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Original Article

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Lessons For COVID-19 Era: Impact of Delays in Surgery on Biochemical Recurrence-Free Survival and Adverse Oncological Outcomes in Patients with Prostate Cancer

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Abstract

Objective: To assess the impact of surgical delay in localized prostate cancer (PCa) on adverse pathological features and oncological outcomes.
Materials and Methods: Patients who underwent surgery for localized PCa were included from the Turkish Urooncology Association PCa database. History of previous treatment or active surveillance was considered an exclusion criterion. Patients were divided into two groups according to the time period between the diagnosis and surgery; less than or equal to 90 days (group 1) or longer than 90 days (group 2). Surgical pathology results and oncological outcomes were compared between the groups.
Results: In total, 2454 out of 3646 patients were assessed. Pathological findings of radical prostatectomy specimens were similar between the two groups. However, there was slightly more seminal vesicle invasion in the final surgical pathology in group 1 (12.9% vs. 9.3%, respectively p=0.042). The 5-year biochemical recurrence-free survival times were similar across all D'Amico risk categories between the two groups. The regression analysis demonstrated seminal vesicle invasion as the only factor affecting the time to prostate-specific antigen progression in high-risk patients (p<0.001 HR=2.51 confidence interval=1.58-4.45).
Conclusion: In conclusion, our results in this large cohort suggest that surgical delay does not cause a deterioration in PCa surgical outcomes, even in high-risk patients. These findings may be helpful for planning limited healthcare resources especially in conditions like the coronavirus disease-2019 pandemic where the availability and optimal use of healthcare system resources are crucial.
Keywords: Bladder cancer, cystectomy, prognosis

Introduction

After a new diagnosis of localized prostate cancer (PCa), treatment options may range from active surveillance (AS) to radical surgery in most cases (1). Patients are often encouraged to take a second opinion before deciding on the final treatment, but this decision-making process could prolong the duration between diagnosis and potential treatment. The current evidence on the impact of this waiting gap on the surgical and oncological outcomes of localized PCa is conflicting (2,3).

The coronavirus disease-2019 (COVID-19) pandemic clearly delayed surgical procedures because of the overwhelming number of infected patients in healthcare systems. Due to

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rapidly changing healthcare circumstances, the European Urological Association (EAU) and some national associations, including the Turkish Urooncology Association (TUA), published recommendations during the pandemic and suggested a delay for definitive surgical treatment of PCa, between 3 and 6 months, with respect to the risk groups of patients (4). Based on these recommendations, we aimed to assess the possible impact of the time between diagnosis and radical prostatectomy (RP) on the surgical and oncological outcomes of the disease.

Materials and Methods

Data of patients who received RP as the initial treatment for PCa were retrospectively reviewed in this study. The data source was the nationwide PCa database of the TUA. A total of 3646 patients were found to be treated with RP for localized diseases in the database. After excluding patients with missing data, the study population was reduced to 2454 patients. Patients were divided into two groups according to the waiting period between diagnosis and RP. The waiting periods in respective groups was; group 1: Less than or equal to 3 months, and group 2: More than 3 months.

Based on the D'amico classification system, patients were stratified into low, intermediate, and high-risk groups. The date of prostate biopsy was considered the diagnosis date, and the time to treatment was calculated as the number of days between the date of RP and the diagnosis date. Patients who received treatment for PCa (radiotherapy or androgen deprivation therapy etc.) prior to RP or patients who were first enrolled on the AS protocol were excluded from the study.

All patients were diagnosed with either standard transrectal ultrasound-guided biopsy or magnetic resonance guided fusion biopsy. All RPs were included in the study regardless of the surgical approach (robot-assisted, laparoscopic or open). Patients were operated on by senior urology staff at each participating center. Both biopsy and RP specimens were evaluated by a dedicated uro-pathologist at each center.

Biochemical recurrence, which was defined as a prostate-specific antigen (PSA) level >0.2 ng/mL during the follow-up after RP, was designated as the primary endpoint for this study. The secondary endpoints of the study were surgical parameters, pathological upgrading, metastasis on follow-up, and the need for additional treatments. For the time-based analysis and comparison of oncological outcomes (biochemical recurrence-free survival, need for adjuvant treatment, or metastasis-free survival), only patients with a follow-up duration of >1 month were included in the statistical tests.

The study data were collected using the REDCap data collection software developed by Vanderbilt University and licensed to TUA (5,6). All data were stored in a secure server, and all personal information of the patients was anonymized.

For statistical analysis, Python Programing Language (Open source v3.7) was used with the help of the pandas, plotlib, NumPy, sciPy, and lifelines (7) libraries. JupyterLab (Open source v1.2.6) was used as the coding interface. The scalar variables were analyzed using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's tests) to determine whether or not they were normally distributed. Descriptive analyses are presented as means and standard deviations when variables were normally distributed. Medians and interquartile ranges were used if variables were not normally distributed. For the comparison of scalar variables between the two groups, the t-test or Mann-Whitney U test was used for normally and non-normally distributed variables, respectively.

Statistical Analysis

Categorical variables were compared using the chi-square test between groups. If the assumptions of chi-square do not hold due to low expected cell counts, Fisher's exact test was used for the comparison of categorical variables. For biochemical recurrence-free survival variables, Kaplan-Meier survival estimates were calculated. A separate log-rank test was used to estimate the independent effect of waiting duration on the time to biochemical recurrence. Possible factors identified during univariate analysis were further evaluated using Cox regression. The proportional hazard assumption was assessed by residual analysis. For all statistical tests, p=0.05 was considered statistically significant.

Results

The mean age of patients was 62.35±6.64 years. The study included 1959 and 495 patients in groups 1 and 2, respectively. Groups were distributed similarly with respect to PSA value on diagnosis, Gleason grade groups of biopsy pathology, and D'amico risk group (Table 1). Pre-diagnostic properties were similar between the two groups for each D'amico risk group (Table 2). The median elapsed time until treatment was 51 (38-65) days for group 1 and 119 (104-141) days for group 2.

Surgical and pathological parameters, including lymph node (LN) dissection, per-operative complications, type of RP, surgical margin (SM) status, LN positivity, extracapsular extension (ECE), seminal vesicle (SV) invasion, and Gleason grade at RP were in low, intermediate and high-risk patients (p>0.05) (Table 3). On the other hand, in intermediate-risk patients, the nerve-sparing rate was found to be higher in group 1 (p=0.032). Additionally, in low-risk patients, in group 1, the Gleason grade group showed a significantly higher RP pathology rate compared with biopsy pathology (p=0.046) (Table 3).

When we compared 2 groups according to surgical and pathological findings, we found no significant differences between the 2 groups regarding any parameters, except SV invasion, nerve-sparing rate, and surgical modality in final pathology. Significantly more SV invasion in final RP pathology was found in group 1. (12.9% vs. 9.3%, respectively p=0.042) Also more nerve-sparing (48.0% vs 41.1, respectively p=0.014) and open surgeries (67.7% vs. 62.0%, p=0.014) were performed in group 1 (Table 4).

Oncological outcomes like the need for adjuvant treatment, PSA recurrence, and development of metastasis on follow-up were similar between the low-risk and intermediate-risk patients (Table 5). In high-risk patients, the adjuvant treatment needs rate was higher in group 1 (p=0.023) whereas there was no statistically significant difference between the groups with respect to metastasis rate and PSA recurrence rate (Table 5). Estimated 5-year biochemical recurrence-free survival rates were

similar in both groups for all three risk categories (p=0.700, 0.932 and 0.085 respectively) (Figure 1).

High-risk patients were further analyzed for factors affecting biochemical recurrence-free survival via multivariate analysis. Cox regression analysis including patients' waiting period, PSA value at the time of diagnosis, Gleason grade in prostate biopsy and RP specimens, presence of positive SMs, and/or SV invasion demonstrated that the main factor affecting time to PSA progression in high-risk patients was SV invasion [p<0.001, HR=2.51, confidence interval (CI)=1,58-4,45]. Other factors, including time to surgery (p=0.156, HR=0.63, CI=0.33-1.19) did not have any statistically significant impact on the outcome.

Discussion

In patients with localized PCa, our results showed that SM status, LN positivity, and the presence of ECE were similar irrespective of the waiting period between diagnosis and RP; however, there was a slightly higher SV invasion rate in the final RP pathology of patients with a "diagnosis to surgery time" 90 days. Similarly, in a low-risk subgroup, Gleason grade group upgrading in RP was significantly higher in group 1 than in group 2. However, the 5-year biochemical recurrence-free survival rates were similar for all three risk categories between the two study groups. In high-risk patients, the need for adjuvant treatment was higher in group 1, and the regression analysis demonstrated that the only factor affecting the time to PSA progression in the high-risk patient population was SV invasion at the time of RP pathology.

