Is Low-risk Prostate Cancer Really Low-risk? Consider Factors Affecting Biochemical Recurrence and Tumour Upgrade

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ABSTRACT

Objective: To evaluate the demographics, preoperative or pathological factors, and findings of magnetic resonance imaging (MRI) to predict the factors affecting biochemical recurrence and tumour upgrade in low-risk prostate cancer.

Study Design: A descriptive study.

Place and Duration of Study: Department of Urology, Bolu Abant Izzet Baysal University, Bolu, Turkey, from January 2017 to December 2021.

Methodology: The data of 135 patients, who underwent radical prostatectomy for low-risk prostate cancer according to prostate-specific antigen (PSA) level, biopsy result and clinical stage, were analysed. Preoperative clinicopathological factors, MRI findings, and the final pathological results were analysed. Prognostic factors affecting the biochemical recurrence in the follow-up and tumour upgrade in the final pathology according to the International Society of Urological Pathology (ISUP) were evaluated.

Results: Mean age and preoperative PSA level were 61.37 ± 5.53 (46-74) years and 6.74 ± 1.97 (range 1.88-9.9) ng/dL, respectively. Multivariate analysis showed that the prostate volume and diameter of lesions were statistically significant in the patients with ISUP upgrade (p=0.006, p=0.025, respectively), and surgical margin positivity in the final pathology specimen was statistically significant for biochemical recurrence (p=0.016). Logistic regression analysis revealed that prostate volume and diameter of the lesion in MRI were independent predictors of ISUP score upgrade. Receiver operating characteristic (ROC) curve analysis showed that tumour size on the MRI had 49.4% sensitivity and 77.8% specificity at 10 mm (AUC:0.634, p=0.009 for predicting).

Conclusion: Lower prostate volume, higher diameter of lesions in multiparametric MRI and surgical margin positivity were associated factors affecting the ISUP score upgrade and biochemical recurrence. Therefore, patients should be evaluated preoperatively and patient-based factors should be considered in the choice of a treatment plan.

Key Words: *Prostate cancer, Cancer upgrade, Tumour size.*

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INTRODUCTION

Prostate cancer is the second most commonly diagnosed cancer in men.[1] Organ-confined prostate cancer detection increased due to the high use of PSA for screening tools over 30 years. Prostate cancer was classified as low, moderate and high according to D'Amico classification based on prostate specific antigen (PSA), digital rectal examination, and Gleason score of transrectal ultrasound-guided prostate biopsy (TRUS-Bx) result.[2] The progression of the disease is slower in the low-risk group. Treatment approach for low-risk prostate cancer includes active surveillance, radical prostatectomy (RP), radiotherapy, and focal therapies.[3]

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A low-risk disease is a heterogeneous group with not always favourable outcomes. A large proportion of patients are defined as low-risk but may have adverse pathologic features.[4] Therefore, active surveillance may not always be the appropriate option, as not every patient is actually in the low-risk group.

It is important to find out which patients tend to be upgraded in the final pathology results compared to the Gleason score of TRUS-Bx. So, each low-risk patient with some prognostic factors require active treatment should be evaluated and differentiated preoperatively for the treatment choice.

The Gleason score which has been widely using over 50 years has changed to ISUP (International Society of Urological Pathology) score to evaluate especially for the importance of Gleason score 4 in the pathological results of prostate cancer.[5] Studies reported previously that there might be a discrepancy between pathologies of prostate biopsy and RP and such demographic factors like serum PSA level, obesity, small prostate size, and older age were the independent prognostic factors for Gleason score upgrade and pathological upstage.[6-8]

The development of prostate MRI over the years has gained importance to diagnose and follow-up of prostate cancer.[9] Multiparametric prostate MRI (mp-MRI) performed before prostate biopsy may give valuable information about lesions in the prostate. Thus, it can serve accurately to detect tumour grade in biopsy and may predict tumour upgrade and biochemical recurrence after treatment.[10,11]

The objective of this study was to evaluate the demographics, preoperative or pathological factors and MRI findings to predict Gleason score upgrade and factors affecting biochemical recurrence in low-risk prostate cancer.

