ARAŞTIRMA MAKALESİ/ ORIGINAL ARTICLE

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Pandemi Çağı: Gelecekteki Pandemilerde Gastrointestinal Kanser Cerrahi Tedavileri Uygulayabilecek Miyiz? Gelişmekte Olan Ülkelerden Biri Olan Ülkemizde COVID-19 Pandemisinden Neler Öğrendik?

Age of Pandemics: WillWe Be Ableto Perform Gastrointestinal Cancer Surgical Treatments in Future Pandemics? What have we Learned from the COVID-19 Pandemic in Our Country, Which is one of the Developing Countries?

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ÖZ

GİRİŞ ve AMAÇ: *11 Mart 2020'de açıklanan Covid 19 virüsünün neden olduğu pandemi, tüm dünyada onkoloji hastalarının tedavi rejimini etkiledi. Bu çalışmada pandeminin kanser hastalarının cerrahi tedavisine etkilerini belirlemeyi ve bu deneyimi gelecekteki pandemiler için bir rehber haline getirmeyi amaçladık.*

YÖNTEM ve GEREÇLER: *Çalışma, pandemi başlangıç tarihinden 6 ay öncesi ve sonrasını (pandemi öncesi ve pandemi dönemi) kapsayan 2 grup halinde tasarlanmıştır. Ayrıca pandemi dönemi, Polimeraz Zincir Reaksiyon testinin ameliyat öncesi taramaya başlama zamanına göre iki gruba ayrıldı. Gastrointestinal kanser tanısı ile rezeksiyon uygulanan ve ameliyat öncesi üst solunum yolu semptomları olmayan 18 yaş üstü toplam 218 hasta çalışmaya dahil edildi.*

BULGULAR: *Pandemik dönemde neoadjuvan tedavideki artış (p: 0,029) dışında gruplar arasında demografik özellikler açısından anlamlı farklılık yoktu ve genel komplikasyon oranı istatistiksel olarak anlamlı değildi (p = 0,327). Ancak komplikasyonların subgrup analizinde pandemi döneminde pulmoner komplikasyonların daha sık geliştiği görüldü (p = 0.000).*

TARTIŞMA ve SONUÇ: *Bu çalışmada COVID-19 döneminde gastrointestinal kanser ameliyatlarında artan pulmoner komplikasyonlar dışında genel morbidite ve mortalite artışı gözlenmemiştir. Aynı zamanda COVID-19 PCR testinin ameliyat öncesi rutin uygulamasının sonuçlarda herhangi bir istatistiksel değişikliğe neden olmadığı görüldü*

Anahtar Kelimeler: *COVID 19, pandemi, kanser, cerrahi*

ABSTRACT

INTRODUCTION: *The pandemic caused by the Covid 19 virus, announced on March 11 2020 has affected the treatment regimen of oncology patients all over the world. In this study, we aimed to determine the effects of the pandemic on the surgical treatment of cancer patients and to make this experience a guide for future pandemics.*

METHODS: *The study was designed in 2 groups, covering the 6 months before and after the pandemic start date (pre-pandemic and pandemic period). In addition, the pandemic period was divided into two groups according to the starting time of the use of the Polymerase Chain Reaction test for preoperative screening. A total of 218 patients older than 18 years of age, who underwent resection with the diagnosis of gastrointestinal cancer and without preoperative upper respiratory tract symptoms were included to the study.*

RESULTS: *There was no significant difference in demographic characteristics between the groups, except for the increase in neoadjuvant therapy during the pandemic period (p: 0.029) and the general complication rate was not statistically significant (p=0.327). However, in the subgroup analysis of complications, it was observed that pulmonary complications developed more frequently during the pandemic period (p= 0.000).*

DISCUSSION AND CONCLUSION: *In this study, no overall increase in morbidity and mortality was observed in gastrointestinal cancer surgeries during COVID-19 period, except increased pulmonary complications. At the same time, it was observed that the routine application of the COVID-19 PCR test before surgery did not cause any statistical change in the results.*

Keywords: *COVID 19, pandemic, cancer, surgery*

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INTRODUCTION

Wuhan, China's Hubei Province and forty-one patients were admitted to hospitals with presentations being fever, cough, weakness and the diagnosis of pneumonia with an unknown etiology (1,2). However, the incidence of isolated or coexisting abdominal and gastrointestinal symptoms such as diarrhea, nausea, vomiting, and abdominal discomfort were also common (3).

