A Modıfied Partın Table to Better Predıct Extracapsular Extensıon in Clınıcally Localızed Prostate Cancer

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Purpose: Prediction of extracapsular extension (ECE) before radical prostatectomy in clinically localized prostate cancer (PCa) is very important for clinical practice. ECE affects our decision on treatment strategy. The aim of this study is to identify the predictors of ECE, determine cut-off values, and compare them with the accuracy of Partin Table parameters to improve tumor staging in clinical practice.

Materials and Methods: 374 patients with clinically localized PCa who underwent open radical retropubic prostatectomy (RRP) were included in this study. Gleason Score (GS), age, digital rectal examination (DRE), prostate specific antigen (PSA), prostate specific antigen density (PSAD), free PSA, Free/Total PSA, prostate volume (PV), number of cores involved, tumor length, and tumor percentage in maximum involved core in biopsy were investigated.

Results: PSAD, tumor percentage, and tumor length are predictive factors of ECE. The cut-off values of PSA, PSAD, maximum tumor length, and maximum tumor percentages in predicting ECE are: > 8.90 ng/mL, > 0.26 ng/mL2, >5mm, and >50%, respectively. The cut-off values for Partin extraprostatic extension (EPE) and organ confined (OC) disease are >29% and ≤ 64%, respectively.

Conclusion: Partin tables could better predict extracapsular extension in clinically localized PCa if they include PSAD, tumor percentage, and tumor length. The cut-off values of these predictive factors can be beneficial in treatment strategies and in the decisions of lymphadenectomy and nerve-sparing surgery at radical prostatectomy.

Keywords: extracapsular extension; localized prostate cancer; partin table; PSA; PSAD; radical prostatectomy

INTRODUCTION

Prostate cancer (Pca) takes second place among all cancers seen in men[(1)]. The epidemiology of PCa differs between geographic regions, countries, and ethnicities. The incidence rate of PCa in Turkish ethnicity was found to be 7.9 per 100.000 by Basiri, A et al.[(2)]. Treatment strategy varies according to the clinical stage of PCa. Excellent results of radical prostatectomy (RP) are obtained when PCa is organ confined[(3)].

Exceeding tumor cells beyond the prostatic capsule, presence of tumor cells in the periprostatic tissue and/or neurovascular plexus, and ≥ pT3 with or without lymph positivity is defined as ECE. Clinically distinguishing organ confined (T stage 1-2 and N0) from locally advanced prostate cancer (LAPC) is very important. Locally advanced disease changes the treatment plan and the prognosis of PCa[(4,5)]. In the presence of locally advanced disease, lymphadenectomy is needed, nerve-sparing surgery cannot be done on the affected side, and rate of positive surgical margin increases [(4,6)]. If we can predict preoperative ECE, we can modify the treatment method and surgical technique in RRP. Lymphadenectomy and nerve-sparing surgery are related to the ECE status of the patient. We can inform the patient about the course of the disease, prognosis, and additional postoperative treatments. All these factors affect the oncologic outcomes, morbidity, and the risk of recurrence in patients.

ECE or lymph node involvement have been seen after RP in some patients diagnosed with localized PCa[(7,8)]. There are many studies in the literature dealing with ECE, upstaging, and upgrading between prostate biopsy and RP specimens[(9)].

Several clinical parameters, such as digital rectal examination (DRE), multiparametric magnetic resonance imaging (mpMRI), and preoperative Nomograms (Partin, Memorial Sloan Kettering Cancer Center, Kattan) are used in the prediction of disease extension in the literature.

We use Partin table frequently in our clinical practice in the prediction of final pathologic stage before RP. Partin uses DRE, biopsy PSA, and biopsy Gleason Score (GS) in the nomogram to predict extraprostatic extension (EPE), organ confined (OC) disease, seminal vesicle involvement (Sv+), and lymph involvement (Ln+) before RP. Partin table has a 95 % confidence interval for predicting the probabilities of each pathologic stage. Partin showed that using PSA, DRE, and biopsy GS together gives more accurate results than using these factors separately[(7,8)]. In recent years there have been various studies on adding mpMRI and some other predictive factors to the preoperative nomograms to improve tumor staging.

