Original Article

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Impact of Delay from Biopsy to Surgery on the Rate of Adverse Pathologic and Oncologic Outcomes for Clinically Localized Prostate Cancer

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Abstract

Objective: Due to the widespread usage of prostate-specific antigen screening, the number of patients diagnosed with prostate cancer is steadily increasing. Many factors such as high operating room demand, insurance reimbursement, patients' desire to assess multiple treatment options, and anxiety can cause delays in radical treatment. In this study, we examined the effect of delay from prostate biopsy to surgery on outcomes of men with localized prostate cancer.

Materials and Methods: The data of 359 patients who underwent radical prostatectomy (RP) in our clinic between 2008 and 2017 were analyzed retrospectively. Surgical delay was defined as the time from transrectal ultrasound-guided prostate biopsy to surgery. Patients were divided into 3 groups according to the interval between prostate biopsy and RP (≤60, 61-120, ≥120 days) and classified according to the D'Amico risk classification.

Results: A total of 248 patients were included in the study. Of these patients, 107 (43.1%) were operated within 60 days of biopsy, 113 (45.6%) 61-120 days after biopsy, and 28 (11.3%) over 120 days after biopsy. Statistical analysis of patients with follow-up of at least 12 months did not reveal a significant difference between the groups in terms of biochemical recurrence (p=0.06). A delay of over 120 days was not associated with adverse pathological or oncological findings at surgery for the low-risk group. Extraprostatic invasion increased significantly in the intermediate-risk group with longer surgical delay (p=0.044).

Conclusion: Our data demonstrated that a delay of more than 120 days was not associated with adverse pathological outcomes in men with low-risk localized prostate cancer. For men with intermediate-risk disease, delays over 60 days were significantly associated with risk of extraprostatic invasion. Our findings indicate that RP should be performed within 60 days of biopsy for intermediate-risk patients.

Keywords: Delay surgery, localized prostate cancer, prostate biopsy, radical prostatectomy

Introduction

Prostate cancer is the most common cancer diagnosed and the second leading cause of cancer-related deaths in men (1). The number of patients diagnosed with prostate cancer has increased due to the growing popularity of prostate-specific antigen (PSA) screening in the last 20 years (2). As a result, different treatment modalities have been discovered and side effects related to these new modalities have also increased. Due to these side effects, most patients dealing with prostate cancer should consider several treatment options and seek multiple opinions. In addition, unavailability of operating rooms due to high demand, insurance reimbursement, and the anxiety experienced by patients may delay radical treatment.

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Due to side effects of radical treatment and the slow progression of low-grade prostate cancer, active surveillance has become an acceptable approach in this low-risk group (3,4). However, upgrading of Gleason scores in surgical specimens is observed in nearly 30% of patients with low-risk prostate cancer. This indicates that patients may skip to the intermediate- or high-risk groups (5,6,7). Therefore, the issues of delaying surgery and active surveillance are controversial.

The effect of delayed radical treatment on pathologic and clinical results is not clear. In spite of many studies in this area, there is no consensus on what is an acceptable delay. It has been shown that delays of up to 180 days do not affect biochemical recurrence (BCR) and pathologic results in localized-low risk prostate cancers (according to D'Amico risk classification) (8). Because active surveillance is not an option for intermediate- and high-risk prostate cancer, there are very few studies regarding these groups.

In this study, we assessed the effect of the time from prostate cancer diagnosis to surgery on pathologic and oncologic outcomes for different risk groups.