METHODOLOGY

The data of 135 patients, who underwent RP at the Bolu Abant Izzet Baysal University, Bolu, Turkey, for low-risk prostate cancer between January 2017 to December 2021, were analysed. All the patients were in the low-risk group, according to the D'amico risk classification (PSA of ⩽10, clinical stage of pT1c and pT2a, and Gleason score of 6).[2]

The files of the patients were retrospectively reviewed from the hospital database. Age, preoperative PSA, body mass index, complete blood count parameters, preoperative MRI findings, prostate biopsy, and RP pathology results were investigated to detect tumour upgrade. The TRUS-Bx procedure was performed with Siemens Sonoline G20 EC9-4 transducer and a 4–9-MHz probe by single urologist expert in TRUS-Bx. The procedure was performed with patients in the left lateral decubitus position with their knees firmly on the abdomen. Before the biopsy, 1 mL of lidocaine was applied on each side between the prostate and the seminal vesicle, and 5 mL of lidocaine was used for peri-prostatic nerve block. The number of cores, number and percentage of positive cores, and Gleason scores of TRUS-Bx results were evaluated by the same expert uropathologist. None of TRUS-Bx pathological results were reported as sum of Gleason score 7 or more.

Mp-MRI scans (Magnetom 3T) was on performed all on patients before the TRUS-Bx. Image interpretation was done by a radiologist at least 5 years of experience in PI-RADS (Prostate Imaging-Reporting and Data System). Such parameters like PI-RADS score, prostate size, presence of extracapsular extension (ECE), and lesion size were recorded.[12]

After RP, surgical margin positivity, presence of LVI and ECE, tumour percentage and ISUP score of specimens, and lymph node positivity were examined. Both biopsy and radical prostatectomy specimens were examined by the same expert uropathologist.

Patients with sum of Gleason score 7 or more (ISUP score 2 or more) in the RP pathological report was defined as tumour upgrade. After RP, biochemical recurrence and follow-up times of the patients were recorded. The PSA cut-off value higher than 0.2 were considered as biochemical recurrence.[13] The receiver operating characteristic (ROC) curve was drawn for the size of nodule in MRI and the highest specificity and sensitivity values were accepted as the threshold values. The parameters affecting the Gleason score upgrade and biochemical recurrence were evaluated.

Characteristics of patients, preoperative MRI, biopsy results, and final pathology findings were compared using a chi-square test or Fisher's exact test for categorical data and student t-test for continuous data. The categorical variables were expressed as counts and percentages, and continuous variables were expressed as mean and standard deviation. Univariate logistic regression was applied to investigate the association of clinical variables with the upgrading of biopsy Gleason score. Variables with $p < 0.05$ in the univariate analysis were further assessed using multivariate logistic regression analysis to identify factors predictive of Gleason score upgrading. The data were analysed with SPSS 21.0 (IBM SPSS Corp., Armonk, NY, USA). The values less than 0.05 were considered statistically significant.

RESULTS

Mean age, follow-up time, and preoperative PSA level were 61.37 ± 5.53 (range 46-74) years, 42 ± 10 months, and 6.74 ± 1.97 (range 1.88-9.9) ng/dL, respectively. Gleason score upgrades were observed in 81 (61.3%) patients. Demographics of patients and final pathological findings of patients in RP radical prostatectomy specimens are shown in Table I.

When the ROC analysis was performed for tumour size, the threshold value was determined to be 10 mm with 49.4% sensitivity and 77.8% specificity (AUC: 0.634, $p<0.009$) (Figure 1). A tumour size of greater than 10 mm was associated with an increased tumour upgrade detection rate ($p=0.001$). The upgrade detection rate for lesion size shorter *vs.* longer than 10 mm was 49.4% *vs.* 76.9%.

