

Effects of the COVID-19 Pandemic on Bladder Cancer Diagnosis and Treatment Processes; A Turkish Multicenter Study

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What's known on the subject? and What does the study add?

The COVID-19 pandemic adversely affects the health system and it is not known exactly when the pandemic will end. As with many diseases, the diagnosis and treatment of bladder cancer has been adversely affected by this process.

Abstract

Objective: The coronavirus disease-2019 (COVID-19) pandemic effect diagnosis and treatment of certain conditions, including bladder cancer (BC). This study aimed to evaluate the effects of the COVID-19 pandemic on BC diagnosis and treatment.

Materials and Methods: Following the approval of the ethics committee for the study, data of 869 patients who underwent surgery for BC in the 2-year period between March 1, 2019 and February 28, 2021 were analyzed retrospectively. The number of surgeries performed for BC, the time elapsed between symptoms and diagnosis, the treatments performed, and the operative pathologies were compared before and during the COVID-19 pandemic.

Results: During the COVID-19 period, there was a decrease in the total number of BC surgeries compared to the pre-COVID-19 period ($p=0.004$). It was observed that this decrease was due to a decrease in patients newly diagnosed with BC ($p=0.001$) as well as the decrease in the number of primary transurethral resection for bladder tumor procedures performed. There was no difference in the tumor stages of the patients at diagnosis ($p=0.9$). Intracavitary Bacillus Calmette-Guérin therapy use in high-risk non-muscle invasive bladder cancers (NMIBC) patients also decreased ($p=0.008$) during the pandemic period. It was observed that the time between symptom and diagnosis was longer in MIBC than in NIMBC during both periods ($p<0.001$).

Conclusion: Diagnosis and treatment of BC have been adversely affected by the ongoing COVID-19 pandemic. The decrease in the number of new diagnoses may not reflect a true decrease in BC incidence, meaning that BC cases that arose during the pandemic are likely to be diagnosed at a more advanced stage.

Keywords: Bladder cancer, COVID-19, diagnosis, treatment

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Introduction

Bladder cancer (BC) is the ninth most common cancer worldwide and 13th in cancer-related death rates (1). BC diagnosis is diagnosed by histopathological evaluation after transurethral resection for bladder tumor (TURBT). Approximately 75% of BCs are diagnosed as non-muscle invasive bladder cancers (NMIBCs) (2). In low-risk NMIBC, cystoscopy is performed to check whether a new tumor has formed following TURBT. In patients with high-risk NMIBC, cystoscopy should be performed periodically following intravesical instillation of the Bacillus Calmette-Guérin (BCG) vaccine to reduce progression and recurrence after TURBT (3). Muscle-invasive bladder cancer (MIBC) constitutes 25% of newly diagnosed BCs (4). Treatment of MIBC involves neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) or bladder-sparing modalities, including radiotherapy and chemotherapy as part of a multimodal treatment plan (5).

In December 2019, the World Health Organization (WHO) reported that pneumonia cases of a previously unknown etiology detected in Wuhan, China, were caused by a coronavirus (SARS-CoV-2), and the disease was named coronavirus disease-2019 (COVID-19). The WHO officially declared COVID-19 a pandemic on March 11, 2020 (6). Across the world, health workers were deployed to combat the pandemic. Intensive care and other units began to be used for COVID-19 patients. The European Association of Urology (EAU) formed a rapid working group to develop adaptive guidelines for dealing with various situations and priorities resulting from the pandemic. This organization defined 4 priority groups for the diagnosis and treatment of BC. Low-priority NIMBC cases could be deferred for up to 6 months, while intermediate priority cases could be deferred for up to 3 months. Cystoscopy with computed tomography urogram and urinary cytology should be performed within 6 weeks for patients with visible hematuria. Emergency diagnosis involving TURBT should be made within <24 hours in patients with clot retention requiring bladder catheterization. As for treatment guidelines, EAU recommendations stated that treatment for lower-priority NIMBC cases could be delayed for 6 months. Intermediate priority cases should be treated within 3 months, while high priority cases should be treated within 6 weeks. For MIBC treatment, the organization stated that delays of up to 12 weeks in the time to RC may be safe (7).

