scores in patients with prostate cancer (p=0.815). Malignancy was observed in 67.8% of patients with high risk according to PSAD. According to PIRADS, 64.4% of patients with high risk have malignancy (Table 6).

There was a 20% positive correlation between PSAD and PIRADS scores in patients with BPE, and a statistically significant correlation was found (p=0.019). In patients with prostate cancer, a 48% positive and statistically significant correlation was found between PSAD and PIRADS scores (p=0.001) (Table 7).

The sensitivity and specificity of PSAD in the diagnosis of prostate cancer were 67.8% and 64.9%, respectively. The sensitivity and specificity of PIRADS were 64.4% and 76.1%, respectively. PSAD and PIRADS scores were used in combination, and the specificity was 87.3%. In the presence of at least one, the sensitivity was found to be 81.4% (Table 8).

Table 1. Distribution of patient data

Variable	Category	n	%
PSAD	Group 1	106	55.9
	Group 2	87	45.1
PIRADS	3	123	63.7
	4	51	26.4
	5	19	9.9
PIRADS	3	123	63.7
	4-5	70	36.3
Pathology	BPE	134	69.4
	Prostate cancer	59	30.6
Pathology	BPE	134	69.4
	ISUP =1	25	13.0
	ISUP ≥2	34	17.6

PSAD: Prostate-specific antigen density, PIRADS: Prostate image reporting and data system, BPE: Benign prostatic enlargement, ISUP: International Society of Urological Pathology

Discussion

PSA may increase because of prostate cancer. In addition, PSA may increase because of BPE, which is more common with aging. Therefore, PSAD is used to distinguish whether the PSA increase is due to cancer or BPE. the use of PSAD increases the effectiveness of PSA in the diagnosis of prostate cancer (16). Studies have indicated that prostate biopsy should be performed in patients with PSAD ≥15%. PSAD is more significant than PSA alone, especially in patients with a PSA value between 4 and 10 ng/mL (17). Boulos et al. (18) found the cancer detection rate to be 22.8% in patients with a PSAD of 15% and 9% in patients with a PSAD of 10%. In another study with a PSAD cutoff value of 15%, it was reported that the sensitivity for cancer detection was 44% and the specificity was 76% (19).

In our study, PSAD was found to be significantly higher in patients with prostate cancer than in those without cancer. The mean PSAD values of the patients were 0.12 in patients with BPE and 0.24 in patients with cancer (p=0.001, Table 2). Prostate cancer was detected in 17.9% of 106 patients with PSAD <0.15 and in 46% of 87 patients with PSAD ≥0.15 (p<0.001, Table 4). Clinically significant prostate cancer was detected in

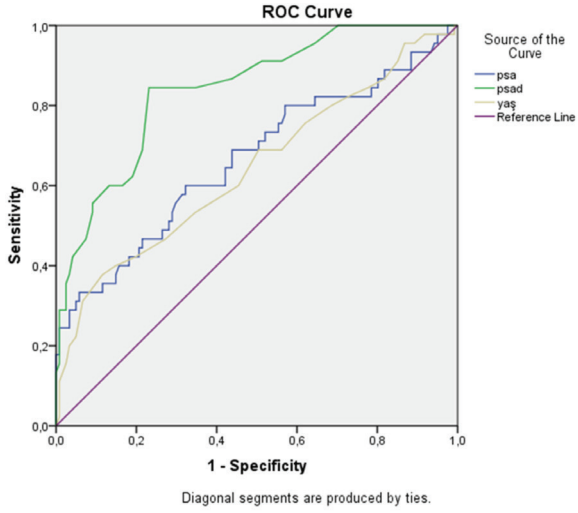

Figure 1. ROC analysis chart

ROC: Receiver operating characteristic

4.7% of patients with PSAD <0.15 and in 33.3% of patients with PSAD ≥0.15. In this respect, there was a statistically significant relationship between biopsy results and PSAD groups (p<0.001, Table 5). According to the ROC analysis results of age, PSA, and PSAD, the areas under the curve for predicting prostate cancer were calculated as 0.609, 0.685, and 0.809, respectively (Figure 1, Table 3). The study conducted in terms of the use of PSAD is similar to other studies in the literature. The sensitivity and