Considering that more than 18 million new cancer cases are detected annually globally, one of the most important problems in this process was the protection and continuity of treatment of immunosuppressive patients such as cancer patients. This unprecedented situation required special considerations for surgeons dealing with abdominal surgery and, specifically gastrointestinal cancer surgery. When the patients infected with Covid 19 were evaluated in the countries where the pandemic first appeared, it was found that the mortality rate was higher in patients with cancer (4,5). It has been claimed that cancer patients' being immunosuppressive due to both their existing diseases and medical and surgical treatments may be the reason for this situation (6,7).

First Covid-19 case was detected on 10 March 2020 in our country and Turkey have experienced a rapid increase in cases. After that, our hospital was appointed as a pandemic hospital and many clinics were converted into Covid-19 clinics. First and foremost, surgical procedures were reorganized in accordance with the local Disease Control Centers (DCC) guidelines and published guidelines of various international surgical associations (8,9). It was decided to operate only urgent patients and patients diagnosed with cancer, and to postpone elective surgical procedures. However, we did not have enough scientific data and experience on how effective these applications would be, as in the whole world.

Here, we aimed to determine the effects of the COVID-19 pandemic on the surgical treatment of cancer patients in our hospital by comparing the pre-pandemic period, and this experience to be a guide for possible pandemics in the future.

MATERIALS AND METHODS

This retrospective study was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Ethical approval was obtained from (censored) Hospital Ethics committee (Decision number:12/7-13.08.2020).

A total of 218 patients older than 18 years of age, who underwent electively resection with the diagnosis of gastrointestinal cancer, and without preoperative upper respiratory tract symptoms in examination and history were included to the study. The patients' ages, gender, neoadjuvant medical history, ASA scores, location of the tumor, the type of surgery performed, the duration of the surgery, the amount of blood replacement applied, the day of hospitalization in the intensive care unit (ICU), postoperative complications, and the pathological stage of the tumor were recorded. Preoperative thorax and abdominal tomography was performed in all patients for staging.

In the "pandemic period", gastrointestinal system cancer patients with positive COVID-19 Polymerase Chain Reaction (PCR) test were transferred to COVID-19 services for treatment if they did not have urgent symptoms such as obstruction and bleeding.

The data of patients diagnosed with cancer and who underwent resection in our clinic between “March 11 2020” (the date declared by World Health Organisation (WHO) as a pandemic) to “September 22 2020” in six mounths period were recorded as "Pandemic period". Before this period, the data of patients with gastrointestinal cancer diagnosis and who underwent resection in our clinic between “August 18 2019” to “March 10 2020” in six mounths period were recorded as “Pre-pandemic period”. "Pre-pandemic period" was designated as group 1, "Pandemic period" as group 2.

The “Pandemic period” was divided into group 2a and group 2b by accepting the cut-off date on May 31 2020, when the COVID-19 PCR test was routinely applied before surgery, in order to perform subgroup analysis.

Statistical Analysis

Statistical software package (SPSS 21 Inc., Chicago, IL, USA) was used for biostatistical analyses. The data obtained from the patients participating in the study were expressed as mean, standard deviation values and in percentages where appropriate. The distribution of the data was checked by the Kolmogorov- Simirnov test. Comparison of parametric data between two independent groups was made using the One-way Anova test. In the comparison of 3 groups, the homogeneity test of variances (Levene test) was accepted as parametric, and the Anova test was continued and the Bonferroni test was applied in the postHoc analysis. If a difference was found between the three groups, the new p value was obtained by Bonferoni correction (p = 0.017). The data that was found to be significant in the Levene test was accepted as non-parametric, and the Welch Anova test and the Tamhane test in the postHoc analysis were performed. Categorical groups were compared by the Chi-Square and Fisher's Exact Test. Nonparametric tests were performed using the Kruskal-Wallis H test.