During the COVID-19 pandemic, numerous surgeries had to be postponed to reduce infection transmission, evacuate hospital beds, and allow healthcare workers to deal with the pandemic (8).

In this study, we evaluated the effects of the COVID-19 pandemic in terms of diagnosis and treatment of BC by comparing

diagnosis and treatment of BC tumors in the year preceding the COVID-19 pandemic and in the first year of the pandemic.

Materials and Methods

Eight centers from different regions of Turkey and hospitals at different levels participated in the study. The data of 869 patients who underwent surgery for BC in the 2-year period between March 1, 2019 and February 28, 2021 were analyzed retrospectively. The pre-COVID-19 period was defined as the range from March 1, 2019 to February 28, 2020. The COVID-19 period was defined as ranging from March 1, 2020 to February 28, 2021. Patient age, gender, time between symptoms and diagnosis, post-operative pathologies, and treatments received were recorded. Patients were divided into two groups: NIMBC and MIBC. These groups were compared across the pre-COVID-19 period and the COVID-19 period. This study was authorized by the Afyonkarahisar Health Sciences University Research Ethics Committee with the decision number: 2021/293.

Statistical Analysis

Statistical analysis of the study data was done by computer with the IBM SPSS (Statistical Package for the Social Sciences) version 15.0 program. The conformity of the variables to the normal distribution was examined using the Kolmogorov-Smirnov (K-S) test. It was observed that all parameters except age showed abnormal distribution and were calculated using non-parametric tests. Student's t-test was used for age. The Mann-Whitney U test was used to compare paired groups in data that did not show normal distribution. Pearson's chi-square test was used for multivariate comparisons. The results were considered statistically significant when $p < 0.05$.

Results

According to their pathology results, the patients included in the study were divided into either the NIMBC or the MIBC group. Of the 869 patients treated during the two-year period, 729 (83.89%) were treated with TURBT for NIMBC. RC due to MIBC was performed on 140 (16.11%) patients. Of the patients, 771 (88.72%) were male and 98 (11.28%) were female. While 473 (77.16%) of 613 patients who were primarily diagnosed with BC were treated with TURBT due to NIMBC, 140 (22.84%) patients underwent RC due to MIBC. Figure 1 shows the number of surgeries performed for BC before and during the COVID-19 period.

In the 1-year period before COVID-19, TURBT was performed on 471 patients. 274 (58.17%) patients received this procedure due to primary BC and 197 (41.83%) due to BC recurrence. The time elapsed between symptoms and the TURBT procedure in patients

diagnosed with primary BC was calculated as 63.19 ± 52.9 (1-180) days. Of the patients with primary diagnosis, 142 (51.83%) were diagnosed with Ta, 132 (48.17%) with T1 BC. 132 (48.17%) high grade and 142 (51.83%) low-grade tumors were detected. 122 (92.42%) of 132 patients diagnosed with T1 BC received intracavitary BCG treatment, whereas 10 (7.58%) patients did not.

In the COVID-19 period, 383 patients underwent TURBT. TURBT was performed on 199 (51.96%) patients due to primary BC and 184 (48.04%) patients due to recurrence. The time elapsed between symptoms and the TURBT procedure in patients diagnosed with primary BC was calculated as 59.82 ± 58.97 (1-180) days. Of the patients with primary diagnosis, 102 (51.3%) were diagnosed with Ta and 97 (48.7%) with T1 BC; 101 (50.76%) high grade and 98 (49.24%) low-grade tumors were detected. 82 (84.54%) of the 97 patients diagnosed with T1 BC received intracavitary BCG treatment, whereas 15 (15.46%) patients did not.

