Original Article

DOI: 10.4274/uob.galenos.2022.2022.10.4

Bull Urooncol 2022;21(4):134-139

The Effect of Delay in Diagnosis and Treatment Process on Recurrence and Progression of Patients with Non-Muscle-Invasive Bladder Cancer During The COVID-19 Pandemic

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Abstract

Objective: The coronavirus disease-2019 (COVID-19) pandemic caused significant delays in the diagnosis and treatment of non-muscle invasive bladder cancer (NMIBC), like many diseases. We investigated the effect of delays due to the COVID-19 pandemic on oncological outcomes in NMIBC.

Materials and Methods: The patients diagnosed and followed up with primary bladder cancer between October 2017 and August 2022 were analyzed retrospectively. Patients were divided into groups the pre-COVID-19 and COVID-19 periods.

Results: A total of 93 patients were included, 54 (58.1%) in the pre-COVID-19 and 39 (41.9%) in the COVID-19 group. The median time from symptoms to diagnosis (p=0.002), time from diagnosis to transurethral resection of the bladder tumor (TUR-BT) (p=0.001), the time to re-TUR-BT (p<0.001) and time to adjuvant therapy (p=0.004) were significantly longer in the COVID-19 period. The maintenance bladder instillation rates were significantly lower in the COVID-19 period (p=0.028). The progression rates were similar in both periods (p=0.347), and the recurrence rate was significantly higher in the COVID-19 period (p=0.041). Recurrence-free survival (RFS) was significantly lower in the pre-COVID-19 period (p=0.024). In multivariate analysis, time from symptoms to diagnosis (p=0.030) and time to adjuvant therapy (p=0.010) were independent predictors of recurrence.

Conclusion: NMIBC patients in the COVID-19 era had worse RFS outcomes. Especially with a delay of >7.5 weeks from symptoms to diagnosis and a delay of >3.5 weeks to adjuvant therapy, recurrence rates increase significantly.

Keywords: Bladder cancer, COVID-19, delay, recurrence, progression

Introduction

Bladder cancer (BC) is the sixth most frequent cancer in men globally. Almost 75% of BC patients have non-muscle invasive bladder cancer (NMIBC) at diagnosis (1). Although it has better oncologic outcomes than muscle-invasive bladder cancer (MIBC), recurrence rates of up to 60% and progression rates of 10-20% have been reported in the first year (2). Therefore, following transurethral resection of the bladder tumor (TUR-BT), appropriate risk groups should be determined together with histopathological confirmation and a risk group-specific follow-up and treatment scheme should be applied (3).

It has been shown that delays in diagnosis and initiation of treatment in many fast-growing cancer types adversely affect the prognosis (4). In MIBC, a delay of more than three months without neoadjuvant chemotherapy between TUR-BT and radical cystectomy adversely affects survival (5). Additionally, in very high-risk (HR) NMIBC patients, early radical cystectomy significantly improved oncological outcomes (6). In some retrospective studies, it has been shown that the prolongation of the time from symptoms to diagnosis adversely affects oncological outcomes (7).

In early 2020, the coronavirus disease of 2019 (COVID-19) emerged and the World Health Organization declared it a pandemic on March 11, 2020. The pandemic process has adversely affected the functioning of healthcare systems around the world. Many clinicians have been assigned to the management processes of COVID-19 patients outside their speciality. Due to both patients' fear of possible transmission of COVID-19 and the lack of adequate clinicians in outpatient clinics

Cite this article as: Ok F, Durmuş E. The Effect of Delay in Diagnosis and Treatment Process on Recurrence and Progression of Patients with Non-Muscle-Invasive Bladder Cancer During The COVID-19 Pandemic. Bull Urooncol 2022;21(4):134-139

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Received: 12.10.2022 **Accepted:** 07.11.2022

other than COVID-19, delays occurred in the management of numerous diseases except COVID-19, especially among malign diseases. Similarly, delays occurred in the diagnosis and treatment processes of many BC patients.