Materials and Methods

Between 2008 and 2017, the data of 359 patients who underwent retropubic radical prostatectomy or robot-assisted radical prostatectomy in our clinic were retrospectively analyzed. We excluded patients who underwent prostate biopsy in an external center (n=104) and patients died with non-cancer specific reasons during follow-up (n=7) from the study. The patients' age, preoperative PSA, preoperative Gleason score, D'Amico risk group stage, surgery type, time from biopsy to surgery, pathologic specimen results, follow-up duration, and PSA values during follow-up were recorded. BCR was defined as serum PSA value ≥0.2 ng/mL measured at least 21 days after radical prostatectomy (9). Patients were divided into 3 groups according to duration of surgical delay. Surgical delay was defined as the time (in days) from transrectal ultrasound-guided prostate biopsy until radical prostatectomy. Surgical delay duration was ≤60 days in group 1, 61-120 days in group 2, and ≥120 days in group 3. Patients were divided into 3 risk groups according to D'Amico risk classification: low (Gleason scores: ≤6, PSA: ≤10 ng/mL, and clinical stage: ≤cT2a), intermediate (Gleason score: 7 or clinical stage: cT2b or PSA: >10 ng/mL and ≤20 ng/mL), and high (Gleason scores: ≥8, PSA: >20 ng/mL, clinical stage: ≥cT2c).

Statistical Analysis

Fisher's exact test and Pearson chi-square analysis were performed for categorical variables. The normality assumptions were checked with Shapiro-Wilk test. ANOVA with Tukey honestly significant difference post-hoc test was used to analyze the differences between time intervals for normally distributed data. Differences between groups were evaluated with the Kruskal-Wallis test for analysis of non-normally distributed numerical data; in presence of statistical significance, the post-hoc Bonferroni-Dunn test was applied. The odds ratios of pathological findings at surgery were calculated for all time intervals using logistic regression. Data are expressed as n (%), mean ± standard deviation or median (minimum-maximum), as appropriate. P values <0.05 were considered statistically significant. Statistical analysis was completed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY).

Results

A total of 248 patients were included in the study. The mean age of patients was 64.2 years. The mean PSA value was 9.96 ng/mL. Surgical delay was ≤60 days for 107 patients (43.1%), 61-120 days for 113 patients (45.6%), and ≥120 days for 28 patients (11.3%). According to D'Amico classification, 122 patients (49.2%) were low-risk, 63 (25.4%) were intermediate-risk, and 63 (25.4%) were high-risk. Surgery was open in 97 cases (30.9%) and robot-assisted in 151 (60.1%); patients who underwent open radical prostatectomy had significantly shorter surgical delay compared to robot-assisted cases (p<0.001). Ninety-eight patients were cT1 and 150 patients were cT2, with surgical delay decreasing significantly with more advanced clinical stage (p=0.006) (Table 1).

When groups were investigated according to D'Amico risk classification, there were no differences in any of the investigated pathologic and oncologic outcomes according to surgical delay in the low- and high-risk groups. In the high-risk group, seminal vesicle invasion was observed in 21 patients (33.3%), positive surgical margin in 39 patients (61.9%), and 36 patients required adjuvant treatment. In the intermediate-risk group, the rate of extraprostatic invasion was significantly higher as surgical delay increased (p=0.044). When pathologic results were examined with logistic regression test for intermediate-risk patients, as the surgical delay increased, the rate of extracapsular prostatic extension was significantly higher (p=0.042) (Table 2).

Mean follow-up duration was 16.1 months (minimum-maximum: 2-72 months), with 55 patients (20.2%) developing BCR during follow-up. However, as surgical delay increased there was no significant difference in terms of BCR between the groups (p=0.189). Statistical analysis of patients with follow-up of at least 12 months did not reveal a significant difference between the groups in terms of BCR (p=0.06) (Table 3).

When we examined the pathologic results, 100 patients (40.2%) had upgrading, 55 patients (22%) had positive surgical margin, 57 patients (23%) had extraprostatic invasion, 34 (13.7%) patients had seminal vesicle invasion, and 14 patients (5.6%) had lymph node positivity. Sixty-one patients required adjuvant radiotherapy or hormonal therapy after radical prostatectomy. However, there was no statistically significant correlation between the duration of surgical delay and the need for additional treatment (p=0.394).

Discussion

With the growing popularity of PSA screening, the number of men diagnosed with low-risk prostate cancer in particular is increasing (9). In other cancer types such as breast and colon cancer, it has been shown that delays in treatment did not affect survival (10,11). For prostate cancer, the effect of treatment delays on long-term survival is uncertain (12).