When the pre-COVID-19 and COVID-19 periods were compared in terms of NMIBC diagnosis and treatment, it was observed that 274 patients with primary BC underwent TURBT during the pre-COVID-19 period while 199 patients underwent the same procedure during the COVID-19 period. The number of patients with newly diagnosed NIMBC decreased significantly ($p=0.001$). As for patients with relapse, TURBT was performed on 197 patients in the pre-COVID-19 period and 184 patients during the COVID-19 period, a statistically insignificant decrease ($p=0.5$). When the two periods were compared, there was no

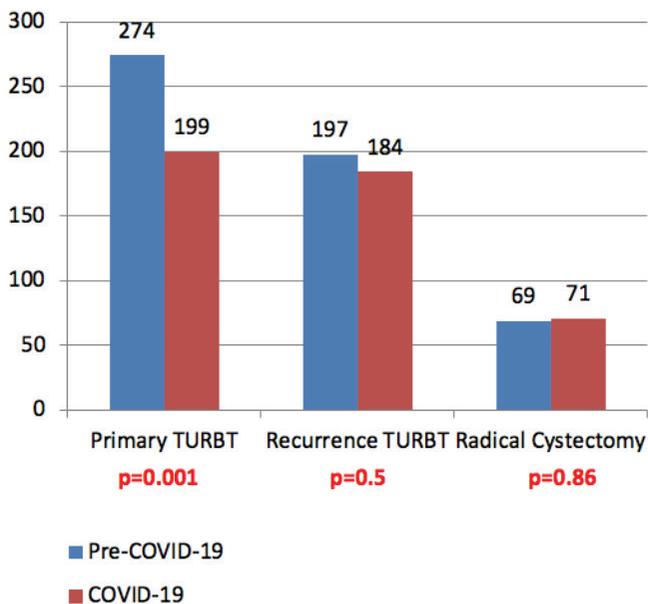


Figure 1. The number of surgeries performed for BC before and during the COVID-19 period

BC: Bladder cancer, COVID-19: Coronavirus disease-2019

statistical difference in terms of gender ($p=0.15$), age ($p=0.64$), time between symptoms and TURBT ($p=0.07$), tumor stages ($p=0.9$) and grade ($p=0.72$). When the patients who underwent primary TURBT and were diagnosed with T1 BC were compared in terms of intracavitary BCG treatment, it was seen that the rate of receiving treatment before COVID-19 was 92.42%, while the rate of receiving treatment after COVID-19 decreased to 84.54%, a statistically significant decrease ($p=0.008$). Table 1 shows the information of patients who underwent primary TURBT for NIMBC before and during the period of COVID-19.

During the study period, 140 patients with MIBC underwent RC. 69 of these patients (49.29%) underwent RC during the pre-COVID-19 period and 71 (50.71%) during the COVID-19 period. There was no difference between the two groups in terms of surgery period ($p=0.86$). The mean age of MIBC patients was 65.63 ± 8.22 (39-88) years. The time between symptom presentation and TURBT was calculated as 91.55 ± 87.40 (3-365) days. The time between TURBT or NAC and RC was calculated as 108.96 ± 89.06 (8-365) days. While 122 (87.14%) patients with MIBC did not receive NAC before RC, 18 (12.9%) patients received NAC before RC. T2 RC was performed in 97 (69.28%) patients, T1 RC in 33 (23.57%) patients, and RC for carcinoma *in situ* (CIS) in 10 (7.15%) patients. RC pathology was T0 in 22 (15.7%) patients, CIS in 9 (6.4%) patients, T1 in 21 (15.0%) patients, T2 in 32 (22.8%) patients, T3 in 30 (21.5%) patients, and T4 in 26 (18.6%) patients. Lymph nodes were negative in 105 (75%) patients, and lymph nodes were positive in 35 (25%) patients. When the pre-COVID-19 period and the COVID-19 period were compared, no difference was found between the two groups in terms of gender ($p=0.2$), age ($p=0.36$), time between symptoms and TURBT ($p=0.6$), time between TURBT or NAC and RC ($p=0.39$), TURBT pathologies before RC ($p=0.5$), RC stage ($p=0.74$), lymph node positivity ($p=0.770$) and NAC administration ($p=0.13$). Although there was no statistical difference in NAC administration, there was a prominent decrease in the COVID-19 period compared to the pre-COVID-19 period ($p=0.13$). Table 2, the information of patients who underwent RC due to MIBC before and during the period of COVID-19 is given.