In the present study, the median time elapsed until treatment was 119 (104-141) days in group 2, and the biochemical recurrence rate in the high-risk patient category at this cut-off point (22.6%) was not statistically significant (p=0.605, data not shown). Since the number of patients with a delay time of >4 months was limited in our study, it was not possible to determine a safe cut-off time. On the other hand, our results

Table 1. General patient characteristics

		Group 1 (≤3 Months)	Group 2 (>3 Months)	p-value
Age	**Mean (SD)**	62.26 (6.63)	62.52 (6.77)	0.176[1]
BMI	**Mean (SD)**	27.14 (3.77)	27.02 (2.97)	0.7138[1]
PSA	**Median (IQR)**	7.20 (5.12-11)	7.22 (5.08-11.26)	0.730[2]
Gleason grade group n (%)	**1**	1017 (51.91)	284 (57.37)	0.133[3]
	2	555 (28.33)	119 (24.04)	
	3	191 (9.75)	52 (10.51)	
	4	110 (5.62)	20 (4.04)	
	5	86 (4.39)	20 (4.04)	
D'amico group n (%)	**Low risk**	775 (39.56)	218 (44.04)	0.193[3]
	Intermediate risk	869 (44.36)	203 (41.01)	
	High risk	315 (16.08)	74 (14.95)	
Biopsy type n(%)	**Classical**	1823 (93.06)	471 (95.15)	0.092[3]
	MR fusion	136 (6.64)	124 (4.85)	

BMI: Body mass index, SD: Standard deviation, IQR: Interquartile range, MR: Magnetic resonance. [1] Independent samples t-test, [2] Mann-Whitney U test, [3] x^2 test

Table 2. General patient characteristics among the risk groups

		Low risk			Intermediate risk			High risk		
		G1	**G2**	**p-value**	**G1**	**G2**	**p**	**G1**	**G2**	**p-value**
Age mean (SD)		60.9 (6.53)	61.59 (6.72)	0.175[1]	62.94 (6.5)	63.25 (6.82)	0.545[1]	63.74 (6.61)	64.53 (6.25)	0.348[1]
BMI mean (SD)		26.67 (3.86)	26.57 (3.02)	0.850[1]	27.24 (3.8)	27.32 (3.18)	0.894[1]	27.67 (3.45)	27.48 (2.01)	0.788[1]
PSA median (IQR)		5.71 (4.5 - 7.2)	5.56 (4.3 - 7.3)	0.317[2]	8.7 (5.8 - 12.0)	10.13 (5.6 - 12.5)	0.187[2]	18.0 (8.0 - 28.9)	20.94 (8.0 - 27.0)	0.990[2]
Gleason grade group n (%)	1	775 (100.0)	218 (100.0)	-	199 (22.9)	53 (26.11)	0.302[3]	43 (13.65)	13 (17.57)	0.697[3]
	2	-	-		514 (59.15)	108 (53.2)		41 (13.02)	11 (14.86)	
	3	-	-		156 (17.95)	42 (20.69)		35 (11.11)	10 (13.51)	
	4	-	-		-	-		110 (34.92)	20 (27.03)	
	5	-	-		-	-		86 (27.3)	20 (27.03)	
Biopsy type n (%)	St	729 (94.06)	209 (95.87)	0.303[3]	795 (91.48)	191 (94.09)	0.219[3]	299 (94.92)	71 (95.95)	0.713[3]
	MR	46 (5.94)	9 (4.13)		74 (8.52)	12 (5.91)		16 (5.08)	3 (4.05)	

SD: Standard deviation, BMI: Body mass index, IQR: Interquartile range, St: Standard, MR: MR Guided G1: Group 1 (≤3 months), G2: Group 2 (>3 months). [1]Independent samples t-test, [2]Mann-Whitney U test, [3] x^2 test

Table 3. Surgical and pathological characteristics according to D'amico risk categories										
		Low risk			Intermediate risk			High risk		
		G1	G2	p-value*	G1	G2	p-value*	G1	G2	p-value*
Nerve sparing n (%)	-	344 (50.74)	101 (54.89)	0.317	369 (49.2)	92 (58.6)	**0.032**	159 (63.6)	40 (72.73)	0.198
	+	334 (49.26)	83 (45.11)		381 (50.8)	65 (41.4)		91 (36.4)	15 (27.27)	
LN dissection n (%)	-	604 (79.16)	168 (79.25)	0.979	450 (52.69)	104 (53.06)	0.926	59 (18.85)	17 (23.29)	0.391
	+	159 (20.84)	44 (20.75)		404 (47.31)	92 (46.94)		254 (81.15)	56 (76.71)	
Per-op complication n (%)	-	717 (95.09)	186 (93.94)	0.513	796 (93.87)	187 (94.92)	0.572	297 (95.81)	67 (95.71)	0.972
	+	37 (4.91)	12 (6.06)		52 (6.13)	10 (5.08)		13 (4.19)	3 (4.29)	
RP type n (%)	O	503 (65.92)	133 (62.15)	0.306	592 (69.0)	123 (61.81)	0.051	211 (68.73)	46 (62.16)	0.279
	R/L	260 (34.08)	81 (37.85)		266 (31.0)	76 (38.19)		96 (31.27)	28 (37.84)	
Surgical margin n (%)	-	571 (76.03)	159 (78.33)	0.494	554 (65.95)	126 (67.38)	0.709	122 (40.13)	28 (43.08)	0.661
	+	180 (23.97)	44 (21.67)		286 (34.05)	61 (32.62)		182 (59.87)	37 (56.92)	
LN positivity n (%)	-	125 (96.9)	31 (96.88)	0.994	339 (91.87)	73 (91.25)	0.855	169 (68.98)	34 (69.39)	0.955
	+	4 (3.1)	1 (3.12)		30 (8.13)	7 (8.75)		76 (31.02)	15 (30.61)	
ECE n (%)	-	589 (83.43)	149 (81.42)	0.519	462 (59.38)	105 (61.4)	0.626	111 (38.95)	22 (31.88)	0.277
	+	117 (16.57)	34 (18.58)		316 (40.62)	66 (38.6)		174 (61.05)	47 (68.12)	
SV invasion n (%)	-	726 (96.41)	197 (98.5)	0.133	729 (87.52)	167 (88.83)	0.619	192 (62.95)	49 (72.06)	0.156
	+	27 (3.59)	3 (1.5)		104 (12.48)	21 (11.17)		113 (37.05)	19 (27.94)	
Gleason grade group (RP) n (%)	**1**	471 (62.06)	150 (69.44)	0.162	158 (18.48)	44 (22.0)	0.123	17 (5.54)	5 (7.04)	0.056
	2	226 (29.78)	53 (24.54)		479 (56.02)	102 (51.0)		72 (23.45)	15 (21.13)	
	3	37 (4.87)	11 (5.09)		155 (18.13)	41 (20.5)		77 (25.08)	10 (14.08)	
	4	16 (2.11)	1 (0.46)		45 (5.26)	5 (2.5)		49 (15.96)	21 (29.58)	
	5	9 (1.19)	1 (0.46)		18 (2.11)	8 (4.0)		92 (29.97)	20 (28.17)	
Gleason grade upgrade n (%)	-	471 (62.06)	150 (69.44)	**0.046**	643 (75.2)	156 (78.0)	0.406	236 (76.87)	52 (73.24)	0.517
	+	288 (37.94)	66 (30.56)		212 (24.8)	44 (22.0)		71 (23.13)	19 (26.76)	

LN: Lymph node, RP: Radical prostatectomy, O: Open, R/L: Robot-assisted/laparoscopic, ECE: Extracapsular extension, SV: Seminal vesicle, G1: Group 1 (≤3 months), G2: Group 2 (>3 months). *x^2 test

clearly indicated a safe waiting period of up to 4 months. To evaluate longer delay times, studies including more patients with longer wait times are needed.

This was one of the studies with the largest number of patients on this subject. Because our data source was a nationwide database with patient information from reference centers throughout Turkey, the results could be generalized to the general population in Turkey. Most of the published data on surgical delay times are derived from AS studies and conducted in low/intermediate-risk groups (8,9). There are few studies that include high-risk patients with PCa, but there is no uniformity in these studies with respect to risk classification criteria or time cut-off levels for surgical delay (10,11). Our study is also one of the few studies that included all of the risk groups. Patients who were first enrolled in AS were excluded from our study, which enabled us to assess time delay more objectively, especially in low-risk patients.

Decision-making regarding a treatment modality based on the available options could be challenging for patients with PCa, especially those with localized diseases. Furthermore, as the COVID-19 pandemic has demonstrated, in some situations, public health regulations and the status of health care systems could necessitate delays in the treatment of patients. In most cases, guidelines specify treatment options, but they do not comment on treatment timing. For most cancer types, debate exists regarding the time intervals and their effects on oncological outcomes (12).

Urological cancers are no exception to these debates, and some studies have investigated the effect of treatment delay in all urological cancers. Urothelial cancer, which is a typical example, has been proven to be adversely affected by delayed treatment. Hollenbeck et al. (13) showed that >25% of patients had delays of >3 months from the first occurrence of hematuria to a definitive diagnosis. They also demonstrated that patients with a longer delay needed more radical interventions, including cystectomy, and the mortality rate was higher in this group (13). On the other hand Wallace et al. (14) showed that, although a shorter delay in the hospital did not have a profound impact, longer delays in treatment due to factors associated with referral patterns cause worse outcomes.

