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

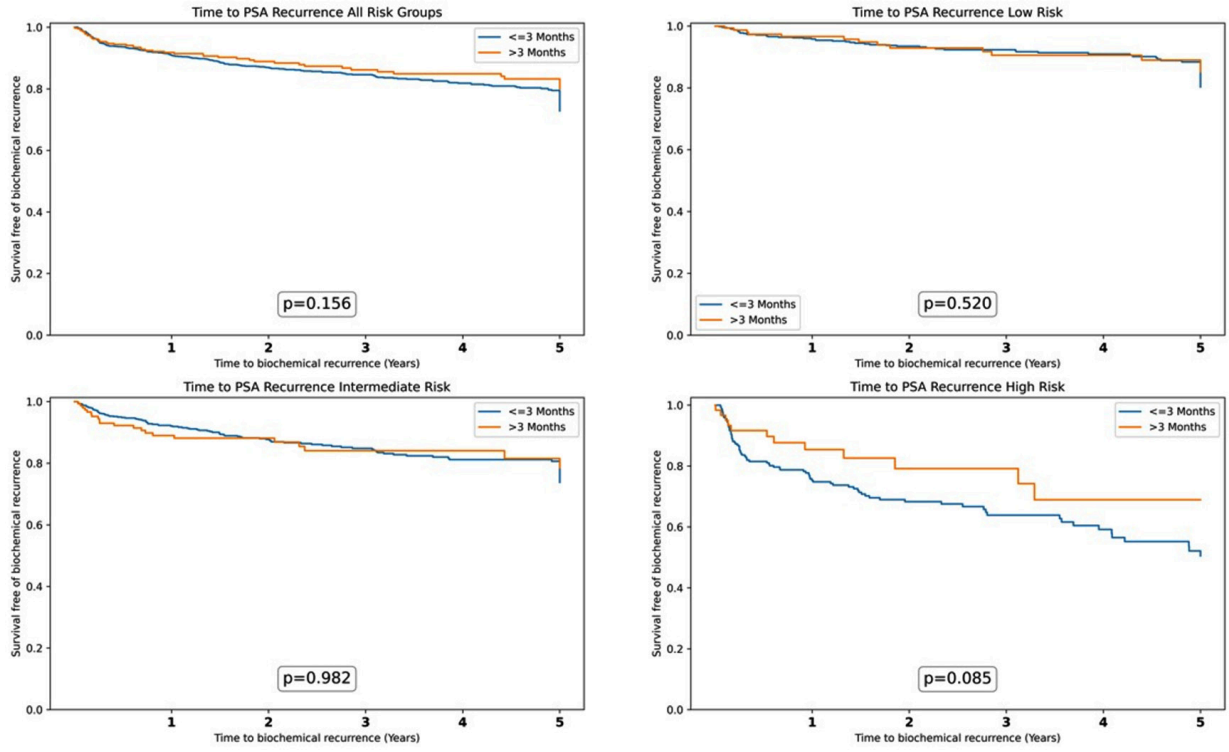

Figure 1. Estimated 5-year biochemical recurrence-free survival rates

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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Authorship Contributions

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