MATERIALS AND METHODS

This study was carried out in the urology department

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Table 1. Demographic, clinical and histopathological parameters in organ confined (group 1) and ECE group (group 2).

		Group 1 (n=248) (Organ Confined)	Group 2 (n=126)(ECE)	*P* value
Age (Years)	Min-Max (median)	53-82 (69)	54-82 (68)	[a]0,866
	Meann ± SD	68,48 ± 6,63	68,3 ± 6,76	
Prostate Volume (cc)	Min-Max (median)	12-125 (41,5)	15-90 (40)	[b]0,101
Mean±SD		49,14±25,0	41,63 ± 18,14	
Biopsy PSA ng/mL	Min-Max (median)	3,4-28 (7)	3,3-42 (10)	[b]0,001*
	Mean ± SD	8 ± 3,9	12,13 ± 7,59	
	<6,1	88 (35,5)	22 (17,5)	[c]0,001*
	6,1-10	116 (46,8)	42 (33,3)	
	>10	44 (17,7)	62 (49,2)	
Free PSA ng/mL	Min-Max (median)	0-2,3 (0)	0-2,4 (0)	[b]0,608
	Mean ± SD	0,19 ± 0,48	0,19 ± 0,53	
PSAD ng/mL2	Min-Mak (median)	0,1-1,2 (0,2)	0,1-1 (0,3)	0,001*
	Mean ± SD 0,20±0,13	0,32 ± 0,19		
F PSA/T PSA %	Min-Max (median)	0-0,7 (0,2)	0,1-0,2 (0,1)	[b]0,481
	Mean ± SD	0,20 ± 0,18	0,14 ± 0,03	
Number of positive cores	Min-Max (median)	1-12 (3)	1-12 (5)	b0,001*
	Mean ± SD	3,17 ± 2,09	5,38 ± 2,59	
	≤2	114 (46,0)	16 (12,7)	c0,001*
	≥3	134 (54,0)	110 (87,3)	
Tumor length in maximum	Min-Max (median)	1-12 (4)	2-18 (8)	b0,001*
involved core (mm)	Mean ± SD	4,15 ± 1,99	8,72 ± 3,38	
Percentage of tumor in	Min-Max (median)	7-90 (30)	12,5-100 (67)	[b]0,001*
maximum involved core %	Mean ± SD	33,64 ± 17,74	70,55 ± 23,45	
	< %25	106 (42,7)	4 (3,2)	[c]0,001*
	%26-50	104 (41,9)	20 (15,9)	
	> %51	38 (15,3)	102 (81,0)	

[a]Student t test [b]Mann Whitney U test [c]Pearson Chi square test *$p < 0,05$

of the university of health sciences, Prof. Dr. Cemil Taşçıoğlu city hospital, Istanbul, Turkey. 374 patients who had open RRP for clinical localized PCa (≤cT2c) between January 2015 and September 2020 were analyzed retrospectively. Prof. Dr. Cemil Taşçıoğlu City Hospital ethics committee approval was obtained and all patients provided informed consent (Date 14.07.2020 and No:304).

Patients with localized PCa (clinical stage ≤cT2) before RRP were included. Patients who were treated previously (radiation therapy or androgen deprivation), those with ≥cT3 or lymph positive preoperatively, those who had an active surveillance program before, and those with missing data were excluded. All 374 patients in our study group were evaluated as localized PCa (≤ cT2) and N0 before RRP.

PCa was diagnosed by transrectal ultrasound- guided prostate biopsy of minimum 12 cores based on elevated serum PSA, and mpMRI findings or palpable nodule at DRE. The clinical stage was evaluated using DRE, bone scan, computed tomography (CT), or mpMRI before RRP.