Table 4. Surgical and pathological characteristics of the study groups				
		G1	G2	p-value*
Nerve sparing n (%)	-	872 (51.97)	233 (58.84)	**0.014**
	+	806 (48.03)	163 (41.16)	
LN dissection n (%)	-	1113 (57.67)	289 (60.08)	0.337
	+	817 (42.33)	192 (39.92)	
Per-op complication n (%)	-	1810 (94.67)	440 (94.62)	0.971
	+	102 (5.33)	25 (5.38)	
RP type n (%)	**O**	1306 (67.74)	302 (62.01)	**0.017**
	R/L	622 (32.26)	185 (37.99)	
Surgical margin n (%)	-	1247 (65.8)	313 (68.79)	0,226
	+	648 (34.2)	142 (31.21)	
LN positivity n (%)	-	633 (85.2)	138 (85.71)	0.866
	+	110 (14.8)	23 (14.29)	
ECE n (%)	-	1162 (65.69)	276 (65.25)	0.865
	+	607 (34.31)	147 (34.75)	
SV invasion n (%)	-	1647 (87.1)	413 (90.57)	**0.042**
	+	244 (12.9)	43 (9.43)	
Gleason grade group (RP) n (%)	**1**	646 (33.63)	199 (40.86)	0.053
	2	777 (40.45)	170 (34.91)	
	3	269 (14.0)	62 (12.73)	
	4	110 (5.73)	27 (5.54)	
	5	119 (6.19)	29 (5.95)	
ISUP upgrade n (%)	-	1350 (70.28)	358 (73.51)	0.160
	+	571 (29.72)	129 (26.49)	

LN: Lymph node, RP: Radical prostatectomy, O: Open, R/L: Robot-assisted/laparoscopic, ECE: Extracapsular extension, SV: Seminal vesicle, ISUP: International Society of Urological Pathology, G1: Group 1 (≤3 Months), G2: Group 2 (>3 months) *x^2 test

Table 5. Oncological outcomes										
		Low risk			Intermediate risk			High risk		
		G1	G2	p-value*	G1	G2	p*	G1	G2	p-value*
PSA recurrence n (%)	-	589 (89.92)	148 (91.36)	0.582	629 (85.69)	129 (86.0)	0.922	178 (67.17)	48 (80.0)	0.051
	+	66 (10.08)	14 (8.64)		105 (14.31)	21 (14.0)		87 (32.83)	12 (20.0)	
Additional therapy n (%)	-	603 (92.06)	147 (90.74)	0.583	609 (82.97)	121 (80.67)	0.498	157 (59.25)	45 (75.0)	**0.023**
	+	52 (7.94)	15 (9.26)		125 (17.03)	29 (19.33)		108 (40.75)	15 (25.0)	
Metastasis on follow up n (%)	-	649 (99.08)	160 (98.77)	0.712	713 (97.14)	144 (96.0)	0.460	243 (91.7)	55 (91.67)	0.994
	+	6 (0.92)	2 (1.23)		21 (2.86)	6 (4.0)		22 (8.3)	5 (8.33)	

G1: Group 1 (≤3 months), G2: Group 2 (>3 months). *x^2 test

Testicular cancer is traditionally considered a urological emergency. Although there are some reports demonstrating the adverse effects of treatment and diagnosis delay in testicular cancer (15,16), there are also studies that do not show any benefit of early surgery in seminomatous tumors (17,18). Since the timing of surgery is still controversial, there are no recommendations regarding the timing of orchiectomy in the guidelines of EAU. Physicians are also encouraged to offer sperm cryopreservation to patients before orchiectomy in EAU guidelines, which could result in short delays in surgery (19).

The number of treatment delays in renal cell carcinoma is even more limited. There are reports indicating that delays in surgery have no impact on disease-specific survival for small (<4 cm) renal masses (20,21). On the other hand, for renal masses >4 cm in diameter, surgery is recommended before 1 month in a recent review, although there is no objective evidence demonstrating the adverse effect of late surgery (22).

Studies on the effect of surgical delay on PCa prognosis are also limited. In 2017, a Canadian study demonstrated that even in patients with high-risk diseases, surgical wait time does not affect pathological outcomes after robot-assisted RP (RARP) (23). Furthermore, a recent study conducted on 2303 men demonstrated that in an unfavorable prognosis group, a waiting period of up to 6 months does not have any adverse effect

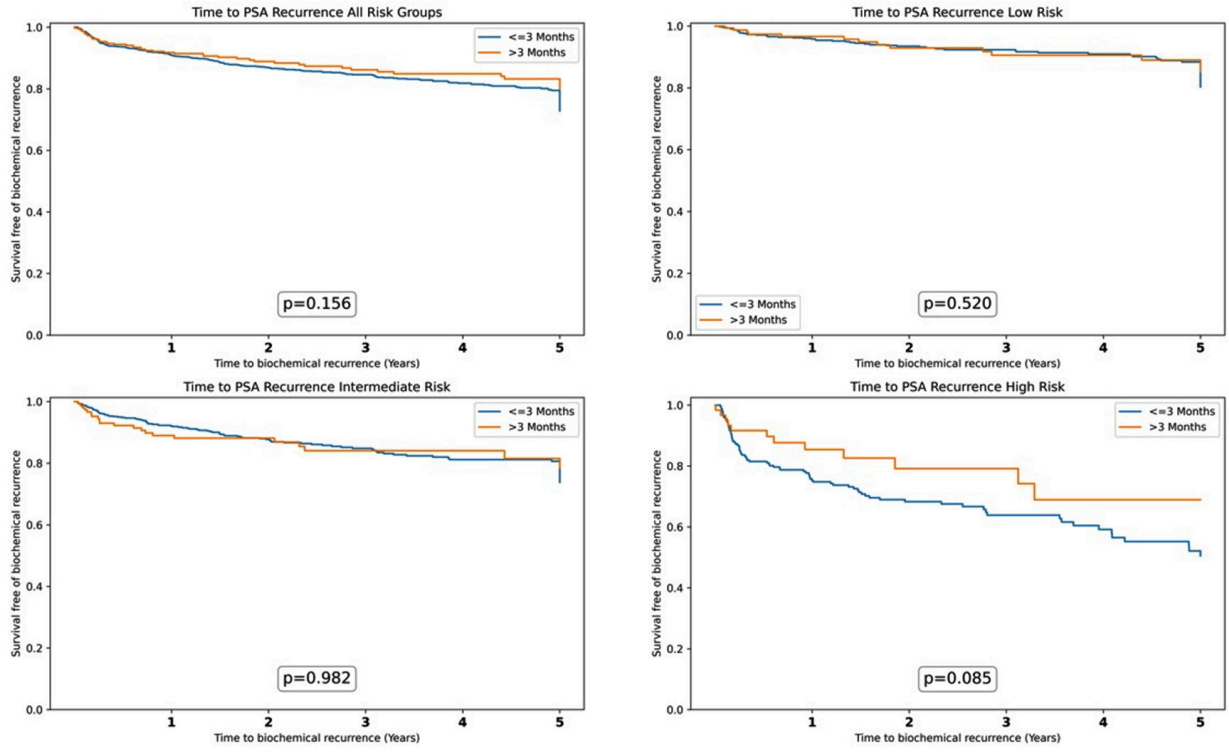

Figure 1. Estimated 5-year biochemical recurrence-free survival rates

on disease outcomes (11). Similarly, Morini et al. (24) showed that even in patients who had a waiting period of more than 6 months before treatment, oncological results were not adversely affected. Other studies have reported similar results and could not find an association between surgical delay time and disease progression (25-27).

Despite the results of some studies showing no effect of surgical delay times in patients with PCa, there are also contrasting reports demonstrating the delay in time to treatment as an unfavorable prognostic factor. In a series of 1111 low-risk PCa patients, O'Brien et al. (28) reported worse oncological outcomes for patients who waited more than 6 months for the surgery. A more recent study performed on RARP patients showed that increased duration from biopsy to surgery may lead to more biochemical recurrence in the high-risk group (10).

Our study, in concordance with previous studies, showed no correlation between surgical delay and biochemical recurrence-free survival in the overall patient cohort and after risk group stratification. Although some studies demonstrated worse outcomes with prolonged surgical delay in high-risk patients, those reports were limited in patient numbers and had a different time cut-offs. The absence of a standardized definition of the duration of the cutoff in studies may be the underlying reason for the contrasting results of the different studies.

Study Limitations

Our study is not without limitations. First, this is a retrospective analysis, and selection bias could be an issue, as in all studies of this kind. Second, this is a multi-institutional study and there are more than one operating surgeon who performed the surgeries and uro-pathologists who assessed the RP specimens. Both surgical experience and surgical technique (open, robot-assisted, or laparoscopic) might have influenced patient outcomes. Our study marked the date of prostate biopsy as the reference point to calculate the time to surgery, but this may not always reflect the actual duration of the disease because the patients' first admission to the physician and the timing of the prostate biopsy may differ between various institutions, even within the same hospital system. In an attempt to overcome bias, we stratified patients according to their D'Amico risk groups to provide a more balanced distribution among cohorts. The median delay time in patients who waited longer than 90 days was 4 months in our study. This is a limiting factor for this study to comment on longer delay times and specify a safe surgical time cut-off.

Conclusion

This study is one of the largest to investigate the effect of surgical delay on the outcome of PCa using data originating from daily practice. Our results indicate that patients could be reassured that delays in the time to surgery will not result in adverse outcomes, even in the high-risk group. Our findings may also be helpful in planning for limited healthcare resources, especially in conditions like the COVID-19 pandemic.

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Original Article

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Correlation of Multiparametric Prostate MRI with Prostate Biopsy and Radical Prostatectomy Histopathology

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Abstract

Objective: Prostate cancer (PCa) is the most common cancer responsible for cancer deaths in men after lung cancer. In this study, we aimed to obtain information about the Gleason score of PCa by prostate image reporting and data system (PIRADS) scoring of multiparametric magnetic resonance imaging (mpMRI) by comparing mpMRI results with the histopathology of prostate biopsy and radical prostatectomy specimen.