RESULTS

The demographic datas of the patients are given in Table 1. No statistical difference was observed between pre-pandemic (Group 1) and pandemic (Group 2) groups in terms of gender, age and American Society of Anesthesiologist (ASA) scores. It was determined that the patients who were operated during the pandemic period were mostly those who received neoadjuvant chemotherapy (nCT) or neoadjuvant chemo(radio)therapy (nCRT) treatment. The difference was statistically significant (pre-pandemic:17.5% vs pandemic: 29.6%, p= 0.029).

Before and during the pandemic period, colorectal surgeries were performed most frequently in both periods, followed by esophagus, stomach and pancreatic surgery.

There was no statistical difference between the two groups in terms of open and minimally invasive surgeries performed before and during the pandemic period (p= 0.246).

It was observed that the duration of the operations performed before the pandemic was statistically shorter than those performed during the pandemic period (189.0 vs 214.8 minutes; respectively. p= 0.001). When the two groups were evaluated in terms of blood transfusion performed during surgery, it was found that a higher rate of blood transfusion was applied to the patients in group 1. There was no difference between the two groups in terms of intensive care and hospital stay, tumor stage and mortality (Table 2).

While the general complication rate was 33.6% in the pre-pandemic period, it was 29.6% during the pandemic period and the difference was not statistically significant. However, in the subgroup analysis of complications, it was observed that pulmonary complications developed more frequently during the pandemic period than pre-pandemic period (13.6% vs 1.5%, respectively; p= 0.000). It was found that surgical bleeding developed more frequently in the period before the pandemic than pandemic period (7.3% vs 1.2% respectively p= 0.041). Anastomotic leak and surgical site infection rates were found to be similar in both groups (Table 2).

COVID-19 PCR test has been routinely applied to every patient since May 31, 2020 in our hospital. The "pandemic period" was divided into two groups, considering the May 31, 2020 deadline. Group 2a was assigned as patients who had not undergone preoperative COVID-19 PCR testing, and group 2b was routinely assigned patients with preoperative COVID-19 PCR testing. In the subgroup analysis of the newly formed groups, it was determined that the patients in group 2b were mostly those who received neoadjuvant therapy. Pulmonary complications were statistically more frequent in group 2a patients. There was no statistical difference between the groups in terms of demographics, total complications, pulmonary complications, length of hospital stay, length of stay in the intensive care unit, number of blood transfusions and mortality (Table 3, table 4).

Table 1. Demographic characteristics of the patients

Gender				
Female	49 (35,9%)	26 (32,1%)	75 (34,4%)	0,345[a]
Male	88 (64,2%)	55 (67,9%)	143 (65,6%)	
Age	61,48±11,49	62,37±12,17	61,81±11,73	0,590[b]
ASA Score				
I	21 (15,3%)	10 (12,3%)	31 (14,2%)	0,811[a]
II	75 (54,7%)	47 (58,0%)	122 (29,8%)	
III	41 (29,9%)	24 (29,6%)	65 (29,8%)	
n-C(R)T				
Yes	24 (17,5%)	24 (29,6%)	48 (22,0%)	**0,029[a]**
No	113 (82,5%)	57 (70,4%)	170 (78,0%)	
TumorLocation				
Colon-Rectum	63 (46,0%)	37 (45,7%)	100 (45,9%)	
Esophagus-Stomach	34 (24,8%)	23 (28,4%)	57 (26,1%)	0,907[a]
Pancreaticobiliary	25 (18,2%)	15 (18,5%)	40 (18,3%)	
Other*	15 (10,9%)	6 (7,4%)	21 (9,6%)	
Type of Surgery				
Open	103 (75,2%)	65 (80,2%)	168 (77,1%)	0,246[a]
Minimallyinvasive	34 (24,8%)	16 (19,8%)	50 (22,9%)	

[a]Pearson Chi-Square, [b]Oneway Anova, ASA: American Society of Anesthesiologist, n-C(R)T : Neoadjuvant Chemo(Radio)Therapy,
** Liver (n:6), Surrenal Gland (n:3), CRS-HIPEC (Cytoreductive Surgery- Hyperthermic intraperitoneal chemotherapy)(n:9), Debulking surgery (n:3)*