Table 2. Descriptive statistical results of patient data

	n	Minimum	Maximum	Mean	SD	p-value
Age						
BPE	134	48	82	65.29	5.71	0.61
Prostate cancer	59	51	82	66.95	6.94	
Prostate volume						
BPE	134	34	400	80.84	43.16	0.001
Prostate cancer	59	25	170	57.17	26.4	
PSA						
BPE	134	3	23.67	8.84	4.08	0.001
Prostate cancer	59	3.58	24.89	12.29	5.57	
PSAD						
BPE	134	0.02	0.29	0.12	0.05	0.001
Prostate cancer	59	0.08	0.62	0.24	0.13	
PIRADS 3	123	0.02	0.57	0.13	0.07	0.001
PIRADS 4	51	0.03	0.46	0.18	0.1	
PIRADS 5	19	0.07	0.62	0.3	0.16	
PIRADS 3	123	0.02	0.57	0.13	0.07	0.001
PIRADS 4-5	70	0.03	0.62	0.21	0.13	

SD: Standard deviation, BPE: Benign prostatic enlargement, PSA: Prostate-specific antigen, PSAD: Prostate-specific antigen density, PIRADS: Prostate image reporting and data system

Table 3. PSAD and PIRADS rates according to the pathology data

Variable	Category	BPE		Prostate cancer		p-value
		n	%	n	%	
PSAD	Group 1	87	82.1	19	17.9	<0.001
	Group 2	47	54.0	40	46.0	
PIRADS	3	102	82.9	21	17.1	<0.001
	4	27	52.9	24	47.1	
	5	5	26.3	14	73.7	
PIRADS	3	102	82.9	21	17.1	<0.001
	4-5	32	45.7	38	54.3	

PSAD: Prostate-specific antigen density, PIRADS: Prostate image reporting and data system, BPE: Benign prostatic enlargement

Table 4. PSAD and PIRADS rates according to ISUP data

Variable	Category	BPE		ISUP 1		ISUP ≥2		p-value
		n	%	n	%	n	%	
PSAD	Group 1	87	82.1	14	13.2	5	4.7	<0.001
	Group 2	47	54.0	11	12.7	29	33.3	
PIRADS	3	102	82.9	11	8.9	10	8.2	<0.001
	4	27	52.9	9	17.7	15	29.4	
	5	5	26.3	5	26.3	9	47.4	
PIRADS	3	102	82.9	11	8.9	10	8.2	<0.001
	4-5	32	45.7	14	20	24	34.3	

PSAD: Prostate-specific antigen density, PIRADS: Prostate image reporting and data system, ISUP: International Society of Urological Pathology, BPE: Benign prostatic enlargement

Table 5. Matching PSAD groups and PIRADS scores

Number of patients: 193			PIRADS 3 n (%)	PIRADS 4-5 n (%)	Total n (%)	p-value
PSAD	Group 1	BPE	72 (86.75)	15 (65.22)	87 (82.07)	0.049
		ISUP 1	8 (9.64)	6 (26.09)	14 (13.21)	
		ISUP ≥2	3 (3.61)	2 (8.69)	5 (4.72)	
		Total	83	23	106	
	Group 2	BPE	30 (75)	17 (36.17)	47 (54.02)	0.001
		ISUP 1	3 (7.5)	8 (17.02)	11 (12.65)	
		ISUP ≥2	7 (17.5)	22 (46.81)	29 (33.33)	
		Total	40	47	87	

PSAD: Prostate-specific antigen density, PIRADS: Prostate image reporting and data system, BPE: Benign prostatic enlargement, ISUP: International Society of Urological Pathology

Table 6. Evaluation of the concordance between PSAD and PIRADS scores according to pathology

BPE			PIRADS		Total	p-value
			3	4-5		
PSAD	Group 1	n (%)	72 (53.7)	15 (11.2)	87 (64.9)	0.036
	Group 2	n (%)	30 (22.4)	17 (12.7)	47 (35.1)	
Total		n (%)	102 (76.1)	32 (23.9)	134 (100%)	
Prostate cancer			**PIRADS**		**Total**	**p-value**
			3	**4-5**		
PSAD	Group 1	n (%)	11 (18.6)	8 (13.6)	19 (32.2)	0.815
	Group 2	n (%)	10 (16.9)	30 (50.8)	40 (67.8)	
Total		n (%)	21 (35.6)	38 (64.4)	59 (100%)	