Materials and Methods: A total of 214 patients who applied to the outpatient clinic of Hatay Mustafa Kemal University Faculty of Medicine, Department of Urology between January 2019 and April 2021 with elevated prostate-specific antigen (PSA) levels were included in the study. All patients underwent mpMRI before the biopsy procedure. PIRADS scoring was performed by the same radiologist. Prostate biopsy was systematically performed by experienced urologists as 12 quadrant biopsies.

Results: When the mpMRI results of the patients are evaluated; the most common patterns are seen as PIRADS 2 and PIRADS 4, followed by PIRADS 3 lesions, followed by PIRADS 5 lesions, and PIRADS 1 lesions, which were the least frequent. When the analysis was applied to predict PCa over the pyrans value, the receiver operating characteristics analysis result for the diagnosis of the disease showed statistically significant levels of area under the curve (0.860; p<0.001), with a sensitivity of 81% and a sensitivity of 3 and above PIRADS 3 and above. It can predict cancer with 75 specificity. In the correlation analysis, there was a low but significant correlation between PIRADS and PSA value (r=0.252; p<0.001).

Conclusion: We found that patients presenting with elevated PSA levels and mpMRI had a high power in detecting PCa. We also found a strong relationship between ISUP rating and PIRADS. As a result, it is thought that the pathology of the patients can be predicted using mpMRI.

Keywords: Gleason score, multiparametric magnetic resonance imaging, prostate cancer, radical prostatectomy

Introduction

Each year, approximately one million men worldwide are diagnosed with prostate cancer (PCa), resulting in approximately 300,000 deaths; PCa ranks as the second leading cause of cancer-related mortality among men, following lung cancer (1). The introduction of the prostate-specific antigen (PSA) test in the 1990s provided an easy and cost-effective means of detecting PCa at an earlier stage (2). Systematic biopsy guided by transrectal ultrasound (TRUS) is the next conventional step in the diagnostic process (3).

PSA has been used as a screening test for PCa because of its high sensitivity, yet it frequently faces criticism for its low specificity (4). The common use of PSA leads to the diagnosis of clinically insignificant PCas and subsequent overtreatment. Currently, PCa diagnosis relies on PSA measurement, and digital rectal examination (DRE) is employed as a screening method. PSA levels can also increase in cases of benign prostate hyperplasia and prostate infections. Screening based on serum PSA levels reduces disease-specific mortality. However, this benefit of PSA has led to a 70-80% rising in prostate biopsies performed (5). Multiparametric magnetic resonance imaging (mpMRI) of the prostate has been shown to be necessary for the diagnosis, treatment, and monitoring of localized PCa with strong evidence (6). MRI has been demonstrated to improve the detection of clinically significant cancer while reducing the identification of

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clinically insignificant cancer (7). Additionally, it is employed to illustrate extracapsular extension in patients diagnosed with PCa via biopsy. The use of mpMRI is beneficial in cases where the biopsy is negative but the PSA level remains consistently high, helping to identify the primary tumor and its exact location. Another indication is to investigate local recurrence in patients who have undergone radical prostatectomy with persistent elevation of PSA (8). The application of mpMRI for PCa has been revolutionary in the diagnosis and staging of PCa (8). MRI is the most efficient method for the detection, localization, and assessment of local invasion of PCa. mpMRI, which combines anatomical and functional sequences, is used for prostate MRI evaluation. Anatomical sequences include T1-weighted and T2-weighted (T1W and T2W) sequences, whereas functional sequences include diffusion-weighted imaging (DWI) and dynamic contrast-enhanced imaging (DCE). In the evaluation of mpMRI, the adoption of a shared language between clinicians and radiologists, the establishment of standardized reporting criteria, and the categorization of the likelihood of clinically significant cancer have contributed to the development of the prostate maging reporting and data system (PIRADS) framework (9).

PSA density (PSAD), while maintaining sensitivity, holds promise in augmenting the diagnostic utility of serum PSA alone by improving specificity. Nevertheless, its adoption in clinical practice remains limited. New multivariate risk prediction tools incorporating the mpMRI suspicion score and PSAD have been developed. The increased use of PSAD and mpMRI has resulted in enhanced localization, risk stratification, and diagnosis of PCa (4). In our study, we also examined the role and significance of PSAD along with mpMRI in the diagnosis and treatment of PCa. Clinically significant PCa defines PCa lesions that could threaten a patient's life or significantly impact their quality of life, indicating the identification of aggressive cancers requiring treatment. It is determined by factors such as tumor size and grade, PSA levels, imaging findings, and clinical characteristics.

Materials and Methods

Our article was retrospectively planned and certified by the Clinical Research Ethics Committee of Hatay Mustafa Kemal University with decision number 01 dated November 1, 2021. As the patients included in the study were retrospectively evaluated, no financial support was received. A total of 214 patients with elevated PSA levels in a University hospital Urology clinic between January 2019 and April 2021 were included in the study. mpMRI was performed on all patients before the biopsy procedure. PIRADS scoring was conducted by the same radiologist. Prostate biopsy was systematically performed by experienced urologists in 12 core biopsy quadrants. Before the biopsy, all patients received antibiotic prophylaxis with ciprofloxacin 500 mg 2x1 (1 day) and gentamicin 160 mg 1x1 (1 day). In addition, all patients were administered a rectal lavage the night before the procedure and in the morning, and the biopsy was performed with the TRUS-guided probe after prostate examination. Prostatic nerve block with lidocaine was administered for local anesthesia. Subsequently, 12-core prostate biopsy was performed, including both lateral and far lateral base and middle, and medial and lateral at the apex. All procedures were completed using standard grayscale ultrasonography and a 7.5-MHz frequency rectal probe, with an 18 Gauge 30 cm biopsy needle and an automatic biopsy gun. Patients were labeled with different numbers and sent for pathological examination. After explaining all possible complications to the patients, they were discharged after a 2-h observation period. Patients were instructed to return for the evaluation of possible biopsy complications in the 1st and 4th weeks following the biopsy.

All patients were T2-weighted with 3-Tesla MRI, dynamic contrast- and diffusion-weighted

The combined three sequences including images were examined.

The mpMRI results of the patients were evaluated by experienced radiologists in accordance with the literature using the PIRADS scoring system (PIRADS 1: Very low-clinically significant cancer is unlikely; PIRADS 2: Low-low likelihood of clinically significant cancer; PIRADS 3: Moderate-uncertain presence of clinically significant cancer; PIRADS 4: High-likely presence of clinically significant cancer; PIRADS 5: Very high-high likelihood of clinically significant cancer).

Before the biopsy procedure, DRE, serum PSA values, mpMRI results, hematological parameters including serum urea, creatinine, neutrophil, lymphocyte, white blood cell, and platelet values, racial distribution of patients (local population and immigrant population), histopathological examination results of biopsy materials, and ISUP grading results were recorded to obtain data.

Statistical Analysis

Data were analyzed using SPSS version 25.0 for Mac (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to determine the normal distribution. When values were not normally distributed, continuous values were presented as the median. Categorical variables are expressed as numbers and percentages. The Mann-Whitney U test was employed to compare values between the two groups, while the chi-square test was used for comparing categorical variables. Receiver operating characteristics (ROC) analysis was performed for effective factors in PCa. P-values less than 0.05 were deemed statistically significant.

Results

The patients had a median age of 66.00 years (61.00-71.00%). Comorbidities were present in 33% patients. The median prostate volume measured by TRUS of the patients was 55 milliliters (44.00-83.00). The median serum PSA and free PSA values of the patients were 7.37 nanograms (5.17-13.70) and 1.64 (1.10-2.98), respectively. When evaluating the mpMRI results of the patients, the most common patterns observed were PIRADS scores 2 and PIRADS scores 4. On histopathological examination, benign pathology constituted 64.5% of our biopsies. Adenocarcinoma Gleason 6 and Gleason 7 patterns followed this pattern.

When the analysis was carried out to predict PCa based on the PIRADS score, it was examined through ROC analysis for disease

diagnosis. The area under the curve (AUC) value for the PIRADS score parameters was found to be significant (AUC 0.860; p<0.001) (Figure 1) (Table 1). In addition, at PIRADS score 3 and above, mpMRI can predict cancer with a sensitivity of 81% and specificity of 75% (Table 2).

When the analysis was applied for the prediction of PCa through the PIRADS value, it was examined by ROC analysis for disease diagnosis (AUC 0.860: p<0.001) of the PIRADS parameters for disease diagnosis was significant (AUC 0.860; p<0.001) (Table 3).

When the correlation between PIRADS and PSA, free PSA, body mass index (BMI), neutrophil-lymphocyte ratio, platelet-to-lymphocyte ratio, and SII values was examined, the correlation analysis results indicated a significant but low correlation between PIRADS and PSA value (r=0.252; p<0.001). Additionally, a significant correlation was observed between free PSA and BMI (r=0.2; p<0.001) as well as free PSA and BMI (r=0.265; p<0.001) (Table 4).