When patients with NIMBC and patients with MIBC were compared in terms of the time between the onset of symptoms and initial diagnosis during both periods, the MIBC duration was 91.55 ± 87.40 (3-365) days, while the NIMBC duration was 58.66 ± 52.41 (1-180) days, a statistically significant difference ($p<0.001$).

Discussion

The WHO declared COVID-19 a pandemic on March 11, 2020, and the first official case in Turkey was detected on the same day. Around the world, increasing numbers of beds and intensive care

units have begun to be used for COVID-19 patients. Healthcare workers and other resources were allocated to the fight against the pandemic, causing many non-urgent operations to be postponed. Curfews due to the COVID-19 pandemic, warnings to stay home unless absolutely necessary, and people's concerns about getting sick decreased the number of patients seeking diagnosis and treatment in hospitals. The number of cancers diagnosed during the COVID-19 period was significantly lower than that in the pre-COVID-19 period (9,10). Tulchiner et al. (11) reported that they observed a decrease in the diagnosis of newly diagnosed BC in the first six months of the pandemic, and that pre-pandemic diagnostic numbers were reached because of an increase in diagnoses in the following six months. It is known that men are more likely to contract COVID-19 than women and are more likely to become severely ill. COVID-19 is more severe in the elderly than in the young (12). Since BC is a cancer that is more common in men and people over the age of 55, it was expected that its diagnosis and treatment would be affected during the COVID-19 period.

Tulchiner et al. (11) compared the one-year period before COVID-19 with the first one-year period of COVID-19 and reported that there was a decrease in the number of surgeries for BC in the first 6-month period but no difference over the entire year due to an increase in the following 6-month period. In NIMBC patients, they found that tumor stage and grade increased during the COVID-19 period compared to before. To the best of our knowledge, this is the first study comparing the pre-COVID-19 period and the first one-year period of the COVID-19 pandemic with regards to BC (11). In our study, when the pre-COVID-19 period and the COVID-19 period were compared, we

found that the total number of BC-related surgeries performed during the COVID-19 period decreased. It was observed that this decrease was due to a decrease in the number of primary TURBT procedures performed, especially for newly diagnosed BC. There was no difference in tumor stage and grade in NIMBC patients. Based on these results, we expect to see an increase in the number of newly diagnosed patients and the diagnosis of tumors of advanced stage and grade in Turkey.

Intravesical BCG induction and maintenance therapy in high-risk NMIBC is an effective treatment that reduces the recurrence and progression of BC (13,14). The latest urology guidelines for the COVID-19 pandemic period recommend that intravesical BCG therapy should not be delayed in high-risk NMIBC (7). In terms of reducing the number of hospital admissions during the COVID-19 epidemic, it has been reported as an expert opinion that two, rather than three, doses of BCG maintenance therapy can be administered for high-risk NMIBC patients and that the treatment can be terminated in patients receiving maintenance BCG therapy for more than 1 year (15). A lower incidence and mortality rate of COVID-19 has been reported in countries with high rates of BCG vaccination. It is unclear whether exposure to intravesical BCG is protective against COVID-19 (16). Akan et al. (17) compared the patient group receiving BCG treatment for BC during the COVID-19 epidemic with the same age group not receiving BCG treatment and reported that COVID-19 infection was more common in patients receiving BCG treatment. They stated that this may be due to recurrent hospital admissions during the pandemic period. Intravesical BCG therapy in high-risk NMIBC is an extremely effective treatment in reducing recurrence

