



ARAŞTIRMA / RESEARCH

Effect of Covid-19 pandemic on the progression of bladder cancer patients

Mesane kanserli hastaların progresyonuna Covid-19 pandemisinin etkisi

Ediz Vuruşkan¹, Kadir Karkin¹, Hakan Erçil¹

¹Adana Şehir Eğitim ve Araştırma Hastanesi Üroloji Kliniği, Adana, Turkey

Cukurova Medical Journal 2021;46(2):627-631

Abstract

Purpose: The aim of this study was to discuss the progression results of patients with muscle invasive bladder cancer (MIBC) who delayed their treatment by not making hospital visits on time for fear of contamination during the COVID-19 pandemic.

Materials and Methods: Records of patients diagnosed with MIBC and recommended radical cystectomy (RC) between March 2020 and June 2020 were reviewed. Whether patients were operated on the scheduled time, and if not, the time elapsed after the first diagnosis or the end of neoadjuvant chemotherapy (NAC) were recorded. The patients who applied to our clinic late were restaged and examined whether there was any progression during the pandemic period.

Results: NAC was recommended before RC in 9 of 24 patients, RC was recommended directly to the remaining 15 patients. After NAC, RC was applied to four patients in the planned period, and 4 patients applied delayed. The mean admission period of the patients who applied late after NAC was 197.8±68.5 days. Lung metastases and pelvic lymphadenopathies were found in two (50%). RC was applied to eight of fifteen patients who did not receive NAC in the planned period. Five of these patients applied for RC in the late period and the average application time after diagnosis was 202.8±31.9 days. In the staging of these five patients who presented late, two (40%) had progression (cT2, N0, M1b).

Conclusion: In times of widespread COVID-19 outbreak, physicians should be alert to potential stage progression and worse survival outcomes resulting from delays in diagnosis and treatment.

Keywords: COVID-19, coronavirus, bladder cancer, delayed treatment, progression

Öz

Amaç: Çalışmamızda COVID-19 pandemisi sırasında kontaminasyon korkusuyla hastane ziyaretlerini zamanında yapmayarak, tedavilerini geciktiren kasa invaziv mesane kanserli (MIBC) hastaların progresyon sonuçlarını tartışılması amaçlanmıştır.

Gereç ve Yöntem: Mart 2020 ile Haziran 2020 tarihleri arasında MIBC tanısı alan ve radikal sistektomi (RC) önerdiğimiz hastaların kayıtları incelendi. Hastaların planlanan zamanda opere edilip edilmediği, edilmediyse ilk tanı anı veya neoadjuvan kemoterapi (NAC) bitiminden sonra geçen süre kaydedildi. Kliniğimize geç başvuran hastalara yeniden evreleme yapılarak pandemi sürecinde progresyon gelişip gelişmediği incelendi.

Bulgular: Yirmidört hastanın dokuzuna RC öncesi NAC önerilirken, kalan 15 hastaya direkt olarak RC önerildi. NAC sonrasında, dört hastaya planlanan sürede RC uygulandı, 4 hasta ise gecikmiş olarak başvuru yaptı. Geç başvuru yapan hastaların NAC sonrası ortalama başvuru süresi 197.8±68.5 gündü. İkisinde (%50) akciğer metastazı ve pelvik lenfadenopatiler bulundu. NAC almayan onbeş hastanın sekizine planlanan sürede RC uygulandı. Bu hastalardan beşi RC yapılmak üzere geç dönemde başvuru yaptı ve tanı konulduktan sonraki ortalama başvuru süresi 202.8±31.9 gündü. Bu beş hastanın ikisinde (%40) progresyon (cT2, N0, M1b) olduğu tespit edildi.

Sonuç: COVID-19 salgının yaygın olduğu dönemlerde hekimler tanı ve tedavideki gecikmelerden kaynaklanan potansiyel evre progresyonu ve daha kötü sağkalım sonuçları açısından dikkatli olmalıdır.

Anahtar kelimeler: COVID-19, coronavirus, mesane kanseri, gecikmiş tedavi, progresyon

Yazışma Adresi/Address for Correspondence: Dr. Kadir Karkin, Adana Şehir Eğitim ve Araştırma Hastanesi Üroloji Kliniği, Adana, Turkey E- mail: kadir_karkin@msn.com
Geliş tarihi/Received: 29.01.2021 Kabul tarihi/Accepted: 22.04.2021 Çevrimiçi yayın/Published online: 20.05.2021

INTRODUCTION

The rapid spread of the 2019 coronavirus disease (COVID-19) caused by a novel betacoronavirus known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has had dramatic effects on individuals and health systems around the world¹. The intense demand for resources, exacerbated by the limited health system capacity, has caused health systems to become insufficient from time to time and hospitals to become a source of virus transmission².