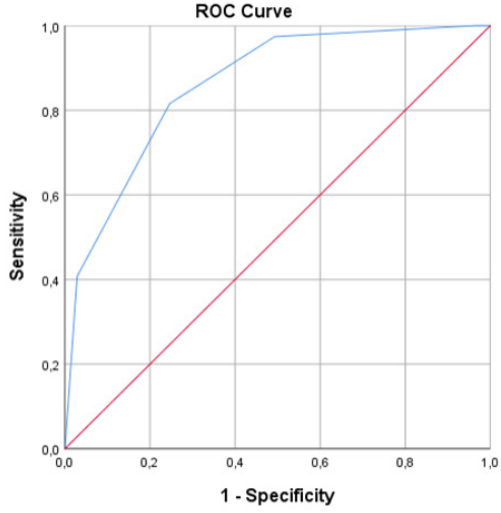

Figure 1. ROC curve for predicting disease with the PIRADS value

ROC: Receiver operating characteristics, PIRADS: Prostate image reporting and data system

Table 1. General demographic data and pathological results of patients		
		Value (Percentage)
Age (Median) (min-max)		66.00 (61-71)
BMI (Median) (min-max)		25.00 (24-26)
Rectal examination findings	**Grade 1**	140 (65%)
	Grade-2	74 (35%)
	Grade-3	0 (0.0)
Komorbid disease	**No**	143 (67%)
	Yes	71 (33%)
Prostate volume		55.00 (44-83%)
Multiparametric MRI	**PIRADS 1**	5 (2%)
	PIRADS 2	67 (31%)
	PIRADS 3	46 (21%)
	PIRADS 4	61 (28%)
	PIRADS 5	35 (16%)
PSA		7.37 (5-13%)
Free PSA		1.64 (1-3%)
Pathology result	**Benign**	138 (64%)
	G6 (3+3)	22 (10%)
	G7 (3+4)	18 (8%)
	G7 (4+3)	15 (7%)
	G8 (4+4)	4 (2%)
	G9 (4+5)	6 (3%)
	G9 (5+4)	3 (1%)
	G10 (5+5)	8 (4%)
ISUP grade	**1.00**	22 (29%)
	2.00	18 (24%)
	3.00	15 (20%)
	4.00	4 (5%)
	5.00	17 (22%)

PIRADS: Prostate image reporting and data system, BMI: Body mass index, MRI: Magnetic resonance imaging, PSA: Prostate-specific antigen, ISUP: International Society of Urological Pathology, min-max: Minimum-maximum

Table 2. ROC analyses' result for predicting prostate cancer with PIRADS classification						
Test result variable(s)	**AUC**	**Std. error[a]**		**Asymptotic sig.[b]**	**Asymptotic 95% CI (lower bound)**	**Asymptotic 95% CI (upper bound)**
PIRADS	0.860	0.025		0.001	0.811	0.910

The test result variable(s): PIRADS has at least one tie between the positive and negative actual state groups. Statistics may be biased. ROC: Receiver operating characteristics, PIRADS: Prostate image reporting and data system, [a]Under the non-parametric assumption, [b]Null hypothesis: true area =0.5
AUC: Area under the curve, CI: Confidence interval

Table 3. PIRADS ROC analyses results						
Test result variable(s)	**Cut-off**	**AUC (%95 CI)**	**Std. error**	**Sensitivity**	**Specificity**	**p-value**
PIRADS	>3.50	0.860 (0.811- 0.910)	0.025	0.816	0.754	<0.001

AUC: Area under the curve, CI: Confidence interval, PIRADS: Prostate image reporting and data system

Table 4. Correlaton analysis results of factors influencing prostate cancer

		PIRADS	WBC	Neutrophil	Lymphocyte	Platelet	Urea	Creatinine	PSA	Free PSA	BMI	NLR	PLR	f/tPSA
Prostate volum	r	-0.198	0.119	0.168	-0.014	0.165	0.115	0.025	0.169	0.274	-0.031	0.179	0.161	0.184
	p	0.004	0.086	0.015	0.840	0.016	0.098	0.721	0.014	0.000	0.656	0.009	0.020	0.014
PIRADS	r	1.000	0.051	0.034	-0.010	0.042	0.107	0.121	0.252	0.281	0.265	-0.008	0.033	-0.170
	p		0.465	0.620	0.883	0.540	0.125	0.079	**<0.001**	**<0.001**	**<0.001**	0.914	0.632	0.023
WBC	r		1.000	0.888	0.418	0.384	0.093	0.062	0.108	0.111	0.005	0.405	-0.077	0.005
	p			0.000	0.000	0.000	0.182	0.376	0.124	0.141	0.944	0.000	0.267	0.942
Neutrophil	r			1.000	0.069	0.328	0.090	0.082	0.143	0.198	0.020	0.724	0.176	0.068
	p				0.322	0.000	0.195	0.237	0.041	0.008	0.773	0.000	0.010	0.367
Lenfosit	r				1.000	0.184	-0.051	-0.063	0.006	-0.091	0.029	-0.569	-0.712	0.007
	p					0.008	0.463	0.368	0.930	0.230	0.678	0.000	0.000	0.928
Platelet	r					1.000	-0.060	-0.055	0.207	0.079	0.099	0.166	0.478	-0.240
	p						0.393	0.432	0.003	0.295	0.152	0.016	0.000	0.001
Urea	r						1.000	0.423	0.123	0.263	-0.014	0.097	0.021	0.061
	p							0.000	0.080	0.000	0.837	0.164	0.760	0.419
Creatinine	r							1.000	0.163	0.256	0.044	0.131	0.035	0.076
	p								0.019	0.001	0.524	0.059	0.611	0.319
PSA	r								1.000	0.792	0.207	0.106	0.151	-0.376
	p									0.000	0.003	0.130	0.031	0.000
Free PSA	r									1.000	0.128	0.195	0.163	0.159
	p										0.088	0.010	0.031	0.034
BMI	r										1.000	-0.009	0.013	-0.088
	p											0.893	0.847	0.242
NLR	r											1.000	0.624	0.053
	p												0.000	0.487
PLR	r												1.000	-0.153
	p													0.043
	p													0.407
f/tPSA	r													1.000
	p													

PIRADS: Prostate image reporting and data system, WBC: White blood cell, PSA: Prostate-specific antigen, BMI: Body mass index, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, free/total prostate-specific antigen, f/tPSA: Free/total prostate-specific antigen

Discussion

According to the 2024 cancer statistics, PCa remains the most prevalent type of cancer among men (10). Until now, the diagnostic pathway for detecting PCa has been initiated using PSA levels and DRE. In our study, we examined the role of mpMRI, which is a recent diagnostic method, in the diagnosis of PCa. mpMRI, along with PSAD, has a high diagnostic yield in the diagnosis of PCa.

Because of the low specificity of PSA in tissue, many unnecessary biopsies are conducted on patients. The current European Association of Urology guidelines recommend prostate biopsy for patients with a PIRADS score ≥3. An illustrative example is the PROMIS prostate MRI study, which demonstrated a sensitivity of approximately 93% in detecting clinically significant PCa (csPCa) (11). However, recent multicenter studies have demonstrated a notable degree of variation: the positive predictive value (PPV) of a PIRADS score of ≥3 for detecting clinically csPCa ranged from 27% to 48% across 26 centers (12).

According to Panebianco et al. (13), PCa was found in 38% of patients who underwent TRUS-guided biopsy. Of the 355 patients who had a negative TRUS-guided biopsy, post-biopsy mpMRI revealed a suspect focus in 208 patients, with 186 of them testing positive in the biopsy (equivalent to 52% of patients following the initial negative biopsy). In the imaging arm, 440 of 570 patients exhibited a positive MRI result, with 417 of them testing positive in the biopsy. In another investigation, the cancer detection rate was reported as 54% in the systematic biopsy group and 63% in the MRI group (14). Additionally, a meta-analysis including 14 studies and 698 patients found an average cancer detection rate of 37.5% after a negative biopsy (range 19.2-68.3). The combined sensitivity and specificity

were calculated as 57% and 90%, respectively. The PPV of mpMRI varied between 17 and 92 in these studies. However, in the majority of these studies, biopsies were conducted after cognitive evaluation following mp-MRI. The lack of standardization is a significant limitation of these studies (15). Likewise, Hoeks et al. (16) documented a 25% cancer invention rate (108 out of 438) among patients with a history of at least one negative biopsy for high PSA who underwent biopsy with mpMRI and MR guidance, with 87% of these cancers deemed clinically significant.

Recently, Le et al. (17) examined 122 men who underwent pre-radical prostatectomy mpMRI and found that mpMRI detected 80% of index tumors, demonstrating its high accuracy in identifying high-grade (Gleason score >6) and large-volume (diameter >1 cm) tumors. Likewise, Petrillo et al. (18) illustrated that the combined score derived from morphological T2-MRI, DWI, and MRSI achieved the highest sensitivity (0.84) and negative predictive value (0.93) in the detection of PCa. It also demonstrated a significant correlation with the Gleason score and exhibited a statistically distinct median value between significant and insignificant Gleason scores (18). Baco et al. (19) demonstrated that 95% of the index lesions identified on mpMRI were concordant with histopathology from 135 radical prostatectomy specimens. Rud et al. (20) assessed 199 men who underwent prostatectomy and found that mpMRI detected the index tumor in 92% of patients.

Weinreb et al. (21) demonstrated that mpMRI tends to underestimate both tumor volume and tumor size in comparison with histology. The ideal imaging plane and wave sequences for accurately measuring lesion size in MR-guided assessments have not been definitively established, necessitating further research to comprehend the significance of variations in lesion size across different wave sequences (21).

One of the biggest criticisms of mpMRI in the literature is its high negative predictive value for clinically significant cancer (22). Given that biopsies are avoided in men with a negative mpMRI result, it fails to capture the accurate cancer detection rate of clinically significant cancers (23). Therefore, the percentage of patients with undetectable cancers with MRG remains uncertain.