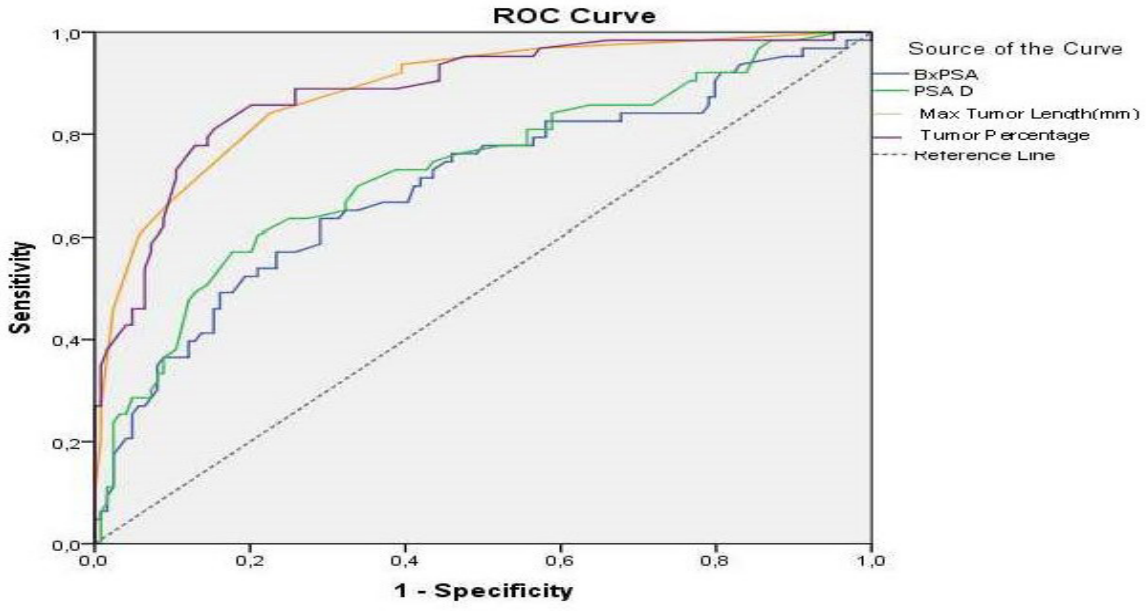

Figure 1. ROC curve of PSA,PSAD, tumor length and tumor percentage

Table 2. Biopsy and postoperative GS, preoperative clinical and postoperative pathologic stages of the patients.

Biopsy GS	3+3	196	52.4
	3+4	120	32.1
	4+3	46	12.3
	4+4	8	2.1
	4+5	4	1.1
Postoperative GS	3+3	116	31.0
	3+4	126	33.7
	4+3	110	29.5
	4+4	14	3.7
	4+5	8	2.1
Preoperative Clinical Stage	T1c	305	81.6
	T2a	61	16.3
	T2b - T2c	8	2.1
Postoperative Pathologic Stage	pT2a	32	8.5
	pT2b	46	12.3
	pT2c	170	45.5
	pT3a	82	21.9
	pT3a N1	10	2.7
	pT3b	26	7
	pT3b N1	8	2.1

Findings of DRE, age, GS of biopsy, PSA, free PSA, PV, PSAD, free/total PSA, Partin table parameters (EPE, OC, SVI, Ln+), tumor positive core numbers, tumor length, and tumor percentage in maximum involved core in prostate biopsy were investigated preoperatively and data were recorded retrospectively.

Extracapsular extension, apical, bladder neck and seminal vesicle involvement, positive surgical margin, vascular and perineural invasion, histology of tumor surrounding tissue, lymph node dissection, and positivity after RRP were recorded.

Biopsy Gleason Scores were graded according to the international society of urological pathology (ISUP) by two uropathology experts in our Hospital. These uropathologists also evaluated the presence of extraprostatic disease and other criteria in the final pathologic analysis of surgical specimens.

Invasion of adipose tissue and/or of the periprostatic neurovascular plexus and ≥pT3 with or without lymph-positivity were accepted as extraprostatic extension (ECE) of disease.

248 of the patients were evaluated as the organ confined group (group 1). They had clinical and pathological stage ≤cT2 before and after RRP. 126 of the patients had clinical and pathological stage ≤cT2 before but pathologic stage ≥pT3 (N0 or N1) after RRP and were evaluated as the ECE group (group 2).