It has been shown that the elderly and men with comorbid diseases suffer from SARS-Cov-2 disease more severely. Most patients with malignancy have these features³. Cancer patients often delayed or canceled hospital visits, even if necessary, due to their vulnerability to COVID-19 and fear of transmission. As a result, this situation caused delays in the initial diagnosis, inadequate treatment or progression, and the prognosis of the patients was negatively affected⁴.

In this study, we aimed to discuss the progression results of patients with muscle invasive bladder cancer (MIBC) who delayed their treatment by not making hospital visits on time for fear of contamination during the COVID-19 pandemic.

MATERIALS AND METHODS

Ethical approval was obtained for this study from Adana City Training and Research Hospital Clinical Research Ethics Committee with the date of 27.01.2021 and number 75/1287. Following the approval of the ethics committee, the computer records and files of the patients who were diagnosed with MIBC in our clinic between March 2020 and June 2020 and for whom we recommended radical cystectomy (RC) were reviewed.

Procedure

For staging purposes, intravenous contrast-enhanced abdominal computed tomography (CT) or magnetic resonance imaging (MRI) and thorax CT were applied to the patients in the preoperative period. The time of first diagnosis, pathology reports, clinical stages (Tumor-Node-Metastasis/TNM)⁵ of patients were recorded. For T2-T4a, cN0M0 bladder cancer, we recommended neoadjuvant chemotherapy (NAC) for all patients without variant histology and contraindications to chemotherapy.

According to these evaluations, patients who were planned neoadjuvant chemotherapy (NAC) before radical cystectomy were referred to the oncology clinic, while the other patients were prepared for anesthesia and planned on the day of the operation. Patients who did not accept radical cystectomy and NAC were excluded from the study. RC operation were planned within 1-3 weeks after the diagnosis of MIBC in patients who did not undergo neoadjuvant chemotherapy. In patients who received NAC, RC operation were planned within 1-3 weeks after the end of treatment. Whether patients were operated on the scheduled time, and if not, the time elapsed after the first diagnosis or the end of neoadjuvant chemotherapy were recorded. Restaging was performed using thoracic CT, abdominal CT or MRI for patients who were admitted to our clinic later than planned. The reasons for delaying the treatment of the patients in our study were asked when the patients came for control, and it was learned that it was due to the pandemic.

During the COVID-19 pandemic process, it was examined whether MIBC patients developed progression (according to the TNM staging system) due to delaying their treatment.

Statistical analysis

SPSS program has been used for the evaluation of this study. Descriptive statistics has been used to describe the cases and prevalences.

RESULTS

Twenty-four patients with a mean age of 62.7 ± 6.2 years, who were pathologically diagnosed with MIBC (cT2-T4a, N0-Nx, M0) between March 2020 and June 2020, were included in the study. Twenty-one of these patients were male and three were female. While NAC was recommended before RC in nine patients, radical cystectomy was recommended directly in fifteen patients.

All nine patients referred to NAC completed their chemotherapy. After chemotherapy, one of the patients did not apply to our clinic for RC. While RC was applied to four patients in the planned period, the remaining four patients applied to our clinic with delay. The mean admission period of the patients who applied late after NAC was 197.8 ± 68.5 days. As a result of the re-staging of four patients who presented delayed, lung metastases and pelvic

lymphadenopathies were detected in two (50%) (cT2, N2, M1b) and these patients were considered inoperable and were referred to the oncology clinic. RC was applied to the other two patients and the pathological stage of one of these patients was determined as pT3, N2, M0, and the stage of the other was determined as pT2, N0, M0.

Eight of the 15 patients with MIBC who were not referred to NAC and who were directly recommended RC, were operated by making anesthesia preparations within the planned period. However, the other seven patients did not apply to the hospital to complete their surgery preparations. Five of these patients applied in the late period for radical cystectomy. The mean admission period of these patients after the diagnosis of MIBC was 202.8 ± 31.9 days. As a result of imaging examinations performed for staging purposes in these five patients

who were not operated in the planned period but admitted late, two (40%) were found to have progression (cT2, N0, M1b) (lung metastasis). These patients were considered inoperable and were referred to the oncology clinic, and radical cystectomy was performed in the other three patients.