The current study evaluated the impact of COVID-19 pandemic-related delays in NMIBC diagnosis and treatment on oncological outcomes.

Materials and Methods

After the Ethics Committee of Siirt University approval (decision no: 2022/04.14, date: 26.04.2022), patients diagnosed with BC in our clinic were analyzed retrospectively. The patients diagnosed with primary BC between March 2020 and August 2022 and followed up during this period were determined as the COVID-19 group. To provide a symmetrical working time interval, patients diagnosed with primary BC between October 2017 and March 2020 and followed up during this period were determined as the pre-COVID-19 group. We established 23, 2020, as the threshold date, when the first COVID-19 case was seen in Turkey. Patients with non-urothelial cancer, less than the one-year follow-up, variant histology, and missing data were excluded. Additionally, patients with MIBC were excluded from the survival analysis.

After the diagnosis of the bladder tumor by imaging or cystoscopy, TUR-BT operations were performed by specialist urologists and the tissues taken from the bladder were analyzed by specialist pathologists. All patients with pT1 underwent re-TUR-BT as to the recommendation (8). Due to the lack of intravesical chemotherapy drugs in our region, intravesical chemotherapy is not applied for both early postoperative and intermediate risk (IR) patients. Intravesical Bacilli Calmette-Guerin (BCG) therapy is administered to patients with intermediate and HR-NMIBC. In HR-NMIBC, intravesical BCG included an induction course (six instillations per week) followed by full dose maintenance (three instillations per week at 3, 6, 12, 18, 24, 30, and 36 months). In IR-NMIBC, maintenance therapy is administered for up to one year following induction. The follow-up was conducted with cystoscopy and urine cytology at 3 and 6 months, then every 3-6 months for 2 years, and afterwards according to management modified for the risk of recurrence.

The primary endpoint was to reveal the delays caused by the COVID-19 pandemic in the diagnosis and treatment of BC. The secondary endpoint was the impact of delays in diagnosis and treatment on recurrence-free survival (RFS) and progression-free survival (PFS) of NMIBC patients. Recurrence was defined as a histologically confirmed tumor on follow-up cystoscopy. During the follow-up, the histopathological elevation of any grade (low to high) or grade (Ta to T1 or any T2) was considered progression.

Statistical Analysis

The IBM SPSS Statistics Version 20.0 statistical software package was used. The normality of continuous variable distribution was confirmed with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables were expressed as numbers and percentages, and continuous variables were summarized as median and interquartile ranges. χ^2-test or Fisher's Exact was used to compare categorical variables between the groups. The Mann-Whitney U test was used to compare continuous variables between the two groups. RFS and PFS analyses were performed using the Kaplan-Meier method and a log-rank test. Multivariable Cox proportional-hazards models were used to determine whether parameters related to delay in diagnosis and treatment during the COVID-19 period are possible predictive factors for RFS. The receiver operator characteristic (ROC) curve analysis was used to determine the optimal threshold via the area under the curve (AUC). Youden's curve index was used to determine an optimum cut-off value of time from symptoms to diagnosis and time to adjuvant therapy for predicting RFS. The statistical level of significance for all tests was considered 0.05.

Results

Patients' Characteristics

Perioperative characteristics of patients diagnosed with primary BC in the entire study cohort are divided by the COVID-19 period. Accordingly, the number of patients who underwent primary TUR-BT was 54 (58.1%) in pre-COVID-19 and 39 (41.9%) in COVID-19. The median age of the patients in both periods was similar (68.0 vs 67.0 years, p=0.128). Patients in both groups were similar in terms of gender distribution (p=0.539), smoking status (p=0.969), Charlson Comorbidity Index (p=0.978), and presenting symptoms (p=0.923) (Table 1).