Table 1. The information of of patients who underwent primary TURBT for NIMBC before and during the period of COVID-19

	Pre-COVID-19	COVID-19	p
Gender			
Male	247 (90.1%)	171 (85.9%)	p=0.15
Female	27 (9.9%)	28 (14.1%)	
Age	66.34±10.65	66.82±11.81	p=0.64
Time between symptoms and TURBT (day)	63.19±52.9 (1-180)	59.82±58.97 (1-180)	p=0.07
Primary TURBT stage			
Ta	142 (51.83%)	102 (51.26%)	p=0.9
T1	132 (48.17%)	97 (48.74%)	
Tumor grade			
Low grade	132 (48.17%)	98 (49.24%)	p=0.72
High grade	142 (51.83%)	101 (50.76%)	
Intracavitary therapy (T1 tumor)			
Yes	122 (92.42%)	82 (84.54%)	p=0.012
No	10 (7.58%)	15 (15.46%)	
Total patients	274	199	p=0.001

TURBT: Trans urethral resection of bladder tumour, NIMBC: Non-muscle-invasive bladder cancer, COVID-19: Coronavirus disease-2019

and progression, but it causes recurrent admissions of patients to the hospital which, during the COVID-19 outbreak, may be associated with a greater likelihood of exposure to COVID-19. In our study, an increase was observed in the number of patients who did not receive treatment during the COVID-19 period compared with the pre-COVID-19 period. This situation may have arisen because patients did not want to make repeated visits to the hospital during the pandemic period. This decrease in treatment may increase recurrence and progression. Intravesical BCG therapy should be continued with necessary precautions against COVID-19 being taken in patients with high-risk NMIBC. Patients should be adequately informed about the importance of treatment.

Tulchiner et al. (11) reported that the number of surgeries performed for MIBC and tumor stage was not affected by the COVID-19 period. Similarly, there was no change in the number of surgeries for MIBC and tumor stage in the pre-COVID-19 period and the COVID-19 period. Studies comparing RC after NAC and RC alone in MIBC found improved patient survival after NAC, and RC is recommended after NAC as a

standard treatment (18,19). Griffiths et al. (20) reported that NAC increased 5-year survival by an average of 6%. In their meta-analysis, Li et al. (21) compared RC after NAC and RC alone and reported that there was no significant difference in average survival. Tulchiner et al. (11) it has been reported that the rate of NAC intake before RC was 50% before COVID-19 and decreased to 40% during the COVID-19 period, but there was no difference between the two periods. Only 18 (12.86%) of 140 patients treated for MIBC during the two-year period included in our study underwent RC after NAC. Twelve of these patients underwent the procedure during the pre-COVID-19 period, while 6 underwent the procedure during the COVID-19 period following NAC treatment. In our study, the number of patients who accepted NAC treatment in MIBC was found to be extremely low. Although not statistically significant during the COVID-19 period, the number of patients receiving NAC decreased by half. Although RC is the recommended treatment following NAC for MIBC, it was observed that its use was limited in practice due to its low effect on life expectancy and side effects related to NAC. It was thought that there was a decrease in the rate of NAC application due to the desire to

Table 2. The information of patients who underwent RC due to MIBC before and during the period of COVID-19