As a result, three of our twenty-four patients who were diagnosed with MIBC (one patient who received NAC and two patients who did not receive NAC) did not come to their controls and were not followed up (13%). A total of nine patients, including four patients who received NAC and five patients who were recommended direct RC, received their treatment delayed (38%). Four of these nine patients (44%) who stated that they delayed their hospital visits due to the risk of contamination developed progression. The demographic data and clinical characteristics of the patients are shown in Table 1.

Table 1. Clinical and demographic characteristics of patients (n=24)

Characteristics of patients	
Age (Mean±SD)	62.7 ± 6.2
Gender	
Male	21 (87%)
Female	3 (13%)
NAC	
Yes	9 (38%)
No	15 (62%)
Pre-treatment stages	
T2,N0,M0	
Receiving NAC	3 (13%)
Not receiving NAC	13 (54%)
T3,N0,M0	
Receiving NAC	6 (25%)
Not receiving NAC	2 (8%)
Delayed treatment	
Total	9 (38%)
Receiving NAC	4 (17%)
Not receiving NAC	5 (21%)
Progression in patients delayed treatment	
Total	4/9 (44%)
Receiving NAC (T2,N2,M1b)	2/4 (50%)
Not receiving NAC (T2,N0,M1b)	2/5 (40%)
Waiting times in patients who delay treatment (days)	
Receiving NAC	197.8 ± 68.5
Not receiving NAC	202.8 ± 31.9

NAC: Neoadjuvant chemotherapy
SD: Standart deviation

DISCUSSION

It is known that COVID-19 is a highly contagious disease that can cause respiratory problems that may require intensive care and ventilator support and can result in death. In the period of COVID-19, due to epidemiological factors and high hospitalizations, elective surgeries were canceled and emergency and oncological surgical procedures were prioritized in order to maintain the capacity of health systems to meet expected cases and to avoid unnecessary exposure to COVID-19⁶. However, despite this priority, some oncology patients have delayed or completely canceled their treatment during the pandemic process. In this context, it was reported that cancer treatment services were partially or completely interrupted in 42% of the 155 countries examined by WHO^{7,8}. COVID-19 has also significantly changed the management of urological cancers⁶. It is known that delay in surgical intervention in MIBC, which is one of the urological cancers, significantly reduces the life expectancy of the patient^{9,10}.

Measures taken in health systems such as the reduction of elective services and diagnostic screening during the pandemic period, recommendations for patients to stay at home, and patients' desire to avoid exposure to a hospital environment have also caused delays in patients' reaching the physician and in diagnosis^{6,11}. Wallace et al. reported that at the time of bladder cancer diagnosis, the time from the onset of symptoms to the hospital visit of more than 14 days was associated with survival and that these patients had 5% worse survival outcomes at 5 years compared to those who did not experience a delay^{6,12}.

More than a third of new cancers in men and 20% of all new cancers develop in the genitourinary tract¹³. In genitourinary cancers, most survival benefit is achieved by surgical removal of the primary tumor⁸. Recommendations for the prioritization of genitourinary cancers in the COVID-19 period were published by Wallis et al². There are publications reporting that delaying radical surgery for more than 90 days in patients with muscle invasive bladder cancer results in worse survival outcomes^{9,10}. In addition, Boeri et al. showed that delaying surgery for more than 10 weeks after the last cycle of neoadjuvant chemotherapy in MIBC patient groups with clinical stage cT2-T4 increased cancer-specific and overall mortality rates¹⁴. In our study, the average

waiting time of patients with muscle-invasive bladder cancer whose treatment was delayed was 197.8 ± 68.5 days in patients who received NAC and 202.8 ± 31.9 days in those who did not receive NAC. As a result of the restaging of four patients who received NAC and admitted late, it was observed that lung metastasis and pelvic lymph nodes developed in two of them, and lung metastasis developed in two of the five patients who did not receive NAC. In total, four (44%) of nine patients whose treatments were delayed had progression. These patients, who delayed their treatment due to the COVID-19 pandemic, were referred to the oncology clinic as inoperable due to the increase in stage.

During the COVID-19 pandemic period, an overall decrease in urological oncological surgical procedures has been reported, but data on the extent of adverse consequences from delayed treatment are not available⁸. Although our study was conducted with a limited number of patients, as far as we know, it is the first study on the subject and we think it will contribute to the literature.