As tumor-specific parameters; T-stage (p=0.355), grade (p=0.272) and size (p=0.697) were similar in both groups. According to the European Association of Urology (EAU) NMIBC prognostic factor risk grouping, in the pre-COVID-19 period, 5 (9.8%) patients were in the low-risk, 11 (21.6%) patients in the IR, and 35 (68.6%) patients in the HR group, similarly, in the COVID-19 period, 2 (5.9%) patients were in the low risk, 9 (26.5%) patients in the IR, and 23 (67.6%) patients in the HR group (p=0.744). The median time from symptom to diagnosis was significantly longer in the COVID-19 period (5.0 vs 7.0 weeks, p=0.002). Also, the median time from diagnosis to TURBT was significantly longer during the COVID-19 period (2.0 vs 3.0 weeks, p=0.001). Although re-TURBT rates were similar in both periods (55.6% vs 38.5%, p=0.104), the time to re-TURBT was significantly longer in the COVID-19 period (3.0 vs 5.0 weeks, p<0.001). Adjuvant bladder instillation rates were similar in both periods (75.9% vs 61.5%, p=0.136), but the median time to adjuvant therapy was significantly longer in the COVID-19 period (3.0 vs 3.5 weeks, p=0.004). The maintenance bladder instillation rates were significantly lower in COVID-19 period (56.5% vs 31.5%, p=0.028) (Table 1).

Oncological Results and Survival Analysis

There were eight pathological ≥T2 patients, three in the pre-COVID-19 period and five in the COVID-19 period. These eight patients were excluded from the oncological outcomes and survival analyses. Even though the progression rates were similar in both periods (5.9% vs 11.8%, p=0.347), the recurrence rate was significantly higher in the COVID-19 period (13.3% vs 33.3%, p=0.041) (Table 1). RFS was significantly lower for the pre-COVID-19 period (p=0.024; Figure 1A). PFS was similar between pre-COVID-19 and COVID-19 periods (p=0.147; Figure 1B).

Table 1. Demographic, clinical and oncological data of pre-COVID 19 and COVID-19 NMIBC patients				
	Pre-COVID 19 (n=54)	**COVID-19 (n=39)**	**Test statistic**	**p-value**
Age (years), median (IQR)	68.0 (7.0)	67.0 (9.25)	Z=-1.524	0.128
Gender Female Male	 11 (20.4) 43 (79.6)	 6 (15.4) 33 (84.6)	X^2=0.377	0.539
Smoking status Never Active Former	 14 (25.9) 26 (48.2) 14 (25.9)	 11 (28.2) 18 (46.2) 10 (25.6)	X^2=0.064	0.969
CCI score 0-2 ≥3	 22 (40.7) 32 (59.3)	 16 (41.0) 23 (59.0)	X^2=0.001	0.978
Symptoms Hematuria Other	 42 (77.8) 12 (22.2)	 30 (76.9) 9 (23.1)	X^2=0.009	0.923
Tumor focality Unifocal Multifocal	 44 (81.5) 10 (18.5)	 30 (76.9) 9 (23.1)	X^2=0.289	0.591
Tumor T-stage Ta T1 ≥T2	 19 (35.2) 32 (59.3) 3 (5.6)	 10 (25.6) 24 (61.5) 5 (12.8)	X^2=2.070	0.355
Tumor grade Grade 1 Grade 2 Grade 3	 5 (9.3) 16 (29.6) 33 (61.1)	 7 (17.9) 7 (17.9) 25 (64.1)	X^2=2.607	0.272
Tumor size <3 cm ≥3 cm	 34 (63.0) 20 (37.0)	 23 (59.0) 16 (41.0)	X^2=0.152	0.697
Concomitant cis	5 (9.3)	5 (12.8)	X^2=0.299	0.584
EAU risk stratification Low Intermediate High	 5 (9.8) 11 (21.6) 35 (68.6)	 2 (5.9) 9 (26.5) 23 (67.6)	X^2=0.592	0.744
Time from symptoms to diagnosis (wk), median (IQR)	5.0 (2.5)	7.0 (4.0)	Z=-3.165	0.002
Time from diagnosis to TURBT (wk), median (IQR)	2.0 (1.0)	3.0 (2.0)	Z=-3.391	0.001
Re-TURBT	30 (55.6)	15 (38.5)	X^2=2.650	0.104
Time to Re-TURBT (wk), median (IQR)	3.0 (1.0)	5.0 (2.0)	Z=-4.512	<0.001
Adjuvant bladder instillation	41 (75.9)	24 (61.5)	X^2=2.228	0.136
Time to adjuvant therapy (wk), median (IQR)	3.0 (1.0)	3.5 (3.0)	Z=-3.676	0.004
Maintenance installations	26 (56.5)	10 (31.3)	X^2=4.850	0.028
Follow-up period (wk), median (IQR)	61.0 (22.5)	60.0 (11.0)	Z=-1.767	0.077
Recurrence	7 (13.7)	10 (33.3)	X^2=4.241	0.039
Progression	3 (5.9)	3 (8.8)	X^2=0.934	0.334