In univariate analysis of demographics of the patients with ISUP upgrade in the final pathology results showed that prostate volume, PSA density, positive core number, percentage of tumour in core, lesion size in MRI, and ECE in MRI were statistically significant ($p<0.001$, $p=0.028$, $p=0.05$, $p=0.001$, and $p=0.05$, respectively). Logistic regression analysis revealed that prostate volume and MR lesion were independent predictors of ISUP score upgrade which were highlighted in Table II ($p=0.006$ and $p=0.025$, respectively).

In the analysis of ISUP upgrade according to pathological results of RP specimen's tumour percent was found a prognostic factor for ISUP score upgrading ($p=0.027$).

Biochemical recurrence was observed in 15 (11.1%) patients and the mean recurrence time was 9±7 months. In univariate analysis, preoperative PSA level, PSA density, ECE in MRI, surgical margin positivity, ECE in final pathology, and LN positivity were statistically significant ($p=0.034$, $p=0.009$, $p=0.012$, $p<0.001$, $p=0.032$, and $p<0.001$, respectively). Logistic regression analysis revealed that only surgical margin positivity was an independent factor for biochemical recurrence ($p=0.016$). Factors affecting the biochemical recurrence in patients with low-grade prostate cancer after RP are summarised and shown in Table III.

Table I: Preoperative characteristics of patients and pathological results of radical prostatectomy specimens.

		n=135
Age (y), mean± SD (min-max)		61.37 ± 5.53 (46-74)
BMI (kg/m^2), mean± SD (min-max)		25.34 ±2.72 (20-31)
N/L ratio mean± SD (min-max)		4.88 ± 2.81 (1.16-15.07)
Prostate volume (cc), mean± SD (min-max)		47.72 ± 13.9 (21-115)
Preoperative PSA (ng/dL), mean± SD (min-max)		6.74 ± 1.97 (1.88-9.9)
PSA density, mean± SD (min-max)		0.15 ± 0.05 (0.05-0.3)
Number of biopsy core, mean± SD (min-max)		10.56 ± 1.3 (6-16)
Number of positive core, mean± SD (min-max)		3.65 ± 2.04 (1-12)
Tumour percent, mean± SD (min-max)		35 ± 19.95 (8-100)
PI-RADS score, mean± SD (min-max)		3.43 ± 0.84 (2-5)
PI-RADS score, n (%)	2	28 (20.7)
	3	24 (17.8)
	4	80 (59.3)
	5	3 (2.2)
IEFF score, mean± SD (min-max)		16.02 ± 4.1 (5-25)
Nodule size in MRI (mm) mean± SD (min-max)		9.56 ± 3.4 (5-28)
SV invasion in MRI n (%)		9 (6.7)
ECE in MRI n (%)		23 (17)
Upgrade in final pathology, n (%)		81 (60)
Surgical margin positivity, n (%)		24 (17.8)
SV invasion, n (%)		9 (6.7)
ECE, n (%)		20 (14.8)
Capsule invasion, n (%)		61 (45.2)
LN positivity, n (%)		4 (3)
ISUP grade in final pathology, n (%)	1	54 (40)
	2	54 (40)
	3	19 (14.1)
	4	5 (3.7)
	5	3 (2.2)

BMI, Body Mass Index; N/L, Neutrophil/ Lymphocyte; PI-RADS, Prostate Imaging-Reporting and Data System; IIEF, International Index of Erectile Function; mean ± SD (min-max), mean ± standard deviation (minimum- maximum); n, number; y, year; SV, seminal vesicle; ECE, Extracapsular extension n, number; %, percent; LN, Lymph node; ISUP, International Society of Urological Pathology.

DISCUSSION

Treatment modalities from active surveillance to more complex radical surgeries in low-risk prostate cancer are still open to discuss due to the possibility of upgrading or upstaging of tumour. Some clinical and radiological parameters like African-American race, higher PSA, PSA density, aging, urban residence, the number of positive cores in biopsy, and PI-RADS grade 3 and higher lesions in multiparametric prostate MRI were reported as predictive factors for upgrading and upstaging of tumours.[14,15] In this study, 60% upstaging in the final pathology shows that low-stage prostate cancer is not always low-stage. So, more aggressive definitive treatment modalities should be kept in mind for low-stage prostate cancer as well.