Table 2. Clinical characteristics and the complications of the patients

	Group 1 (Pre-pandemic) N:137	Group 2 (Pandemic) N:81	Total N:218	P value
Operation Time (Mean) ±SD (Minute)	189,0±51,4	214,8±55,8	198,6±54,4	**0,001[a]**
Amount of Blood Transfussion (Unit)	1,53±2,19	0,95±1,31	1,31±1,92	**0,032[a]**
Length of ICU Stay	1,94±5,00	2,01±3,95	1,97±4,63	0,914[a]
Length of HospitalStay	8,09±5,52	8,14±5,31	8,11±5,43	0,950[a]
Complications				
Yes	46 (33,6%)	24 (29,6%)	70 (32,1%)	0,327[b]
No	91 (66,4%)	57 (70,4%)	148 (67,9%)	
Surgical site infections	12 (8,8%)	4 (4,9%)	16 (7,3%)	0,222[c]
Pulmonarycomplicatios	2 (1,5%)	11 (13,6%)	13 (6,0%)	**0,000[c]**
Anastomoticleakage	20 (14,6%)	8 (9,9%)	28 (12,8%)	0,214[c]
Surgicalbleeding	10 (7,3%)	1 (1,2%)	11 (5,0%)	**0,041[c]**
TNM Stage				
1	40 (29,2%)	19 (23,5%)	59 (27,1%)	0,748[b]
2	43 (31,4%)	25 (30,9%)	68 (31,2%)	
3	34 (24,8%)	22 (27,2%)	56 (25,7%)	
4	20 (14,6%)	15 (18,5%)	35 (16,1%)	
Mortality (%)	6 (4,4%)	6 (7,4%)	12 (5,5%)	0,257[b]

[a]Oneway Anova, [b]Pearson Chi-Square, [c]Fisher's Exact Test, SD:Standard Deviation, ICU:Intensive Care Unit, TNM: Tumor Node Metastasis

Table 3. Demographics of the patiens at COVID-19 pandemic period				
	Group 2a N:33	**Group 2b N:48**	**Total N:81**	**P value**
Gender				
Female	11 (33,3%)	15 (31,2%)	26 (32,1%)	0,516[a]
Male	22 (66,7%)	33 (68.8%)	55 (67,9%)	
Age	63,88±13,8	61,33±10,9	62,37±12,17	0,358[b]
ASA Score				
I	5 (15,2%)	5 (10,4%)	10 (12,3%)	0,794[a]
II	19 (57,6%)	28 (58,3%)	47 (58,0%)	
III	9 (27,3%)	15 (31,2%)	24 (29,6%)	
n-C(R)T				
Yes	4 (12,1%)	20 (41,7%)	24 (29,6%)	**0,004[c]**
No	29 (87,9%)	28 (58,3%)	57 (70,4%)	
TumorLocation				
Colorectal	11 (33,3%)	26 (54,2%)	37 (45,7%)	0,144[a]
Esophagus-Stomach	12 (36,4%)	11 (22,9%)	23 (28,4%)	
Pancreas	9 (27,3%)	6 (12,5%)	15 (18,5%)	
Other*	1 (3,0%)	5 (10,4%)	6 (7,4%)	
Type of Surgery				
Open	29 (87,9%)	36 (75,0%)	65 (80,2%)	0,125[a]
MinimallyInvasive	4 (12,1%)	12 (25,0%)	16 (19,8%)	

[a]Pearson Chi-Square, [b]Oneway Anova,[c] Fisher's Exact Test, ASA: American Society of Anesthesiologist, n-C(R)T: Neoadjuvant Chemo (Radio) Therapy