As a result, although elective surgeries were postponed and oncological surgeries were prioritized during the COVID-19 pandemic period, there are concerns about the delayed treatment of urological cancer patients due to their hesitation in their visits to health institutions. In times of widespread COVID-19 outbreak, physicians should be careful about potential stage progression in cancer patients. Long-term studies with larger numbers of patients are needed to assess oncological outcomes, such as worse survival or diagnosis at higher stages resulting from delay in diagnosis and treatment of certain types of cancer during the COVID-19 outbreak.

Yazar Katkıları: Çalışma konsepti/Tasarımı: EV; Veri toplama: KK; Veri analizi ve yorumlama: KK; Yazı taslağı: EV; İçerğin eleştirel incelenmesi: HE; Son onay ve sorumluluk: KK, EV, HE; Teknik ve malzeme desteği: -; Süpervizyon: HE; Fon sağlama (mevcut ise): yok.

Etik Onay: Bu çalışma için Adana Şehir Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulundan 27.01.2021 tarih ve 75/1287 no ile onay alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.

Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.

Author Contributions: Concept/Design : EV; Data acquisition: KK; Data analysis and interpretation: KK; Drafting manuscript: EV; Critical revision of manuscript: HE; Final approval and accountability: KK, EV, HE; Technical or material support: -; Supervision: HE; Securing funding (if available): n/a.

Ethical Approval: Ethical approval was obtained for this study from Adana City Training and Research Hospital Clinical Research Ethics Committee with the date of 27.01.2021 and number 75/1287..

Peer-review: Externally peer-reviewed.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support

REFERENCES

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He X et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* 2020;382:1708-20.
2. Wallis CJD, Novara G, Marandino L, Bex A, Kamat AM, Karnes RJ et al. Risks from deferring treatment for genitourinary cancers: a collaborative review to aid triage and management during the covid-19 pandemic. *Eur Urol.* 2020;78:29-42.
3. CDC COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) - United States, February 12-March 16, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69:343-46.
4. Crispo A, Montagnese C, Perri F, Grimaldi M, Bimonte S, Augustin LS et al. COVID-19 Emergency and post-emergency in Italian cancer patients: how can patients be assisted? *Front Oncol.* 2020;10:1571.
5. Paner GP, Stadler WM, Hansel DE, Montironi R, Lin DW, Amin MB. Updates in the eighth edition of the Tumor-Node-Metastasis Staging Classification for Urologic Cancers. *Eur Urol.* 2018;73:560-9.
6. Tachibana I, Ferguson EL, Mahenthiran A, Natarajan JP, Masterson TA, Bahler CD et al. delaying cancer cases in urology during COVID-19: Review of the literature. *J Urol.* 2020;204:926-33.
7. COVIDSurg Collaborative. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. *Lancet.* 2020;396:27-38.
8. Mian BM, Siddiqui S, Ahmad AE. Management of urologic cancers during the pandemic and potential impact of treatment deferrals on outcomes. *Urol Oncol.* 2020; doi: 10.1016/j.urolonc.2020.10.013.
9. Russell B, Liedberg F, Khan MS, Nair R, Thurairaja R, Malde S et al. A Systematic review and meta-analysis of delay in radical cystectomy and the effect on survival in bladder cancer patients. *Eur Urol Oncol.* 2020;3:239-49.
10. Gore JL, Lai J, Setodji CM, Litwin MS, Saigal CS. Mortality increases when radical cystectomy is delayed more than 12 weeks: results from a Surveillance, Epidemiology, and End Results-Medicare analysis. *Cancer.* 2009;115:988-96.
11. Maganty A, Yu M, Anyaeche VI, Hay JM, Davies BJ, Yabes JG et al. Referral pattern for urologic malignancies before and during the COVID-19 pandemic. *Urol Oncol.* 2020; doi: 10.1016/j.urolonc.2020.11.027.
12. Wallace DM, Bryan RT, Dunn JA, Begum G, Bathers S. Delay and survival in bladder cancer. *BJU Int.* 2002;89:868-78.
13. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin.* 2019;69:7-34.
14. Boeri L, Soligo M, Frank I, Boorjian SA, Thompson RH, Tollefson M et al. Delaying radical cystectomy after neoadjuvant chemotherapy for muscle-invasive bladder cancer is associated with adverse survival outcomes. *Eur Urol Oncol.* 2019;2:390-6.