We investigated clinical and histopathological parameters, PSAD, and Partin Nomogram parameters in predicting ECE in both groups and these values were compared to each other in terms of improving the accuracy of tumor staging.

Statistical analysis

We used the Number Cruncher Statistical System (NCSS) Statistical Software (NCSS, LLC, Kaysville, Utah, USA) in all statistical analysis.

Student's *t*- test, Mann-Whitney *U* test, Pearson's Chi-squared test, and ROC curve analysis were used. Logistic regression analysis was also performed. *P* values were considered statistically significant if $p < 0.05$.

RESULTS

Demographic, clinical and histopathological parameters in the organ confined (group 1) and ECE (group 2) groups are shown in **Table 1**.

Nodule on DRE, PSA, PSAD, number of positive cores, tumor length, and tumor percentage on maximum involved core showed a statistically significant difference between the two groups. Age, prostate volume, free PSA, and free PSA/total PSA values were not statistically different between the groups. Regarding PCa risk groups, distribution of patients with low, moderate, and high-risk groups were 52.4%, 38.5%, and 9.1%, respectively.

Overall, DRE positivity, ECE, and upgrading rates were 17.6%, 33.7%, and 37.5%, respectively.

Biopsy and postoperative GS, preoperative clinical and postoperative pathologic stages of the patients are shown in **Table 2**.

We detected ECE in 126 of 374 (33.7%) patients (group 2). 82 of these 126 patients (65.1%) upstaged to pT3a, 26 (20.6%) upstaged to pT3b, 10 (7.9%) upstaged to T3a N1, and 8 (6.3%) upstaged to T3b N1.

Upgrading rates in the ECE group in Gleason Score 3+3, 3+4, 4+3, and 4+4 patients were 24.2%, 7.3%, 3.5%, and 2.5%, respectively. Downgrading rates in Gleason Score 3+4, 4+3, and 4+5 patients were 2.4%, 2.6%, and 0.8%, respectively.

Determination of cut-off values for PSA, PSAD, tumor length, and tumor percentage in maximum involved core related to ECE is shown in **Table 3**.

Table 4 shows the logistic regression analysis of risk factors that affect upstaging.

The cut-off values for PSA, PSAD, tumor length, and tumor percentage were: >8.90ng/ml, >0.26ng/ml2, >5mm, and >50%, respectively. The accuracy rates of PSAD, tumor length, and tumor percentage were 73.8%, 79.7%, and 83.4% respectively.

The ODDS ratios (95% CI) for tumor percentage, tumor length, and PSAD were 9.898, 4.259, and 3.361, respectively.

ROC curves for PSA, PSAD, tumor length, and tumor percentage are shown in **figure 1**.

The AuROC (95% CI) of PSAD was higher than PSA, and the AuROC of tumor length and tumor percentage

Table 3. Determination of cut off values of PSA, PSAD, maximum tumor length and tumor percentage related to ECE.

	Biopsy PSA ng/mL (%95 CI 0.628-0.764)	**PSAD ng/mL2 (%95 CI 0.661-0.793)**	**Max Tumor Length (mm) (%95 CI 0.832-0.928)**	**Tumor Percentage (%95 CI 0.831-0.927)**
Area Under the ROC Curve AuROC (95%CI)	0.700 (0.628 0.764)	0.731 (0.661. 0.793)	0.886 (0.832. 0.928)	0.886 (0.831. 0.927)
Cut-off	>8.90	>0.26	>5	>50
Sensitivity	61.90 (48.8-73.9)	52.38 (39.4-65.1)	84.13 (72.7-92.1)	80.95 (69.1-89.8)
Specificity	70.97 (62.1-78.8)	84.68 (77.1-90.5)	77.42 (69.0-84.4)	84.68(77.1-90.5)
Positive Predictive Value (PPV)	52.00 (43.6-60.3)	63.50 (51.9-73.7)	65.40 (57.3-72.7)	72.90 (63.6-80.5)
Negative Predictive Value (NPV)	78.60 (72.4-83.7)	77.80 (72.8-82.1)	90.60 (84.4-94.5)	89.7 (83.9-93.6)
Accuracy	67.9 (58.4-81.0)	73.8 (62.9-84.7)	79.7 (69.8-89.6)	83.4 (74.2-92.6)