Table 4. Analysis of the complications in patiens at COVID-19 pandemic period.				
	Group 2a N:33	**Group 2b N:48**	**Total N:81**	**P value**
Surgical Site Infection	1 (3,0%)	3 (6,2%)	4 (4,9%)	0,586[a]
PulmonaryComplication	6 (18,2%)	5 (10,4%)	11 (13,6%)	0,429[a]
AnastomoticLeakage	2 (6,1%)	6 (12,5%)	8 (9,9%)	0,517[a]
SurgicalBleeding	0	1 (2,1%)	1 (1,2%)	0,386[a]
Operation Time (Mean) ±SD (Minute)	213,0±57,1	216,0±55,5	214,8±55,8	0,813[a]
Amount of Blood Transfussion (Unit)	0,73±1,2	1,1±1,37	0,95±1,31	0,206[a]
Length of ICU Stay	2,27±5,2	1,83±2,8	2,01±3,95	0,626[a]
Length of HospitalStay	7,12±3,5	8,83±6,2	8,14±5,3	0,155[a]
TNM Stage				
1	8 (24,2%)	11 (22,9%)	19 (23,5%)	0,102[b]
2	13 (39,4%)	12 (25,0%)	25 (30,9%)	
3	10 (30,3%)	12 (25,0%)	22 (27,2%)	
4	2 (6,1%)	13 (27,1%)	15 (18,5%)	
Mortality (%)	4 (12,1%)	2 (4,2%)	6(7,4%)	0,181[b]

[a]Pearson Chi-Square, [b]Oneway Anova, SD:Standard Deviation, ICU:Intensive Care Unit, TNM: Tumor Node Metastasis

DISCUSSION

In this study, the results of gastrointestinal system cancer surgeries performed during the COVID-19 pandemic period, in line with the recommendations of international guidelines, were compared with the pre-pandemic results. The aim of the study is to observe how the treatment of gastrointestinal cancer surgery is affected during this period and to make a prediction for surgical applications for pandemics that may develop in the following years.

In this study, no overall increase in morbidity and mortality was observed in gastrointestinal cancer surgeries during COVID-19 period, except increased pulmonary complications and reduction in intraoperative blood transfusion. At the same time, it was observed that the routine application of the COVID-19 PCR test preoperatively to patients who underwent surgery did not cause any statistical change in surgical results.

In the early stages of the COVID-19 pandemic, an estimated 2.3 million cancer operations worldwide were delayed due to the risk of hospital transmission (10). However, some guidelines have been published to manage the treatment of cancer patients (11-14). Some changes were made in

surgical practices in line with these recommendations. For example, because of the spread of the virus causing COVID-19 is mainly through droplets and surfaces, a negative-pressure operating room (OR) has been recommended in order to optimize the protection of health personel from contagious pathogens (15). Another recommendation is the donning of Personal Protective Equipment (PPE) including N95 mask, cap, gloves, face and eye protection.

As in all over the world, a significant decrease was observed in the number of gastrointestinal cancer surgeries in our hospital during the pandemic period. The most important reasons for this were that patients wanted to postpone their operations until after the pandemic due to the concerns of COVID-19 transmission, and a part of the hospital beds were reserved for pandemic patients within the framework of national health measures and the two-person patient rooms were reduced to one person in order to minimize the risk of contamination. At the same time, surgeons' indications for nC(R)T have expanded due to the reduction of beds reserved for patients other than COVID-19 positive patients. However, inevitably, as seen in the pandemic period of our study, patients who had completed nC(R)T treatment began to apply to clinics for surgical treatment after a while. However, we did not observe a statistically significant difference between the results of the operations performed between the pandemic period mostly in which patients received nC(R)T treatment were operated and the pre-pandemic period.

These changes in daily surgical practice and the recommendations made in the guidelines created some additional problems, especially for developing countries. Particularly due to the economic burden of the pandemic and the high cost of some of the suggestions made in the guidelines - such as negative pressure operation rooms - it was difficult to fulfill all these suggestions in developing countries like us. We continued our own surgical practice within the framework of recommendations made in international guidelines. For example;

Some authors suggest that performing a closed, controlled procedure is potentially safer than having an open abdomen which is widely dispersible fluids and smoke, while others have stated that it is safer to avoid laparoscopy due to the risk of viral spread because of pneumoperitoneum. There are also some recommendations regarding operating room safety during minimally invasive surgery (MIS). Since active replication of the COVID-19 virus has been reported to occur in the respiratory and gastrointestinal systems, it is mentioned that aerosol transmission may pose a potential danger during gastrointestinal system surgery (16,17). Passive evacuation systems which are using electrostatic filters have been proposed, but in our hospital where such filters are not available, no adverse results have been observed after surgeries with standard protective equipment (18).