COVID-19: Coronavirus disease-2019, NMIBC: Non-muscle invasive bladder cancer, IQR: Interquartile range, TURBT: Transurethral resection of the bladder, CCI: Charlson Comorbidity Index, EAU: European Association of Urology

A Cox proportional hazards model was used to assess delays in diagnosis and treatment due to the COVID-19 era as possible predictors of RFS and PFS. In multivariate analysis, time from symptoms to diagnosis [HR: 2.238, 95% confidence interval (CI): 1.083-4.622; p=0.030] and time to adjuvant therapy (HR: 4.048, 95% CI: 1.390-11.793; p=0.010) were independent predictors of RFS (Table 2).

In the ROC curve analysis for RFS, the optimal cut-off values for the time from symptoms to diagnosis and time to adjuvant therapy were 7.5 weeks and 3.5 weeks, respectively. The AUC were 0.879 (95% CI: 0.783-0.974) and 0.864 (95% CI: 0.738-0.991) for the time from symptoms to diagnosis and time to adjuvant therapy, respectively. The highest sensitivity and specificity were 0.875 and 0.735 for the time from symptom to diagnosis, 0.813 and 0.796 for the time to adjuvant therapy (Figure 2).

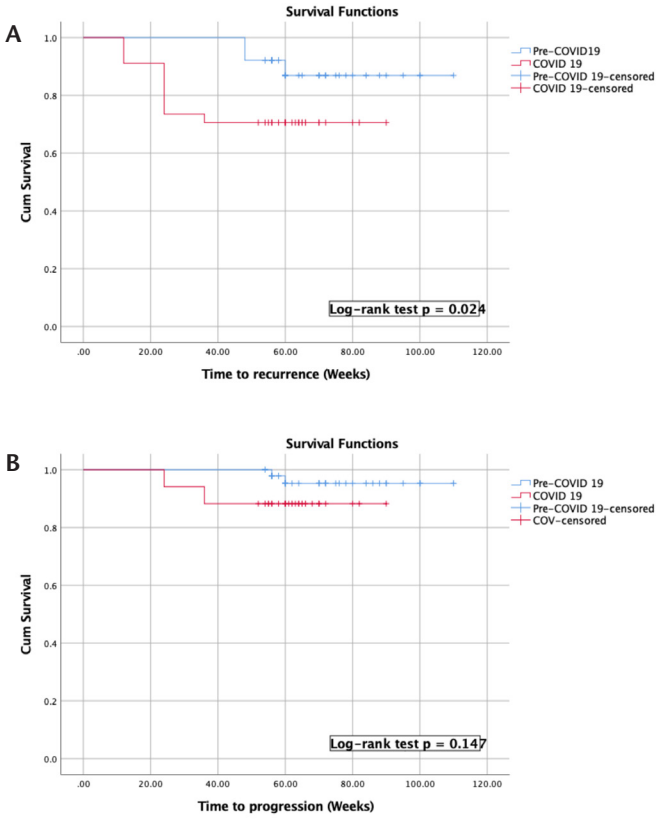

Figure 1. (A) Kaplan-Meier curve of RFS for NMIBC patients pre-COVID-19 and COVID-19 period. (B) Kaplan-Meier curve of PFS for NMIBC patients pre-COVID 19 and COVID-19 period