Table 4. Logistic regression analysis of factors that affect upstaging.

	p	Odds	95% C.I.Odds	
			Lower	Upper
Tumor length in max. involved core (mm) (>5)	0.030*	4.259	1.155	15.704
Tumor percentage % (>50)	0.000**	9.898	3.725	26.296
Number of positive cores (≥3)	0.096	2.480	0.851	7.224
PSAD ng/ml2 (>0.26)	0.005**	3.361	1.445	7.815

*$p < 0.05$

were higher than PSA and PSAD.
The cut-off values for Partin table parameters are shown in Table 5. The lowest accuracy rate was found in the Partin LN-positive parameter. The highest accuracy rate was in Partin OC.
The ROC curves of Partin table parameters are shown in **Figure 2**.
The AuROC of PSAD, max tumor length, and tumor percentage were 0.731, 0.886, and 0.886, respectively, all being higher than PSA (0.700), which is one of the Partin table criteria. The AuROC of Partin table EPE was 0.785, lower than max tumor length and tumor percentage.
192 of the 374 patients (51.3 %) had lymph node dissection. 122 of the 248 patients in the organ confined group (49.2 %) and 70 of the 126 patients in the ECE group (55.5%) had lymph node dissection.
We found the rate of apical involvement after RP as 60.2%, perineural invasion as 72.6%, ECE as 33.7%, bladder neck involvement as 8.1%, vascular invasion as 8.0 %, capsular invasion as 33.9%, SV+ as 9.1%, positive surgical margin as 14.3 %, LN+ as 4.8%, and high pin as 60.7%.
Histopathological characteristics in tumor surrounding tissues after surgery were nodular hyperplasia (89.3%), chronic prostatitis and nodular hyperplasia (5.9%), and chronic prostatitis (4.8%).

DISCUSSION

Some patients with prostate cancer have pathologic upstaging (ECE) and GS upgrading after RP[9]. The rate of upstaging varies between 29%-34% and upgrading varies between 24%-41% in the literature[9,10,11,12]). Upstaging and upgrading results may be associated with diagnostic problems in prostate biopsy like insufficient biopsy material and histopathologic evaluation of the Gleason grade of the tumor in biopsy[13]. This is related to the experience of the histopathologist who examines the tissue, and the urologist or radiologist who makes the biopsy. Number of biopsy cores and involved cores may also cause this difference.

Although our physicians who performed the prostate biopsy and the histopathologists who examined the tissue were very experienced, our ECE and upgrade rates were found very close to those in the literature.Extraprostatic extension (ECE) and positive surgical margins in PCa affect prognosis and survival[14,15,16].
In our study, 71.4% of overall upstaging occurred in cT1c patients, and 66.1% of overall upgrading occurred in biopsy Gleason score 3+3 patients. This shows that upstaging and upgrading occurs mostly in organ confined patients where ECE was not suspected according to preoperative findings. Therefore, predictive factors are very important in detecting upstaging, upgrading, ECE, and OC disease in clinical practice. In our study, the rates of upstaging (ECE) was 33.7% and upgrading was 37.5%.
Several studies in the literature have investigated the clinical and pathological predictors in the diagnosis of ECE. Age has been reported as one of the significant predictors of ECE in some studies[17,18]. However, we could not find age to be a significant predictor of ECE in our cohort ($p = 0.866$).
Valette et al., showed that tumor percentage is a predictor of EPE and adding it to the preoperative nomograms increases the accuracy of the nomogram[19]. We found the same result in our study. The highest accuracy rate for predicting ECE was found in tumor percentage (83.4%). X. Gao et al. included T1c-2b patients with Gleason scores ≤ 7 and PSA ≤ 10 ng/ml and found that the maximum percentage of tumor on the most involved core was predictive for EPE in both univariate and multivariate analysis[20] similar to our findings.
Horiguchi et al. found prostate volume to be a significant predictor for ECE in localized PCa[21]. However, Sayyid et al. did not find prostate volume to be a significant factor, similar to findings[18].
On the other hand, both Horiguchi et al. and Sayyid et al. found that PSA was a significant predictor of ECE, in parallel with our findings. Horiguchi et al. also determined, PSAD and Gleason score to be significant predictors [18,21]. Their ECE rate was 33.4% [21]. We found PSAD to be a significant predictor with an AuROC of 0.731 at 95% CI.
Horiguchi et al. reported that PSAD showed the largest area under the ROC curve among other parameters