Similarly, in our study, cancer was identified in 36.5% of patients with a PIRADS 3 lesion and above. Our study also demonstrated that the PIRADS parameters are statistically significantly associated with the detection of cancer (AUC 0.860; $p<0.001$), and mpMRI can identify cancer with 81% sensitivity and 75% specificity.

Study Limitations

One of the major limitations of this study is its retrospective design. The relatively lower number of patients compared with other studies is also a limitation. Although the MRG interpretation was performed by a single radiology expert, the MRG device has changed over the years, which is a disadvantage. However, biopsies were performed by different doctors because they were in a training clinic, and the records were reviewed.

Conclusion

Our study showed that the combination of PSA elevation and mpMRI demonstrated high diagnostic efficacy in detecting PCa, and when combined with PSAD, its predictive value increased. In addition, we found a strong relationship between ISUP grading and PIRADS and a significant correlation between PSAD and PIRADS. In conclusion, we believe that mpMRI, along with PSAD, can predict clinically significant cancer in patients, and this correlation will be.

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Ethics

Ethics Committee Approval: Our article certified by the Clinical Research Ethics Committee of Hatay Mustafa Kemal University with decision number 01 dated November 1, 2021.

Informed Consent: Retrospective study.

Authorship Contributions

Concept: H.Ş., S.G., F.G., Design: H.Ş., S.G., F.G., E.Y., Data Collection or Processing: H.Ş., N.T., S.B.P., Analysis or Interpretation: H.Ş., S.B.P., E.Y., Literature Search: H.Ş., N.T., Writing: H.Ş., S.G., F.G.

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Original Article

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The Cancer of the Bladder Risk Assessment Score and Mortality-Survival Relationship Among Patients Who Have Undergone Radical Cystectomy in the Turkish Urooncology Association Database

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Abstract

Objective: The Cancer of the Bladder Risk Assessment (COBRA) score is a practical method that can be used to predict survival in patients who have undergone radical cystectomy (RC). We aimed to evaluate COBRA scores in our patient group.

Materials and Methods: Patients were classified according to tumor stage and lymph node (TLN) involvement; mortality rates and survival were analyzed according to both the TLN classification and COBRA score from the Turkish Urooncology Association database. The chi-square test and Fisher-Freeman-Halton Exact chi-square test were used to compare qualitative data as well as descriptive statistical methods. Cox regression analysis was used for multivariate analysis. Kaplan-Meier and log-rank tests were used for survival analysis.

Results: There was a statistically significant difference between the COBRA scores and survival rates in terms of cancer-specific mortality according to TLN classification (p=0.000; p<0.05). A COBRA score of 6 was associated with a lower mortality rate than a COBRA score of 5. In the Cox regression analysis of cancer-related death, a one-unit increase in the COBRA score increased the cancer-related death rate 1.54-fold [hazard ratio (HR)=1.540; 95% confidence interval (CI)=1.402-1.691] (p<0.05). When the COBRA score was compared to 0, the highest risk was observed for COBRA 5. If the COBRA score was 5, the risk of cancer-related death increased 14.63 times (HR=14.627; 95% CI=7.041-30.385) (p<0.05). If the COBRA score was 6, the risk of cancer-related death increased by 11.54 times (HR=11.547; 95% CI=5.270-25.278) (p<0.05).

Conclusion: The COBRA score increased, the prognosis worsened, and our results are consistent with the first validated study.

Keywords: Bladder cancer, cystectomy, prognosis.

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Introduction

Bladder cancer (BC) is the sixth most common cancer in men and the eleventh most common cancer in both sexes, and BC is the eighth most common lethal cancer in men (1). Seventy-five percent of patients with BC are non-muscle-invasive upon diagnosis, whereas the rest are muscle-invasive patients (2). The standard treatments for muscle-invasive BC are radical cystectomy (RC) and bilateral pelvic lymphadenectomy, which have a 5-year survival rate of 50%. Cisplatin-based neoadjuvant chemotherapy (NAC) has been used since the 1980s to improve survival (2). Postoperative survival is related to tumor stage, tumor invasion depth, and lymph node (LN) involvement (3). Additionally, other histopathological parameters, such as tumor location and lymphovascular invasion, were associated with prognosis in previous studies (4-6).

Determining postoperative patient prognosis may affect adjuvant treatment for patients with muscle-invasive BC. Although nomograms predicting survival after cystectomy have been developed previously, the necessity of a large number of parameters, and the difficulty of recording evaluation, these nomograms are not widely used in clinic (7,8). For this purpose, in 2017, Welty et al. (9) reported the Cancer of the Bladder Risk Assessment (COBRA) score, which is a more practical scoring system that includes age, tumor stage and LN involvement rate, which predicts survival after cystectomy.

Materials and Methods

Patients

Patients who underwent RC and lymphadenectomy and had at least 3 months of follow-up were identified from the Turkish Urooncology Association BC database and were included in this retrospective study. Patients were recruited from 16 different centers with experience in the field of urooncology. It was planned to classify patients according to tumor stage and lymph node (TLN) involvement; and also we aimed to analyze mortality rates and survival periods according to both the TLN classification and the COBRA score. Our database does not contain information about the type of LN dissection, whether standard or extended.

COBRA scores are based on patient age, tumor stage, and LN density. LN density was calculated as the total number of positive lymph nodes divided by the total number of removed lymph nodes. Briefly, patients under the age of 80 are given a score of 0, while those aged 80 and over are given a score of 1. Depending on the tumor stage in RC pathology, 0 pans are given to those with T1 and below, 1 pan is given to those with T2, and 3 pans are given to those with T3 and T4. Those with a LN density of 0 are given 0 points; those with ≥0-0.33 are given 1 point; those with ≥0.333-0.5 are given 2 points; and those with ≥0.5-1 points are given 3 points. The obtained scores were summed to obtain a minimum of 0 and a maximum of 7 points (9). Ethical Committee approval (protocol no: 09.2020.909, date: 24.07.2020) was received from Marmara University.

Patients with missing information regarding the total number of removed LNs, number of positive lymph nodes, incomplete pathological data, and duration of postoperative follow-up 3 months were excluded from the study.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 22 program. The chi-square test and Fisher's freeman's Halton exact chi-square test were used to compare qualitative data as well as descriptive statistical methods (mean, standard deviation, frequency). Cox regression analysis was used for multivariate analysis. Kaplan-Meier and log-rank tests were used for survival analysis. Significant differences were evaluated at the $p<0.05$ level.

Results

A total of 910 cases, 450 (49.5%) male and 460 (50.5%) female, aged 34-98 years were included in the study who underwent cystectomy and pelvic LN dissection between 2002 and 2021. The median follow-up period was 24 months. In Table 1, general distribution of age, sex, histological type, history of NAC, number of lymph nodes removed, number of positive lymph nodes, COBRA scores, and TLN classification of the patients. We have only 36 patients aged over 80 years. Histological types in cystectomy pathology were urothelial in 92.3% of cases, squamous in 3%, adenocarcinoma in 0.9%, and other in 3.8%.

There was no statistical difference between patients with positive and negative lymph nodes in terms of age, gender, smoking status, histological type, and number of positive lymph nodes (Table 2). The mortality rate in patients with positive lymph nodes (49.1%) was significantly higher than that in patients with negative lymph nodes (26.9%) ($p=0.000$; $p<0.05$). The cancer-specific death rate in those with positive lymph nodes (33.8%) was statistically significantly higher than those with negative lymph nodes (16.6%) ($p=0.000$; $p<0.05$). The lymphovascular invasion rate in lymph node-positive patients (64.6%) was significantly higher than LN negative (20.2%) ($p=0.000$; $p<0.05$). There was a statistically significant correlation between LN positivity and COBRA score ($p=0.000$; $p<0.05$). Although the rates of COBRA scores of 0 (33%), 1 (32.3%), and 3 (31.2%) in LN (-) patients were high; the rates of COBRA scores of 2 (17.2%), 4 (53.4%), 5 (10.4%), and 6 (10.8%) in LN (+) patients are high (Table 2).

There was a statistically significant difference in cancer-specific death rates among COBRA scores ($p=0.000$; $p<0.05$). The cancer-specific death rate was 61.9% in score 5 score; and this is significantly higher than score 0 (9.1%), score 1 (14.8%), score 2 (15.7%), 3 (26.1%), and 4 (34.4%) ($p<0.05$). The cancer-specific death rate at score 6 (50%) was significantly higher than that at scores 0, 1, 2, and 3 ($p<0.05$). The incidence of cancer-specific death was significantly higher for score 4 (34.4%) than for scores 0, 1, and 2 ($p<0.05$). The incidence of cancer-specific death was significantly higher for score 3 (34.4%) than for scores 0 and score 1 ($p<0.05$). There were no significant differences among the other COBRA scores ($p>0.05$) (Table 3).

There was a statistically significant difference in cancer-specific death rates between the TLN groups ($p=0.000$; $p<0.05$). The cancer-specific death rate was 41% in the T3-T4 LN-positive group, which was significantly higher than <T2 LN-negative

(9.4%), <T2 LN-positive (7.7%), T2 LN-negative (14.8%), T2 LN-positive (19.1%), and T3-T4 LN-negative (25.7%) classes (p<0.05). The cancer-specific death rate was 25.7% in the T3-T4 LN-negative group, which was significantly higher than <T2 LN-negative, <T2 LN-positive, and T2 LN-negative groups is high (p<0.05). There were no significant differences between the other TLN groups (p>0.05) (Table 4).