Both the development of mp MRI and the experience of the evaluation with PI-RADS helped to enhance patient selection and identify clinically significant lesions to take a targeted or conventional biopsies. In recent studies, the higher PI-RADS are associated with the upstaging and suggested that it is an independent risk predictor for upstaging.[16,17] In this study, preoperative MRI revealed that 59.3% of the lesions were PI-RADS 4 and most of the upgraded patients were PI-RADS grade more than 3, though the authors could not find the statistically significant difference (64.2% *vs.* 55.8% and p=0.427).

The detection of clinically significant prostate cancer is increasing with the higher size of the lesion in mp MRI and a lower volume of the prostate. A study done by Ozden *et al*. showed that lesions diameter higher than 10 mL and volume of prostate lower than 30 mL had higher clinically significant prostate cancer detection rate.[18] Another study also showed that smaller prostate is much more likely to compose higher grade of tumour percent, local advanced disease, and Gleason upgrading.[8] Similar to those previous studies, prostate volume, PSA density, number of positive core and tumoural core percent, the diameter of lesions, and extracapsular extension in MRI were found the prognostic factors for upgrading in the univariate analysis, but only prostate size (43.9 mL *vs.* 53.5 mL) and diameter of lesions were the significant difference for upgrade in multivariable analysis which are seen in Table III (p=0.006 and 0.025, respectively).

Although biochemical recurrence (BCR) after primary treatment of a localised prostate cancer does not certainly lead to a clinically evident progressive disease, BCR and so additional salvage therapies like radiotherapy is the annoying complication after RP for low-risk patients.[19] Previous studies showed that higher body mass index, extraprostatic extension, and capsular invasion had a higher risk for a BCR in prostate cancer.[20-22] In fact, it seems that the factors affecting BCR and current lesions are caused by a higher tumour stage according to the tumour node metastasis (TNM) classification. This study supported the previous studies and showed aggressivity of tumours due to the factors of preoperative PSA level and PSA density, and ECE extension in MRI related to BCR. Furthermore, ECE, positive surgical margin, and LN metastasis were postoperative factors affecting BCR. Only the factor of positive surgical margin was the independent factor for BCR after RP in low-risk patients (p=0.016). This surgical margin positivity should be due to the cause of more intent to keep the neurovascular bundle to maintain erectile functions.

Patients with very slow or non-progressing cancer, like low-risk prostate cancer do not want to be in active therapies and thus do not have to suffer from the side effects of these focal therapies or radical surgeries. When the patients who met the criteria for active surveillance were offered the option of active surveillance, a study showed that 82% of the patients accepted active surveillance, and the main factors affecting the patients who did not accept active surveillance were higher mean PSA levels (8 *vs.* 7ng/mL, p= 0.02), the higher mean amount of cancer tissue (7 *vs.* 3 mm, p<0.001), and higher mean generic anxiety scores (42 *vs.* 38, p= 0.03).[23]

Table II: Demographics of patients according to international society of pathology upgrading in the final pathology.