Table 5. Cut-off values for Partin table parameters in our study

	Partin Epe (%95 CI)	Partin Oc (%95 CI)	Partin Sv+ (%95 CI)	Partin Ln+ (%95 CI)
AuROC (95%CI)	0.785 (0.716. 0.885)	0.791 (0.725. 0.847)	0.759 (0.684. 0.835)	0.773 (0.698. 0.848)
Cut-off	>29	≤64	>4	>1
Sensitivity	49.20 (36.9-61.5)	52.38 (40.0-64.7)	49.21 (36.9-61.6)	84.12 (75.1-93.1)
Specificity	91.13 (84.1-98.2)	90.32 (83.0-97.9)	91.94 (85.2-98.7)	50.81 (75.1-93.1)
PPV	73.81 (63.0-84.7)	73.33 (62.4-84.3)	75.61 (65.0-86.2)	46.49 (34.2-58.8)
NPV	77.93 (67.7-88.2)	78.87 (68.8-89.0)	78.08 (67.9-88.3)	86.30 (77.8-94.8)
Accuracy	77.01 (66.6-87.4)	77.54 (67.2-87.8)	77.54 (67.2-87.8)	62.03 (50.0-74.0)

Abbreviations: AuROC: Area under the ROC curve; PPV: Positive Predictive Value; NPV: Negative Predictive Value; CI: Confidence interval