Active surveillance is an acceptable approach for certain patients in the low-risk group. This protocol protects patients from side effects such as erectile dysfunction and urinary incontinence that can result from surgical treatment. A study by Iremashvili

Table 1. Patient demographics and clinical characteristics

	Time intervals (n=248)			
	0-60	**60-120**	**≥120**	**p value**
Age, mean ± SD	64.2±6.5	64.1±6.7	65.3±5.6	0.677
PSA, median (minimum-maximum)	7.3 (3.5-52.59)	7.7 (3.2-55.01)	7.2 (2.34-38)	0.388
PSA range, n (%)	-	-	-	0.552
<10	77 (72)	73 (64.6)	19 (67.9)	-
10-20	20 (18.7)	29 (25.7)	8 (28.6)	-
>20	10 (9.3)	11(9.7)	1 (3.6)	-
Biopsy Gleason score, n (%)	-	-	-	0.532
6	79 (73.8)	75 (66.4)	22 (78.6)	-
7	23 (21.5)	28 (24.8)	5 (17.9)	-
≥8	5 (4.7)	10 (8.8)	1 (3.6)	-
Clinical stage, n (%)	-	-	-	**0.009**
T1c	44 (41.1)	36 (31.9)	18 (64.3)	-
T2a	35 (32.7)	36 (31.9)	5 (17.9)	-
T2b	6 (5.6)	20 (17.7)	1 (3.6)	-
T2c	22 (20.6)	21 (18.6)	4 (14.3)	-
Clinical stage, n (%)	-	-	-	**0.006**
T1	44 (41.1)	36 (31.9)	18 (64.3)	-
T2	63 (58.9)	77 (68.1)	10 (35.7)	-
D'Amico, n (%)	-	-	-	0.463
LR	57 (53.3)	49 (43.4)	16 (57.1)	-
IR	23 (21.5)	33 (29.2)	7 (25)	-
HR	27 (25.2)	31 (27.4)	5 (17.9)	-
Operation type, n (%)	-	-	-	**<0.001**
Open	57 (53.3)	31 (27.4)	9 (32.1)	-
Robotic	50 (46.7)	82 (72.6)	19 (67.9)	-
Follow-up time, median (minimum-maximum)	13 (2-72)	10 (2-76)	11.5 (3-75)	0.095

PSA: Prostate-specific antigen, SD: Standard deviation, LR: Low-risk, IR: Intermediate-risk, HR: High-risk

Table 2. Odds ratio of adverse pathological findings during surgery for intermediate risk group

	≤60 days	**61-120 days OR (95% CI)**	**>120 days OR (95% CI)**	**p value**
Extraprostatic invasion	Reference	2.250 (1.029-4.918)	0.694 (0.206-2.341)	**0.042**, 0.556
Seminal vesicle invasion	Reference	0.396 (0.143-1.092)	0.162 (0.024-1.111)	0.073, 0.064
Surgical margin	Reference	1.569 (0.735-3.351)	1.674 (0.509-5.513)	0.244, 0.397
Lymph node	Reference	1.500 (0.362-6.213)	1.640 (0.110-24.540)	0.576, 0.720

OR: Odds ratio, CI: Confidence interval

Table 3. Comparison of biochemical recurrence and additional treatment data according to time intervals with at least 12 months follow-up				
	Time intervals (n=121)			p value
	0-60 days	60-120 days	≥120 days	
Oncological results				
Biochemical recurrence, n (%)	-	-	-	0.061
Negative	42 (72.4)	34 (69.4)	14 (100)	-
Positive	16 (27.6)	15 (30.6)	0 (0)	-
Additional treatment, n (%)	-	-	-	0.102
Negative	41 (70.7)	31 (63.3)	13 (92.9)	-
Positive	17 (29.3)	18 (36.7)	1 (7.1)	-