RFS: Recurrence free-survival, NMIBC: Non-muscle invasive bladder cancer, COVID-19: Coronavirus disease-2019, PFS: Progression free-survival

Table 2. Multivariable Cox regression analysis predicting RFS in patients with NMIBC

	RFS		p-value
Variables	Adjusted* hazard ratio	95% CI	
EAU risk group Intermediate High	 Reference 1.661	 0.480-5.743	 **0.423**
Time from symptoms to diagnosis	2.238	1.083-4.622	**0.030**
Time from diagnosis to TURBT	1.207	0.254-5.743	**0.813**
Time to Re-TURBT	0.538	0.145-2.002	**0.355**
Time to adjuvant therapy	4.048	1.390-11.793	**0.010**
Maintance instillations	0.241	0.018-3.251	0.284

*Adjusted for age, gender and Charlson Comorbidity Index, EAU: European Association of Urology, TURBT: Transurethral resection of the bladder, RFS: Recurrence free-survival, CI: Confidence interval, PFS: Progression free-survival
There was no recurrence in the EAU low risk group, so only IR and HR groups were used in the cox regression analysis. No analysis was performed for progression because of the low number of events

RFS was significantly lower for the time from symptoms to diagnosis >7.5 weeks (p<0.001; Figure 3A) and time to adjuvant therapy >3.5 weeks (p<0.001; Figure 3B).

Discussion

Study data reveal that the COVID-19 pandemic has negative impacts on the results of RFS by causing delays in the time from symptoms to diagnosis and time to adjuvant therapy of NMIBC patients. A delay of >7.5 weeks for the time from symptoms to diagnosis was associated with worse RFS outcomes. Similarly, >3.5-week delay of time to adjuvant bladder instillation had worse RFS results.

As seen in our study, the COVID-19 pandemic has caused significant delays in diagnosis and treatment processes. The EAU has suggested supplementary guidelines to assist clinicians in daily practice to reduce the potential impact of pandemic-related delays (9). EAU divided NMIBC patients into four priority groups based on clinical status: low priority group (small papillary recurrences <1 cm and/or Ta/1 history of low-grade BC) that should be delayed for 6 months; intermediate priority group (BC >1 cm), which should not be delayed for more than 3-4 months; high priority group (HR-BC or macroscopic hematuria) that should not be delayed for more than 6 weeks. Additionally, cases such as very HR-NMIBC or BCG failure are in the emergency priority group and interventions that cannot be postponed, such as emergency radical cystectomy, have been recommended (9).

Notably fewer BC diagnoses were made in our study cohort during the COVID-19 pandemic than before the pandemic in a similar period (54 vs 39 patients). In parallel, there were significant delays in time from symptoms to diagnosis (5.0 vs 7.0 weeks), time from diagnosis to TURBT (2.0 vs 3.0 weeks), time to Re-TURBT (3.0 vs 5.0 weeks) and time to adjuvant therapy (3.0 vs 3.5 weeks) during the pandemic period. Additionally, a significant reduction was observed in maintenance bladder instillation of BCG (56.5% vs 31.3%). In a study conducted with 2,591 patients from 27 different centres in Italy, fewer patients were diagnosed with BC by primary TUR-BT during the pandemic period compared with the pre-COVID-19 period (59.2% vs 40.8%) (10). Additionally, they reported that the time of diagnosis to TURBT (65 vs 52 days) and the median time to secondary resection (55 vs 48 days) were significantly longer during the COVID-19 period (10). They also revealed that the rate of maintenance treatment decreased significantly during the pandemic period (79.5% vs 60.4%) (10). The declining activity of clinicians in small or medium-capacity cities like our region, may have further contributed to these delays. As our hospital is the only well-equipped health centre in the city, the vast majority of inpatients during the pandemic were COVID-19 cases for a long time. As demonstrated by Naspro and Da Pozzo (11), the appointment of health personnel in newly opened COVID-19 units and the resulting decrease in effective staff caused serious disruptions in ordinary clinical and surgical applications. Apart from the changes in the health system related to the pandemic, low education and socioeconomic condition, and deficiency of knowledge about symptoms such as cancer-related hematuria or denial of the patient, although alarming, may cause delays in the diagnostic process (7).