BPE: Benign prostatic enlargement, PIRADS: Prostate image reporting and data system, PSAD: Prostate-specific antigen density

Table 7. Evaluation of the correlation between PSAD and PIRADS scores

Pathology			PIRADS
BPE	PSAD	r	0.20
		p	0.019
		n	134
Prostate cancer	PSAD	r	0.48
		p	0.001
		n	59

PIRADS: Prostate image reporting and data system, PSAD: Prostate-specific antigen density, BPE: Benign prostatic enlargement

Table 8. Prostate cancer detection rates of PSAD and PIRADS

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PSAD	67.8	64.9	46.0	82.1
PIRADS	64.4	76.1	54.3	82.9
Combined	50.8	87.3	63.8	80.1
In the presence of at least one	81.4	53.7	43.6	86.7

PIRADS: Prostate image reporting and data system, PSAD: Prostate-specific antigen density, PPV: Positive predictive values, NPV: Negative predictive values

specificity of PSAD were found to be high compared with similar studies. We think that this is because the upper limit of PSA was 25 ng/mL in the study. According to all these data, it can be said that PSAD is a more significant parameter than PSA in predicting prostate cancer.

In recent years, with the developments in MRI techniques, the use and diagnostic accuracy of mp-MRI in the detection of prostate cancer has been increasing. In the study of Schlemmer (20), the sensitivity and specificity of MRI were found to be 80% and 90%, respectively, in detecting prostate cancer. In the study of John et al. (21), in which 131 patients with PSA values between 2.1 and 64 were examined, clinically significant prostate cancer was found in 11.1% of those with PIRADS 3 lesions, in 42.9% of those with PIRADS 4 lesions, and in 35.6% of those with PIRADS 5 lesions.

As the PIRADS lesion score increased, both the incidence of cancer and clinically significant prostate cancer increased. In total, 17.1% of 123 patients with PIRADS 3 lesions, 47.1% of 51 patients with PIRADS 4 lesions, and 73.7% of 19 patients with PIRADS 5 lesions were diagnosed with prostate cancer ($p<0.001$, Table 4). Clinically significant prostate cancer was detected in 8.2% of patients with a PIRADS score of 3, in 29.4% of patients with a PIRADS score of 4, and in 47.4% of patients with a PIRADS score of 5 ($p<0.001$, Table 4). As the PIRADS score increases, the incidence of clinically important prostate cancer increases. However, in patients with PIRADS 3 lesions, the cancer rate is unrecognizably high. This may be because the PSA values of the patients in our study group were higher than those of the other study groups, or the difficulties in PIRADS 3 and 4 discrimination in MR interpretation. Thus, clinicians should be more careful in deciding on prostate biopsy of PIRADS 3 lesions.

Prostate biopsy and predictive factors of clinically significant prostate cancer were evaluated in a study of patients with PSA levels between 4 and 10 ng/mL. After 222 prostate biopsies, 121 patients were diagnosed with prostate cancer, 92 of whom had clinically significant prostate cancer. Patient age, prostate volume, PSAD, lesion location, and PIRADS v2.1 score were correlated with prostate cancer and clinically significant prostate cancer. Among them, the PIRADS v2.1 score was found to be the best predictor of transition zone lesions with 93.1% negative predictive value, 81.8% sensitivity, and 77.1% specificity. Similar results have been obtained for peripheral zone lesions (22).

There is no definitive test for predicting prostate cancer, but diagnostic parameters can be used in combination to increase its accuracy. Sonmez et al. (23) evaluated the PSA <10 and PIRADS 3 patient groups in their study. In the study, it was found that the probability of prostate cancer increases as the number of positive risk factors such as PSA, free/total PSA ratio, familial prostate cancer history, and PIRAD3 lesion diameter increases. In our study, it was shown that the diagnostic accuracy increased with the combined use of PSAD and PIRADS scores (23).

In our study, 59 of 193 patients were diagnosed with cancer. Clinically significant prostate cancer was detected in 34 patients. Age, prostate volume, PSA, and PSAD levels were evaluated, and a clinically significant relationship was found ($p<0.05$, Table 2). In patients with BPE, the PIRADS score was better than the PSAD score ($p=0.036$, Table 6). In patients with prostate cancer, although PSAD was slightly better than the PIRADS score, no significant difference was found ($p=0.815$, Table 6). According to the data of the study, it can be said that PSAD is partially reliable in detecting cancer compared with MRI. One of the reasons for this is that the upper limit of PSA was 25 ng/mL in the study. This increases PSAD. Another reason is that patients with PIRADS 1 and 2 lesions were not included in the study when categorizing the PIRADS scores. In addition, the fact that the lesions were categorized as PIRADS 3 (intermediate risk) and PIRADS 4-5 (high risk) may also be a factor.