	Upgrade		Univariate	Multivariate
	Yes (n=81)	No (n=54)	p-value	p-value**
Age (y), mean± SD	61.9 ± 5.2	60.6 ± 5.9	0.117	
BMI (kg/m^2), mean± SD	24.8 ± 2.8	25.8 ± 2.5	0.092	
N/L ratio, mean± SD	4.9 ± 2.7	4.8 ± 3.02	0.602	
Prostate volume (cc), mean± SD	43.9 ± 11.3	53.5 ± 15.6	<0.001	0.006
Preoperative PSA (ng/dL) mean± SD	6.6 ± 2.0	6.9 ± 1.9	0.434	
PSA density, mean± SD	0.16 ± 0.05	0.13 ± 0.04	0.025	0.761
Number of biopsy core, mean± SD	10.6 ± 1.2	10.5 ± 1.5	0.810	
Number of positive core, mean± SD	4 ± 2.2	3.11 ± 1.5	0.028	0.266
Core percent (%), mean± SD	38.1 ± 21.8	30.3 ± 15.8	0.050	0.660
IEFF score, mean± SD	15.4 ± 4.4	16.8 ± 3.5	0.162	
Lesions in MRI, n (%)				
PI-RADS ≤3	29 (55.8)	23 (44.2)	0.427	
PI-RADS >3	52 (64.2)	31 (37.3)		
Diameter of lesions, n (%)				
<10 mm	41 (49.4)	42 (50.6)	0.001	0.025
≥10 mm	40 (76.9)	12 (23.1)		
SV invasion in MRI, n (%)	7 (8.6)	2 (3.7)	0.315*	
ECE in MRI, n (%)	18 (22.2)	5 (9.3)	0.050	0.290
RRP pathology				
Surgical margin positivity, n (%)	16 (19.8)	8 (14.8)	0.462$^+$	
SV invasion, n (%)	6 (7.4)	3 (5.6)	0.673$^+$	
ECE positivity, n (%)	15 (18.5)	5 (9.3)	0.138$^+$	
Capsule invasion, n (%)	38 (46.9)	23 (42.6)	0.621$^+$	
LN positivity, n (%)	4 (100)	0 (0)	0.150*	
Tumour percent, med (IQR)	20 (19)	10 (17)	0.027$^{\&}$	0.284

BMI, Body Mass Index; N/L, Neutrophyl/ Lymphocyte; PI-RADS, Prostate Imaging- Reporting and Data System; IIEF, International Index of Erectile Function; mean ± SD, mean ± standard deviation); n, number; y, year; %, percent; cc, cubic centimeter; SV, seminal vesicle; ECE, Extracapsular extension, med (IQR), median (interquartile range). $^+$Denoted the Chi-square test, *Denoted the Fisher's exact test, and $^{\&}$Denoted the Mann Whitney U test.

Table III: Factors affecting the biochemical recurrence in patients with low grade prostate cancer after radical prostatectomy.

	Biochemical Recurrence		Univariate	Multivariate
	Yes (n=15)	No (n=120)	p-value	p-value**
Age (y) mean± SD	63.3 ± 5.2	61.1 ± 5.5	0.160	
BMI (kg/m^2), mean± SD	24.2 ± 3.1	25.4 ± 2.6	0.154	
N/L (ratio), mean± SD	4.1 ± 2.6	4.4 ± 2.8	0.252	
Prostate volume (cc), mean± SD	43.4 ± 15	48.2 ± 13.7	0.134	
Preoperative PSA (ng/dL), mean± SD	7.73 ± 1.88	6.62 ± 1.95	0.034	0.826
PSA density, mean± SD	0.19 ± 0.05	0.14 ± 0.05	0.009	0.359
Core (n), mean± SD	10.5 ± 0.91	10.5 ± 1.35	0.979	
Positive core (n), mean± SD	4.07 ± 3.05	3.6 ± 1.9	0.924	
Core percent mean± SD	38.47 ± 27.5	34.5 ± 18.9	0.941	
Lesions in MRI, n (%)				
PI-RADS ≤3	3 (5.8)	49 (94.2)	0.118	
PI-RADS >3	12 (14.5)	71 (85.5)		
Diameter of lesions, n (%)				
<10 mm	6 (7.2)	77 (92.8)	0.070	
≥10 mm	9 (17.3)	43 (82.7)		
SV positivity in MRI, n (%)	2 (13.3)	7 (5.8)	0.272*	
ECE in MRI, n (%)	6 (40.0)	17 (14.2)	0.012	0.437
Final pathology				
Surgical margin positivity, n (%)	9 (60)	15 (12.5)	<0.001	0.016
SV positivity, n (%)	3 (20)	6 (5)	0.062*	
ECE positivity, n (%)	5 (33.3)	15 (12.5)	0.032	0.292
Capsule invasion, n (%)	10 (66.7)	51 (42.5)	0.076	
LN positivity, n (%)	4 (26.7)	0 (0)	<0.001*	0.999
Tumour percent, mean± SD	24.73 ± 16.4	17.35 ± 12.27	0.076	

Abbreviations: BMI, Body Mass Index; N/L,neutrophyl/ Lymphocyte; PI-RADS, Prostate Imaging- Reporting and Data System; IIEF, International Index of Erectile Function; SD, standard deviation; n, number; y, year; %, percent; cc, cubic centimeter; SV, seminal vesicle; ECE, Extracapsular extension; LN, Lymph node.