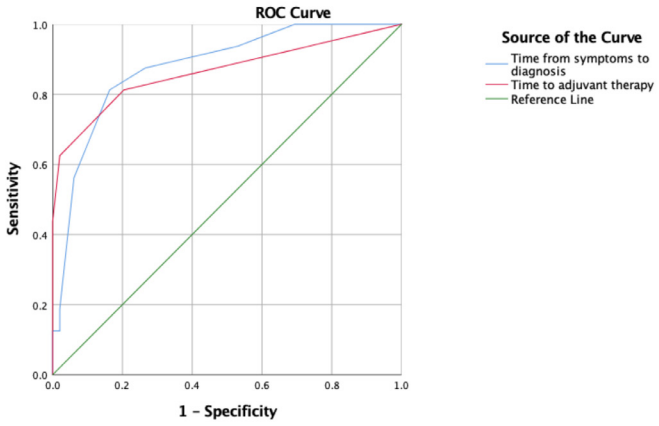

Figure 2. The ROC curve analysis of the time from symptoms to diagnosis and time to adjuvant therapy for recurrence-free survival

ROC: Receiver operating characteristic

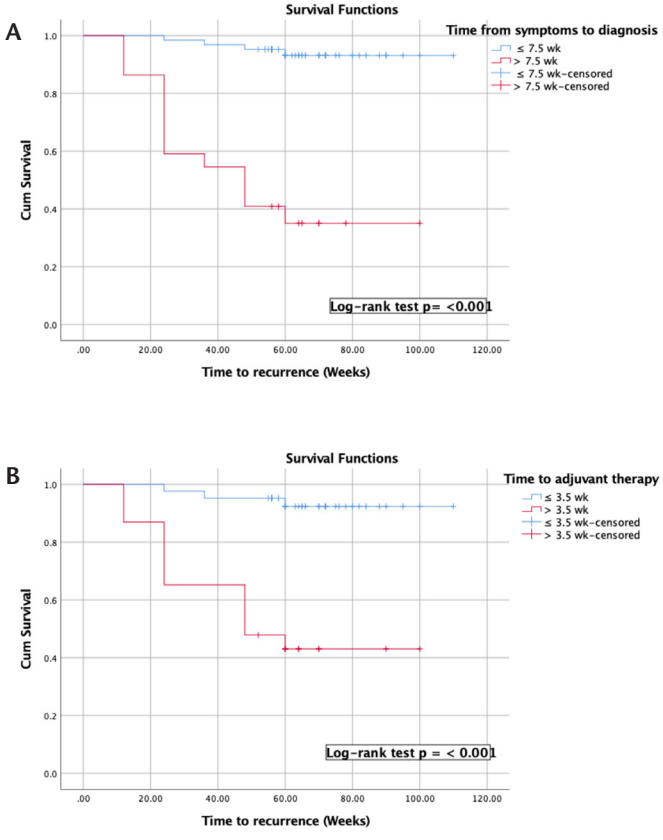

Figure 3. (A) Kaplan-Meier curve of recurrence-free survival probability according to time from symptom to diagnosis in NMIBC patients. (B) Kaplan-Meier curve of recurrence-free survival probability according to time to adjuvant therapy in NMIBC patients