In a meta-analysis study by Woo et al. (24), the sensitivity of PIRADSv2-guided MRI was 89% and the specificity 73% in detecting prostate cancer in 3857 patients. In another study, prostate cancer was detected in 15% of lesions reported as PIRADS 3 and in 81% of lesions reported as PIRADS 4 or 5 (25). In the study by Kuru et al. (26), the negative predictive value of lesions reported as PIRADS 2 or 3 was 99%, and the positive predictive value of PIRADS 4 or 5 lesions was 83% (26). In our study, the sensitivity for MRI was 64.4% and the specificity was 76.1%. The positive predictive value was 54.3% and the negative predictive value was 82.9% (Table 8). The difference in the data in our study compared with similar studies may be due to the fact that conventional TRUS prostate biopsy was performed on the patients, whereas cognitive and/or MRI/TRUS fusion biopsy technique was used in the literature studies. In addition, the fact that PIRADS 1-2 lesions were also included in similar studies may be another reason.

When PIRADS v2 score and PSAD were examined together, PIRADS score ≥4 and PSAD ≥0.15, or PIRADS score 3 and PSAD ≥0.3, the highest clinically significant prostate cancer rate was found in the first biopsy (76-97%). In those with negative biopsy results, 22% of these patients were later diagnosed with cancer. In contrast, no clinically significant prostate cancer was detected in the group with a PIRADS score ≤3 and a PSAD <0.15 (27). Of the 47 patients reported as PSAD ≥0.15 and PIRADS score ≥4, 46.81% (n=22) were identified as having clinically significant prostate cancer. Of the 83 patients reported as PSAD <0.15 and PIRADS score of 3, 3.61% (n=3) were found to have clinically significant prostate cancer (Table 5). Because clinically significant prostate cancer was detected in 3 patients with PSAD <0.15 and three PIRADS lesions, more care should be taken in postponing the biopsy decision in this patient group.

Heterogeneity in patient groups and the small number of patients compared with similar studies are the main limitations of this study. Moreover, the study was not a randomized controlled study, but a retrospective one.

Conclusion

Prostate cancer is a common health problem worldwide. Therefore, there are many studies in the literature on diagnosis and treatment. In order to increase the sensitivity and specificity of PSA and to reduce the number of extra prostate biopsies, PSA derivatives and imaging methods have been developed. In this study, the role of PSAD as a PSA derivative and mp-MRI of the prostate in the diagnosis of prostate cancer was investigated. The combined use of PSAD and mp-MRI can prevent unnecessary

biopsy and subsequent complications. It can also significantly reduce the overtreatment burden.

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Ethics

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Authorship Contributions

Surgical and Medical Practices: H.S., A.Asd., Concept: A.A., İ.E.E., A.Asd., E.K., Design: A.Ö., A.F.V., Data Collection or Processing: A.A., A.Ö., A.F.V., Analysis or Interpretation: H.S., A.Ö., İ.E.E., A.F.V., Literature Search: H.S.,A.Asd., E.K., Writing: A.A., İ.E.E., E.K.

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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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ERRATUM

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Yarış M. Effects of Androgen Deprivation Therapy on Blood Lipids and Fasting Blood Glucose in Patients with Prostate Cancer. Bull Urooncol 2022;21(1):5-9

The changes made in the article "Effects of Androgen Deprivation Therapy on Blood Lipids and Fasting Blood Glucose in Patients with Prostate Cancer" in the Materials and Methods section published in Bull Urooncol 2022;21(1) are as follows:

Page 5

Published;

This retrospective study reviewed the files of 98 patients who were diagnosed with prostate cancer in our clinic and started LHRH agonists or underwent ADT after bilateral orchiectomy in 2014.

Correction;

The files of a total of 98 patients who were diagnosed with prostate cancer in our clinic since the beginning of 2014 and started LHRH agonists or underwent ADT after bilateral orchiectomy were retrospectively reviewed.