Table 1. General distribution of age, sex, histological type, number of lymph nodes removed, number of positive lymph nodes, COBRA Scores, and TLN classification of the patients included in the study

		n	%
Sex	**Men**	**450**	**49.5**
	Women	460	50.5
Age	<60	271	29.8
	60-69	381	41.9
	70+	258	28.4
Histological type	Urotelial	840	92.3
	Squamous	27	3.0
	Adenocancer	8	0.9
	Other	35	3.8
Neoadjuvant chemotherapy	Yes	91	10
	No	764	84
	NA	55	6
Number of total removed nodes	0-5	62	6.8
	6-10	155	17
	11-15	229	25.2
	16-20	193	21.2
	21-25	119	13.1
	≥26	152	16.7
Number of positive lymph nodes	0	631	69.3
	1	96	10.5
	2-4	104	11.4
	5+	79	8.7
COBRA score	0	209	23.0
	1	216	23.7
	2	59	6.5
	3	206	22.6
	4	160	17.6
	5	29	3.2
	6	30	3.3
	7	1	0.1
TLN classification	<T2 node -	214	23.5
	<T2 node +	15	1.6
	T2 node	209	23.0
	T2 node +	57	6.3
	T3-T4 node -	207	22.7
	T3-T4 node +	208	22.9

NA: Not available, COBRA: Cancer of the Bladder Risk Assessment, TLN: Tumor stage and lymph node

Cancer-specific death was observed in 73 (33.8%) of 215 cases with (+) lymph nodes, whereas cancer-specific death was observed in 92 (16.6%) of 553 cases with LN (-). As expected, evaluated using the log-rank test, the survival rates of patients with LN (+) were significantly lower than those with LN (-) (p=0.000; p<0.05) (Figure 1).

When survival rates were evaluated using the log-rank test according to the COBRA score, a statistically significant difference was found between them (p=0.000; p<0.05). Survival rates were significantly higher in people with a COBRA score of 0 than in those with a score of 3 (p=0.000), 4 (p=0.000), 5 (p=0.000) and 6 (p=0.000) (p<0.05). Survival rates were significantly higher for people with a COBRA score of 1 than for those with a score of 3 (p=0.005), 4 (p=0.000), 5 (p=0.000) and 6 (p=0.000) (p<0.05). Survival rates were significantly higher in individuals with a COBRA score of 2 than in those with 4 (p=0.007), 5 (p=0.000) and 6 (p=0.000) (p<0.05). Survival rates were significantly higher in individuals with a COBRA score of 3 than in those with 4 (p=0.020), 5 (p=0.000) and 6 (p=0.000) (p<0.05). Survival rates were significantly higher for people with a COBRA score of 4 than for those with a score of 5 (p=0.002) and significantly lower than those with a 6 (p=0.032) score (p<0.05). There were no significant differences between the other scores (p>0.05) (Figure 2).

When the survival rates according to the TLN group were evaluated using the log-rank test, a statistically significant difference was found between them (p=0.000; p<0.05). The survival rate of cases with T3-T4 LN positivity was significantly lower than that of the cases (p<0.05), <T2 node (-) (p=0.000), <T2 node (+) (p=0.036), T2 node (-) (p=0.000), T2 node (+) (p=0.001), and T3-T4 node (-) (p=0.000). The survival rate of cases with <T2 node (-) were significantly higher than that of cases (p<0.05), T2 node (-) (p=0.044), T2 node (+) (p=0.033),

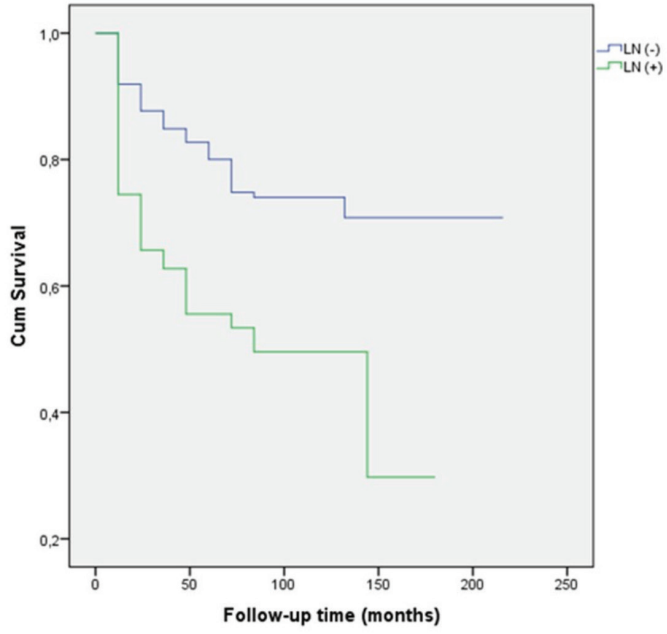

Figure 1. Graph of survival for cancer-related death according to lymph node positivity

Table 2. Comparison of clinical and pathological data between patients with positive and negative lymph nodes					
		LN (-)	LN (+)	Total	
		n (%)	n (%)	n (%)	p-value
Sex (n=910)	Men	303 (48%)	147 (52.7%)	450 (49.5%)	0.194
	Women	328 (52%)	132 (47.3%)	460 (50.5%)	
Age (n=910)	<60	195 (30.9%)	76 (27.2%)	271 (29.8%)	0.530
	60-69	259 (41%)	122 (43.7%)	381 (41.9%)	
	70+	177 (28.1%)	81 (29%)	258 (28.4%)	
Smoking cigarette(n=645)	Yes	266 (61.6%)	136 (63.8%)	402 (62.3%)	0.613
	No	92 (21.3%)	47 (22.1%)	139 (21.6%)	
	Stopped	74 (17.1%)	30 (14.1%)	104 (16.1%)	
Histological type (n=910)	Urotelial	576 (91.3%)	264 (94.6%)	840 (92.3%)	0.089
	Squamose	19 (3%)	8 (2.9%)	27 (3%)	
	Adenocancer	5 (0.8%)	3 (1.1%)	8 (0.9%)	
	Other	31 (4.9%)	4 (1.4%)	35 (3.8%)	
Tumor stage (n=901)	T0	77 (12.4%)	6 (2.2%)	83 (9.2%)	0.000*
	TA	25 (4%)	2 (0.7%)	27 (3%)	
	It is	21 (3.4%)	1 (0.4%)	22 (2.4%)	
	T1	84 (13.5%)	5 (1.8%)	89 (9.9%)	
	T2	208 (33.4%)	57 (20.5%)	265 (29.4%)	
	T3	141 (22.6%)	135 (48.6%)	276 (30.6%)	
	T4	67 (10.8%)	72 (25.9%)	139 (15.4%)	
Lymphovascular invasion (n=879)	Yes	122 (20.2%)	177 (64.6%)	299 (34%)	0.000*
	No	483 (79.8%)	97 (35.4%)	580 (66%)	
Number of positive lymph nodes (n=910)	0	631 (100%)	0 (0%)	631 (69.3%)	0.000*
	1	0 (0%)	96 (34.4%)	96 (10.5%)	
	2-4	0 (0%)	104 (37.3%)	104 (11.4%)	
	5+	0 (0%)	79 (28.3%)	79 (8.7%)	
COBRA score (n=910)	0	208 (33%)	1 (0.4%)	209 (23%)	0.000*
	1	204 (32.3%)	12 (4.3%)	216 (23.7%)	
	2	11 (1.7%)	48 (17.2%)	59 (6.5%)	
	3	197 (31.2%)	9 (3.2%)	206 (22.6%)	
	4	11 (1.7%)	149 (53.4%)	160 (17.6%)	
	5	0 (0%)	29 (10.4%)	29 (3.2%)	
	6	0 (0%)	30 (10.8%)	30 (3.3%)	
	7	0 (0%)	1 (0.4%)	1 (0.1%)	
Mortality (n=910)	Alive	461 (73.1%)	142 (50.9%)	603 (66.3%)	0.000*
	Dead	170 (26.9%)	137 (49.1%)	307 (33.7%)	
Cancer spesific death (n=769)	Yes	92 (16.6%)	73 (33.8%)	165 (21.5%)	0.000*
	No	461 (83.4%)	143 (66.2%)	604 (78.5%)	

Chi-square test, +Fisher Freeman-Halton Exact test, *p<0.05
LN: Lymph node, COBRA: Cancer of the Bladder Risk Assessment, TLN: Tumor stage and lymph node

T3-T4 node (-) (p=0.000) and T3-T4 node (+) (p=0.000). There were no significant differences between the other TLN classes (p>0.05) (Figure 3).

In total, a one-unit increase in the COBRA score increased the cancer-specific death rate 1.54 times (HR=1.540; 95% CI=1.402-1.691) (p<0.05). Compared with COBRA 0, the highest risk is observed with COBRA 5. If the COBRA score is 5, the risk of cancer-related death increases by 14.63-fold (HR=14.627; 95% CI=7.041-30.385) (p<0.05). This is followed by the COBRA 6 score. If the COBRA score was 6, the risk of cancer-related death increased by 11.54 times (HR=11.547; 95% CI=5.270-25.278) (p<0.05). When evaluated according to the previous COBRA score, the significant scores were the COBRA 4 and 5 scores (p<0.05) (Table 5).

Discussion

Our study revealed that the COBRA score can be a practical prognostic tool in RC patients. As the COBRA score increases, the prognosis worsens.