et al. (9) compared the outcomes of low-risk patients who underwent surgery after a duration of active surveillance and patients underwent surgery immediately, and found that tumor grade and volume were significantly higher in the patients who group who had surgery after active surveillance (p=0.009). Additionally, there was no significant difference between the 2 groups for parameters like BCR, Gleason score, surgical margin positivity, or extracapsular extension (9). Van den Bergh et al. (13) divided 158 patients with low-risk prostate cancer into 2 groups. The first group underwent surgery after a mean active surveillance period of 6 months and second group underwent surgery after a mean active surveillance period of 2.6 years. They found that the duration between diagnosis and radical prostatectomy did not correlate with poor outcomes (13). Our results are consistent with the literature, with no significant difference identified with delays of over 4 months in 122 patients with low-risk prostate cancer.

Many reports concluding that delays are safe for low-risk prostate cancer note that the same cannot be said for the intermediate-risk group (14,15,16,17). A study including 748 intermediate-risk patients reported that delays longer than 9 months were associated with significantly higher BCR and surgical margin positivity (p<0.01). The same study investigated a subgroup of intermediate-risk patients with low tumor volume in prostate biopsy and found that delays longer than 9 months resulted in significantly higher extracapsular extension rates. However, the same significance was not identified for BCR and surgical margin positivity (18). In a study of 1568 patients in different risk groups, Korets et al. (19) reported that time to surgery did not affect BCR and pathologic results even in the high-risk group. In our study, we found that longer time to surgery was associated with a significant increase in the risk of extraprostatic invasion in intermediate-risk patients.

Surgical specimen reports after radical prostatectomy and PSA screening at certain intervals are the basic parameters used to assess oncologic outcomes. Pathologic specimen reports of radical prostatectomy with extracapsular extension indicate that the patient is pathologically and clinically in T3a stage. The BCR rate after radical prostatectomy varies from 15-40% (20). Of patients with BCR, 52% have an extracapsular extension (21). A large-series study of 2907 T3a stage patients indicated that tumors with focal invasion of the extraprostatic region did not cause a significant difference in terms of BCR. The same study investigated patients with non-focal extraprostatic invasion and reported that BCR was significantly higher in these patients. The authors emphasized that invasion should be separated into focal and non-focal types, and it was necessary to discuss adjuvant therapy for the non-focal group (22).

Studies in the high-risk group are very limited. Zanaty et al. (23) showed in a recent study that delaying surgery did not affect pathologic and oncologic outcomes. The average delay in this study was reported as 138 days. In our study, we found no significant difference between delay groups in pathologic and oncologic outcomes for the high-risk group.

Robot-assisted radical prostatectomy was first performed in 2000. Its popularity continues to increase due to surgeon comfort and early postoperative recovery for the patient (24). In our study, patients who underwent open radical prostatectomy had significantly shorter surgical delays compared to patients who underwent robot-assisted radical prostatectomy. The reason for this is that most patients preferred robot-assisted surgery and this resulted in later appointment dates for surgery.

Study Limitations

This study has several limitations. Firstly, it was a retrospective study with the bias specific to retrospective studies. Radical prostatectomy was performed by 5 different surgeons. Additionally, the postoperative follow-up duration of patients was short and survival outcomes were not included. Our center is a tertiary hospital with large patient population referred from surrounding provinces and counties. This caused loss of patient data such as preoperative PSA and prostate biopsy results.

Conclusion

The results of our study including 248 patients in different risk groups showed that surgical delays longer than 120 days did not affect pathologic and oncologic outcomes in low-risk patients. As surgical delay increased in intermediate-risk group patients, there was a significant increase in extracapsular extension. We believe that surgery should be performed in the first 60 days for the intermediate-risk group due to the high risk of BCR shown in the literature for these patients.

Ethics

Ethics Committee Approval: Retrospective study.
Informed Consent: Retrospective study.
Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.S., M.A., Concept: H.A., K.K., M.Y., Design: H.A., E.İ., S.T., Data Collection or Processing: Ç.Ö., M.Y., Analysis or Interpretation: S.T., E.İ., Literature Search: H.A., K.K., Writing: H.A.

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