NMIBC: Non-muscle invasive bladder cancer

It has been shown that shortening the duration of the initiation of symptoms and the first examination in BC improves disease-specific survival (7). In their study of 1,537 BC patients, Wallace et al. (12) reported a mean delay of 68 days in transitioning from a general practitioner (GP) to TUR-BT. They reported that solely the delay from symptom onset to GP was associated with poor survival; but, all pathological stages of BC (pTa, pT1, ≥ pT2) were included (12). In a large literature review, Fahmy et al. (13), associated delays in BC treatment with worse outcomes. In a study by Ourfali et al. (7), which examined 434 NMIBC patients, delays of >6 weeks to the first TUR-BT in IR and HR patients, and more than 7 weeks to the first instillation in IR patients are associated with increases in the risk of recurrence. They also found that time to re-TUR-BT of more than 7 weeks is also associated with a higher risk of progression (7). In our study, time from symptoms to diagnosis (HR: 2.238) and time to adjuvant therapy (HR: 4.048) were determined as independent predictive factors for RFS. Since the number of events was not sufficient, further survival analyses related to progression could not be performed. We found that a delay of >7.5 weeks for the time from symptoms to diagnosis and >3.5 weeks from time to adjuvant intravesical BCG therapy was associated with worse RFS outcomes. However, Ourfali et al. (7) found EAU risk classification as an independent predictive value for recurrence in multivariate analysis (HR: 1.32), but it did not reach a significant level in our cohort. The lower rate of IR patients in our cohort (23.5% vs 38.7%) and the fact that we used BCG as an intravesical treatment in the IR group may explain this result.

When 3-year maintenance of intravesical BCG therapy was compared with 1-year maintenance, it was reported that there was no effect on progression or death, but a significant difference in the recurrence rate (14). In our study, we observed that there is a significant decrease in the rate of maintenance treatment during the pandemic process (56.5% vs 32.5%). There were disruptions in maintenance treatments due to the limitation in outpatient practices due to the pandemic and the BCG shortage. However, maintenance BCG therapy could not be an independent predictive value for RFS, probably because of the short follow-up period of our study.

Study Limitations

To our knowledge, this is the first research to examine the impact of delays due to the COVID-19 pandemic in the diagnosis and treatment of NMIBC on recurrence and progression. However, some of the limitations are noteworthy. Firstly, this was a retrospective study with a limited number of patients in a single centre. Because of the insufficient number of patients, we could not perform subgroup analyzes within the EAU risk groups. Secondly, the effect of delay in diagnosis and treatment of NMIBC on specific survival could not be evaluated because of insufficient follow-up and the small number of patients experiencing disease progression. Additionally, due to the lack of intravesical chemotherapy agents in our institution, the use of only BCG therapy in IR patients and the inability to give a single dose instillation in the low-risk group may be another limitation. To better grasp the act of these disruptions in the diagnosis and treatment of NMIBC, we believe that long-term follow-up of these patients will yield more accurate results.

Conclusion

The COVID-19 pandemic has caused significant delays in the diagnosis and treatment process of NMIBC, in many cancer types. Due to these delays, NMIBC patients in the COVID-19 era had worse RFS outcomes. Especially with a delay of >7.5 weeks from symptoms to diagnosis and a delay of >3.5 weeks to adjuvant therapy, recurrence rates increase significantly. To prove our findings multicenter studies with longer follow-ups are necessary.

Acknowledgements

Publication: The results of the study were not published in full or in part in form of abstracts.

Contribution: There is not any contributors who may not be listed as authors.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Ethics

Ethics Committee Approval: After the Ethics Committee of Siirt University approval (decision no: 2022/04.14, date: 26.04.2022), patients diagnosed with BC in our clinic were analyzed retrospectively.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.O., E.D., Concept: F.O., Design: F.O., Data Collection or Processing: E.D., Analysis-Interpretation: F.O., Literature Search: F.O., E.D., Writing: F.O.

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