The study included 910 patients. After the COBRA score study by Welty et al.'s (9), 4 more studies using this scoring were reported (10-13). The number of patients in these studies ranged from 412 to 2395. The number of patients in our study was comparable with that of other studies. While the Korean study was conducted at a single center, the study by Muilwijk et al. (11) included patients from 2 different centers (13). Moreover, the cancer genome atlas project was conducted using patient data from 36 different centers, and the study by De Nunzio

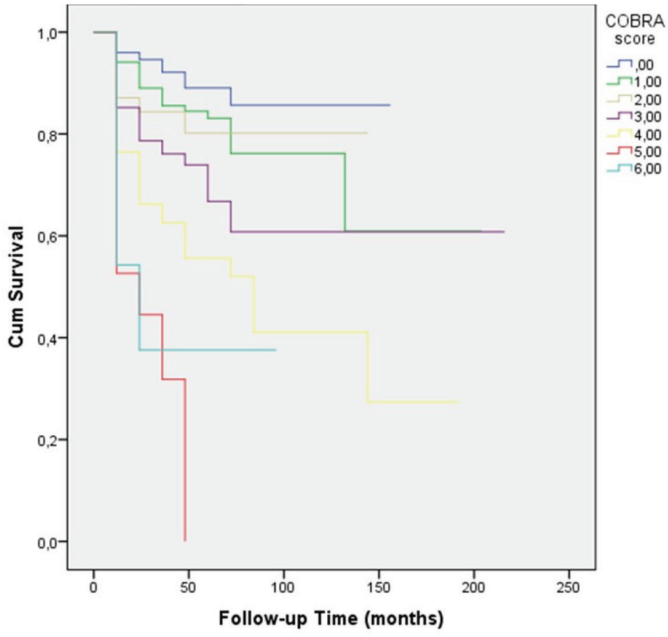

Figure 2. Graph of survival for cancer-related death according to COBRA score
COBRA: Cancer of the Bladder Risk Assessment

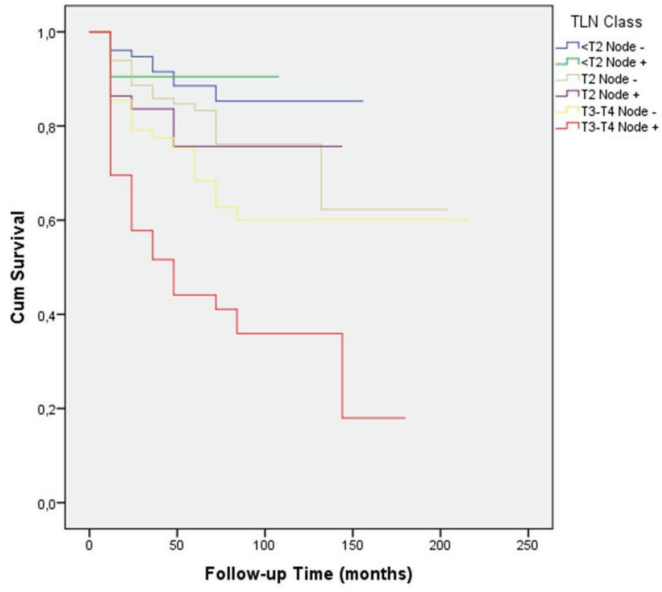

Figure 3. Survival graph for cancer-related death by TLN group
TLN: Tumor stage and lymph node

Table 3. Cancer specific death rates according to COBRA scores

Cancer-specific death	COBRA score							
	0	1	2	3	4	5	6	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	p-value
No	169 (90.9%)	161 (85.2%)	43 (84.3%)	130 (73.9%)	82 (65.6%)	8 (38.1%)	10 (50%)	0.000*
Yes	17 (9.1%)	28 (14.8%)	8 (15.7%)	46 (26.1%)	43 (34.4%)	13 (61.9%)	10 (50%)	

COBRA: Cancer of the Bladder Risk Assessment

Table 4. Cancer-specific death rates according to TLN classifications

Cancer-specific death	TLN classification						
	<T2 node -	<T2 node +	T2 node	T2 node +	T3-T4 node -	T3-T4 node +	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	p-value
No	173 (90.6%)	12 (92.3%)	156 (85.2%)	38 (80.9%)	133 (74.3%)	92 (59%)	0.000*
Yes	18 (9.4%)	1 (7.7%)	27 (14.8%)	9 (19.1%)	46 (25.7%)	64 (41%)	

TLN: Tumor stage and lymph node

Table 5. Cox regression analysis results for cancer-related death according to COBRA scores								
		Compared with COBRA:0			Compared with prior COBRA levels			
		95% CI				95% CI		
	HR	Lower	Upper	p-value	HR	Lower	Upper	p-value
Continuous	1.540	1.402	1.691	0.001*				
COBRA (0)	Ref	-	-	-				
COBRA (1)	1.772	0.969	3.238	0.063	1.797	0.982	3.289	0.057
COBRA (2)	2.028	0.875	4.701	0.099	1.142	0.520	2.506	0.741
COBRA (3)	3.409	1.954	5.948	0.001*	1.698	0.801	3.597	0.167
COBRA (4)	5.658	3.221	9.939	0.001*	1.631	1.073	2.477	0.022*
COBRA (5)	14.627	7.041	30.385	0.001*	2.607	1.384	4.910	0.003*
COBRA (6)	11.542	5.27	25.278	0.001*	0.878	0.381	2.025	0.760
COBRA: Cancer of the Bladder Risk Assessment, CI: Confidence interval, HR: Hazard ratio								

et al. (12) was conducted using data from 4 different centers (10). Our study included patients from 16 different experienced Urooncology centers and reflected the Turkish BC database results.

Importantly, our study differs from previous studies by including patients with non-urothelial histological type (9,11-13). In our study, there was no statistically significant difference between patients with negative and positive lymph nodes according to histological type (p=0.089). Chappidi et al. (10) investigated the association between the COBRA score and survival in subtypes of urothelial histology in BC patients with the cancer genome atlas. According to the results of their study, basal, luminal-infiltrated, and luminal papillary tumors with high COBRA scores had significantly higher mortality rates.

In our study, the mortality rate (49.1%) was significantly higher in those with positive lymph nodes than in those with negative lymph nodes (26.9%) (p=0.000; p<0.05). The cancer-related death rate (33.8%) was significantly higher in those with positive lymph nodes than in those with negative lymph nodes (16.6%) (p=0.000; p<0.05). The overall mortality rate was 33.7%, and cancer-related mortality was 18.1% in our study, which is close to the rate reported as 31% in the study of Welty et al. (9). Cancer-related mortality rates were 25% in the study of Kim et al. (13), 27% in the study of De Nunzio et al. (12), and %32 in the Muilwijk (11) study (13).

In a pioneer study, a one-unit increase in the COBRA score was reported to be associated with cancer-related death by 1.61 times (9). In our study, a one-unit increase in the COBRA score increased the cancer-related death rate 1.54 times (HR=1.540; 95% CI=1.402-1.691) (p<0.05). This rate was reported as 1.52 in the study of Muilwijk et al. (11). In the study of Kim et al. (13), the rate of cancer-related death was 1.50, and when the highest COBRA score was 6, cancer-related death increased 11 times (13). In our study, a COBRA score of 5 increased the risk of death due to cancer 14.63 times (HR=14.627; 95% CI=7.041-30.385), and this was the highest risk score. De Nunzio et al. (12) reported that cancer-related death rates increased 1.54-fold with the COBRA score and that the risk of death increased 134-fold at the highest COBRA score of 7. Thus, all of these studies, including ours, revealed that increasing COBRA scores were associated with increased cancer-related death rates.

We also performed survival analysis according to the TLN classification. Welty et al. (9) reported that the survival curve of T2 node-positive patients was similar to that of T3-4 node-negative patients in their study and emphasized this situation. We, like Welty et al. (9), did not find any difference in survival between these two groups. There was no statistically significant difference between the mortality rate of T3-T4 N(-) (25.7%) and T2N(+) (19.1%) (p>0.05) (Table 4). Kim et al. (13) reported the same findings between T2N-positive patients and T3-4 node-negative patients (13). Muilwijk et al. (11) also analyzed the TLN classification, but they only concluded that node-positive patients had worse outcomes than expected. The other two studies did not provide any information about TLN classification (10,12).

Welty et al. (9) could not manage to perform any analysis regarding the effect of NAC because they used the SEER database, which had no information about the chemotherapy status (9). In the present study, 91 patients received NAC. There was no difference between the groups with and without LN positivity in terms of receiving NAC. NAC data were not given clearly in the Kim (13) and De Nunzio (12) studies, and NAC data were not included in the other two studies (10-13).

Study Limitations

The first current study was designed retrospectively. Second, the limits of pelvic lymphadenectomy at the centers were not clearly reported. Multicentricity may be considered as another limitation because the surgical techniques may differ from one center to another. However, all the centers in our study are experienced centers performing urooncological procedures in Turkey. Apart from these limitations, our study differs from previous studies in that it included histological types other than urothelial carcinoma.

Conclusions

The COBRA score can be used as a prognostic tool in RC patients. The prognosis worsened as the COBRA score increased, and our results are consistent with the first validated study. A one-unit increase in the COBRA score increased the cancer-specific death rate 1.54-fold in our cohort. Our study also included RC patients with histological type other than urothelial carcinoma, and the results should be evaluated in a larger series in the future.

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Authorship Contributions

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