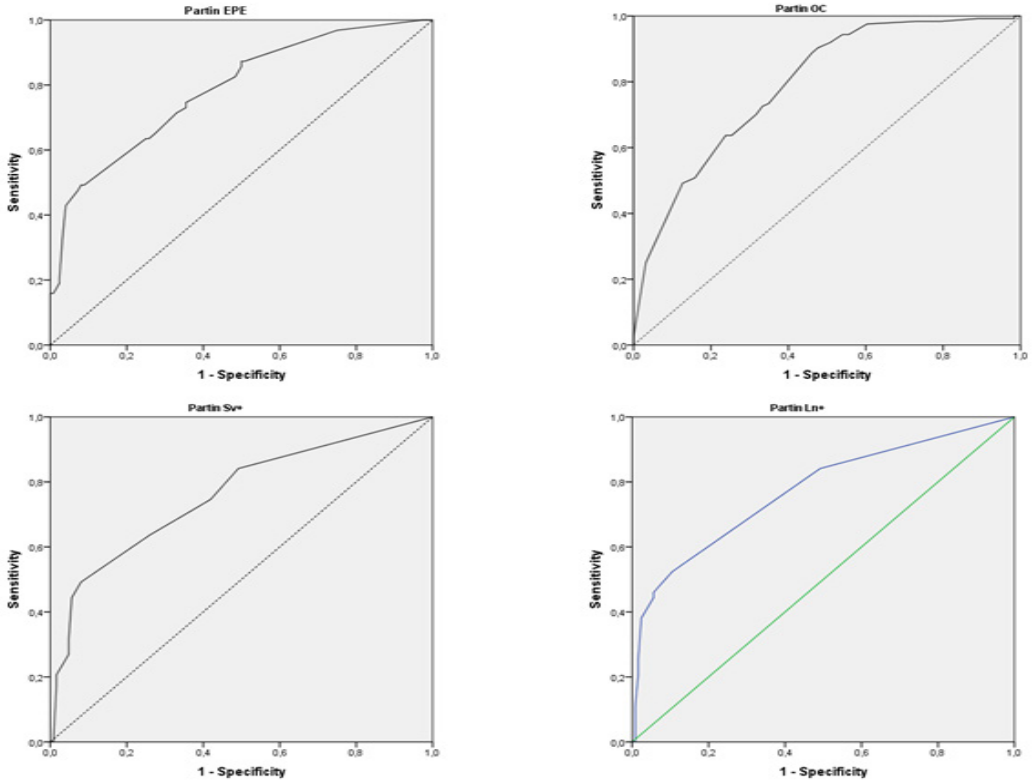

Figure 2. ROC Curves of Partin Table Parameters

(AuC=0.732). They found that using PSAD, MRI findings, and biopsy Gleason scores all together could give more information on staging[21].

Number of involved cores was found to be statistically different in our univariate analysis, but not in the multivariate analysis ($p = 0.096$).

We found DRE to be a predictive factor ($p = 0.005$). 82.4% of our patients had no positive finding in DRE. DRE is an easy, low-cost, and practical method, although with low sensitivity and a tendency to understage the disease[22]. It is difficult to find or feel small, centrally or anteriorly located tumors in DRE. Obesity is another problem for DRE. In our opinion, DRE is the weakest of the 3 criteria used in Partin Table to predict ECE, OC, SVI, and Ln+. Biopsy and clinical parameters are the findings at our disposal, that do not require anything else, are practical, useable, easily accessible, and cheaper; hence, we use them routinely in our clinical practice.

Tumor percentage, tumor length, and PSAD can be added to the Partin Table to predict tumor staging more accurately or these predictive factors can be used instead of DRE to predict ECE, OC, SVI, and Ln+ in localized PCa. In the coming years, depending on the advancements in technology, mpMRI criteria can may be added to Partin Tables (instead of DRE) to increase the accuracy of preoperative staging. So, we can make treatment plans more preicisely and make decisions of lymphadenectomy and nerve-sparing surgery more accurately.

Partin Tables have low sensitivity (28.1%) and PPV (42.9%), but high specificity (88.1%) and NPV (79.5%) for the diagnosis of EPE[23]. Here, we found Partin **Tables** to have a sensitivity, specificity, PPV, and NNP of 49.20%, 91.13%, 73.81%, and 77.93%, respectively for EPE. De Rooij et al. found the sensitivity and specificity of mpMRI in the detection of ECE as 57% and 91%, respectively[24].

There are different studies in the literature about adding mpMRI and some other predictive factors to preoperative nomograms to improve the accuracy of tumor staging. Jansen et al. showed that combining mpMRI with Partin and Memorial Sloan Kettering Cancer Center nomograms did not increase the accuracy rate of staging[25]. Gupta et al. compared the accuracy of mpMRI and Partin tables and showed that the diagnosis of organ confined disease was superior in mpMRI compared to Partin tables. They found the AuROC of mpMRI and Partin Tables to be 0.88 and 0.70, respectively[26].

We found the AuROC of Partin Table 0.791 and the AuROC of both tumor percentage and tumor length as 0.886, higher than the findings of Gupta et al.

The retrospective, and single-center nature of our research, along with the relatively small number of patients and the lack of mpMRI and targeted biopsies were the limitations in this study.

The indication and role of lymph node dissection in localized PCa has not been standardized yet. We use the value of Partin Ln+ as >5% for lymphadenectomy in our clinical practice. In this study, we found that Partin Ln+ had a cut-off value of >1%. If Partin Ln+ is >1%, we must perform lymphadenectomy without nerve-sparing surgery on the affected side in these patients due to the high possibility of ECE.

We found Partin Sv+ to have a cut-off value of >4%. We should consider lymphadenectomy in these patients as well.

CONCLUSIONS

PSA, PSAD, tumor percentage, and tumor length are predictive of ECE. If these factors are included in the content of the Partin Table, the accuracy rate of the Partin Table in tumor staging will increase significantly. The cut-off values of these predictive factors will be very useful in treatment strategies and the decisions for performing lymphadenectomy and nerve-sparing surgery.

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