	Pre-COVID-19	COVID-19	p
Gender			
Male	58 (84.1%)	65 (91.5%)	p=0.2
Female	11 (15.9%)	6 (8.5%)	
Age	66.3±9.56	64.96±8.04	p=0.36
Time between symptoms and TURBT (day)	103.8±102.01	79.65±69.05	p=0.6
TURBT stage before cystectomy			
CIS	4 (5.8%)	6 (8.5%)	p=0.5
T1	19 (27.5%)	14 (19.7%)	
T2	46 (66.7%)	51 (71.8%)	
NAC			
Yes	12 (17.4%)	6 (8.5%)	p=0.13
No	57 (82.6%)	65 (91.5%)	
Time between TURBT or NAC and RC (days)	93.9±68.9	123.6±103	p=0.39
RC stage			
T0	10 (14.5%)	12 (16.9%)	p=0.74
CIS	6 (8.7%)	3 (4.2%)	
T1	10 (14.5%)	11 (15.5%)	
T2	16 (23.2%)	16 (22.5%)	
T3	16 (23.2%)	14 (19.7%)	
T4	11 (15.9%)	15 (21.2%)	
Lymph node positivity			
Yes	18 (26.1%)	17 (23.9%)	p=0.770
No	51 (73.9%)	54 (76.1%)	
Total patients	69	71	p=0.86
TURBT: Trans urethral resection of bladder tumour, NMIBC: Non-muscle-invasive bladder cancer, RC: Radical cystectomy, COVID-19: Coronavirus disease-2019, NAC: Neoadjuvant chemotherapy			

reduce hospitalizations due to the COVID-19 pandemic or the infection concerns of the patients.

Boeri et al. (22) patients being studied with MIBC (cT2-T4) and reported that a delay of more than 10 weeks after the last NAC administration and RC resulted in worse outcomes for cancer-specific and overall mortality. Similarly, EAU guidelines recommend RC in MIBC to be performed within 12 weeks (7). The time between the last TURBT or NAC and RC of the patients included in our study was calculated as 108.96 ± 89.06 days (8-365). When the two periods were compared, it was observed that the duration was longer in the COVID-19 period, although there was no statistically significant difference between the pre-COVID-19 period and the COVID-19 period. Note that the time between TURBT or NAC and RC in the patients included in the study is longer than in the existing literature, and this may have negative effects on progression and overall survival. Patients who are recommended to have RC due to MIBC should be given sufficient information about NAC and the importance of early intervention in terms of survival should be explained.

When the time elapsed between the onset of symptoms and diagnosis in all patients included in the study was compared, it was observed that the time between symptom onset and diagnosis was longer in MIBC than in NIMBC. This shows the importance of early diagnosis in a disease such as BC, where treatment changes according to the disease stage.

Our study is important because it is a multicenter study examining the effect of the COVID-19 pandemic on the diagnosis and treatment of BC in a 1-year period in Turkey and is the first Turkish study on this subject. A review of the literature shows that our study is the first to demonstrate that administration of intravesical BCG therapy in NIMBC is adversely affected by COVID-19.

Study Limitations

There were some limitations to our study. The study design was retrospective and patients whose file information could not be accessed were not included in the study. Therefore, prospective studies with large BC patient populations will be needed to understand the pandemic's effects on BC diagnosis and treatment.

Conclusion

In our study, a decrease was found in the number of TURBT procedures performed for primary BC due to the decrease in hospital visits during the COVID-19 period. A decrease was observed in the number of high-risk NIMBC patients receiving intravesical BCG therapy during the COVID-19 period. Although the guidelines recommended NAC before RC for MIBC, our

results indicate that this recommendation was not followed sufficiently.

The COVID-19 pandemic is ongoing, and it is clear that it has adversely affected the diagnosis and treatment of BC in Turkey. We predict that BC will be diagnosed at higher stages and grades due to the ongoing pandemic situation.

Ethics

Ethics Committee Approval: This study was authorized by the Afyonkarahisar Health Sciences University Research Ethics Committee with the decision number: 2021/293.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.K., O.G., A.Ö., S.Z.S., B.Y.E., C.B., M.A.K., Concept: A.G., A.D., S.Z.S., A.E.D., Design: A.G., B.B., Ü.Ö., E.E., Data Collection or Processing: B.B., İ.K., O.G., Ü.Ö., A.Ç., Analysis or Interpretation: İ.K., A.Ö., A.E.D., Literature Search: A.D., İ.U., E.E., Writing: A.G., M.K., İ.U., A.Ç.

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