Another important issue is postoperative extubation and it is claimed to be extremely dangerous for viral spread. For this reason, it is recommended to use negative pressure OR during the pandemic (19). However, negative pressure ORs are quite costly and it may not be possible to convert existing operating rooms to negative pressure rooms in case of a sudden pandemic. Similarly, high-efficiency particulate air (HEPA) filters are recommended to prevent toxic aerosol circulation in operating rooms (20). There are only two negative pressure operation rooms in our hospital and these rooms are used only for patients with COVID (+). All other operating rooms are standard rooms with HEPA filters and during the pandemic these rooms were used for all surgical procedures - except for patients with proven COVID (+). In these conditions, viral contamination was not observed in any patients and healthcare personnel after all gastrointestinal surgical operations performed in standard HEPA filtered ORs. It is also claimed that typical modern ventilation systems use ceiling purified air and suck in contaminated air near the floor. Therefore, aerosols contaminated with the COVID-19 virus guided to the floor, then to the side walls and corners of the operating room (21). For this reason, an operating table placed in the center of the operating room, around which the patient and surgical personnel are located, seems to be the safest area. Although the number of patients decreased during the pandemic period, minimally invasive gastrointestinal system cancer operations

were continued both laparoscopically and robotically in our clinic and as suggested by some authors (22), minimally invasive surgical procedures were performed with low intraabdominal pressure, minimal electrocautery using, and standard personal protective equipment (N95 mask, cap, gloves, face and eye protection). In our study, no difference was observed between the results of minimally invasive gastrointestinal system cancer surgery performed during the pandemic period and those performed before the pandemic.

The two results of our study were the prolongation of the operation times during the pandemic period and the decrease in the number of blood transfusions performed during the operation. The longer operation time during the pandemic period may be due to the more careful intubation and extubation practices of anesthesiologists, in line with the recommendations of international guidelines. Due to the increasing need for intensive care beds for COVID-19 (+) patients, also surgeons may be concerned about minimizing possible contamination during surgery and minimizing the need for intensive care bed due to postoperative complications. All these factors may be the reason of the increase operatin time during the pandemic period, as well as the reason of the decreased need for blood transfusion during surgery.

Despite these, in our study, an increase was observed in pulmonary complications in gastrointestinal cancer patients operated during the pandemic period compared to the pre-pandemic period. Interestingly, all of these patients had no pulmonary symptoms in their physical examination and no radiologic findings in their preoperative staging tomography. Routine COVID-19 PCR testing may be considered in the preoperative period to reduce pulmonary complications during the pandemic period. However, we found no statistically significant difference in terms of pulmonary complications when the patients who were operated before and after the period when we routinely started the preoperative COVID-19 PCR test during the pandemic period. Moreover, the COVID-19 PCR test performed while the intensive care follow-up of a patient who died due to pulmonary complications during the pandemic period was also found negative. Although it is difficult to explain this situation, it may be thought that performing a preoperative routine COVID-19 PCR test does not provide an additional benefit in terms of surgical results other than detecting COVID-19 positive patients and protecting healthcare personnel.

Studies published in Italy and China during the pandemic period, no difference was observed compared to the pre-pandemic period in terms of postoperative morbidity such as surgical site infection, hospital stay and cost (23,24). In our study, too, no statistically significant difference was observed in mortality and postoperative morbidity between the two periods - except for pulmonary complications. All postoperative mortalities during the pandemic period were due to surgical complications - all of them septic condition after anastomotic leak.

CONCLUSION

The COVID-19 pandemic probably most affected developing countries. In addition to the economic crisis in these countries, it has become very difficult to maintain the current health system. Especially in gastrointestinal cancer surgery, it was very difficult to manage this process by trying to put the applications recommended in the international guidelines into surgical practice and on the other hand, the obligation of operate these patients. Moreover, it may not be possible for all countries to provide high-cost surgery conditions recommended for open and minimally invasive surgical procedures. Even if it is economically possible, such transformations may not be made urgently in cases of sudden pandemics. As seen in our study - although retrospective and uncontrolled - gastrointestinal cancer surgeries can be performed without any serios morbidities in standard HEPA filtered operating rooms under routine use of personal protective equipment (N95 mask, cap, gloves, face and eye protection).

For future pandemics, at least HEPA filtered operation rooms and personal protective equipment such as N95 mask, cap, gloves, face and eye protection should be included in standard practices.

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