Although similar prostate cancer-specific mortality rates in favourable-risk prostate cancer were reported in the studies, to choose a therapy more aggressive treatment than active surveillance, patients should be evaluated by keeping in mind that the patient-specific criteria like tumour size and prostate volume for tumour upgrade which were shown statistically significant in this study.

This study has potential limitations. The first and the most obvious limitation is its retrospective design and single centre study. The second, MRI- ultrasound fusion biopsy was not performed prior to radical surgery. So, it may cause to report the patient by mistake as low-risk and it may end up by a higher rate of ISUP upgrade in the final pathology. Other important limitation is the relatively short follow-up time. In relation with this short follow-up, disease-specific

survival was not examined. However, this study has some strengths. It should be considered that this study makes an important contribution since multiparametric MRI was performed on all patients to measure the exact prostate size and the diameter of lesions, which were independent predictive factors for ISUP upgrade.

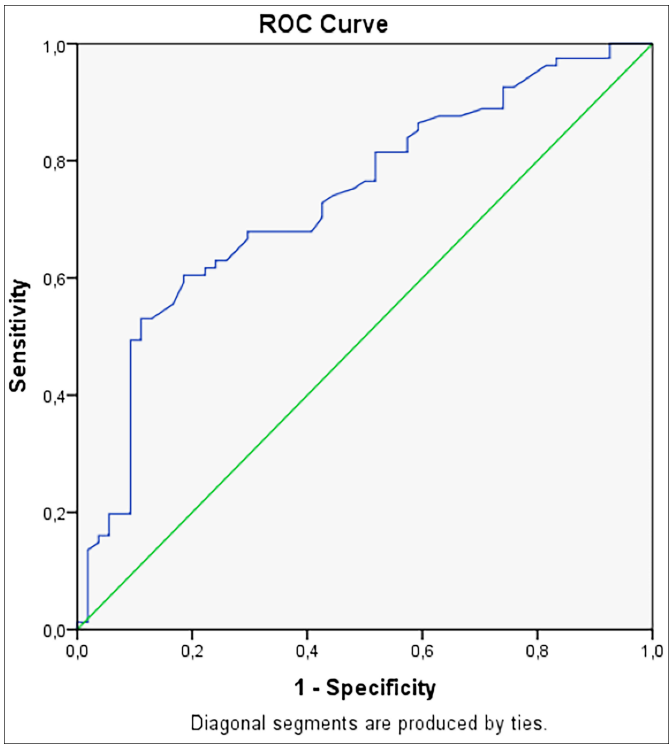

Figure 1: Receiver operating characteristic (ROC) curve of nodule size in MRI with and without ISUP upgrade.

CONCLUSION

More than half of the low-risk prostate cancer has a potential for ISUP score upgrade in the final pathology. Lower prostate volume and higher diameter of lesions in multiparametric MRI were associated factors affecting ISUP upgrade. Therefore, these patient-based factors should be considered to choose the treatment plan.

ETHICAL APPROVAL:

This study was approved by the Bolu Abant Izzet Baysal University research ethics review committee by providing the decision/protocol number of 2022/67 in May, 2022. This study was performed in accordance with the ethical standards of the Declaration of Helsinki.

PATIENTS' CONSENT:

An information leaflet was given, and informed consent were obtained from all the patients.

COMPETING INTEREST:

The authors declared no competing interest.

AUTHORS' CONTRIBUTION:

ES, BC: Design, data entry, writing, and editing.

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