The impact of the Covid 19 pandemic in colorectal cancer

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AIM: *COVID-19 was first seen in China at the end of December 2019. The disease spread rapidly and was declared as a pandemic by the World Health Organization (WHO) on March 11, 2020. Only urgent surgical cases and oncological surgeries that cannot be postponed were performed during this pandemic process. As a wasting disease, colorectal cancer (CRC) itself and its corresponding treatment may weaken the immune response to respiratory bacteria, makes patients more susceptible to virus infection. Besides, colorectal cancer patients are immunosuppressed because of the side effects of chemotherapy and/or radiotherapy taken. The choice of surgical procedures and perioperative management of the patients with CRC has become even more important in the COVID-19 pandemic. The impact on CRC surgery is unknown. In this study, we aimed to evaluate the effects of the COVID-19 pandemic on the preopartive, intraoperative, and postoperative findings of patients operated for colorectal cancer in our clinic.*
MATERIAL-METHOD*: We defined the 'COVID-19' period as occurring between 12-03-2020 and 31-08-2020. All the enrolled patients were divided into two groups, pre-COVID-19 group (Pre-CG; 66 cases) and COVID-19 group (CG; 43 cases). A total of 109 patients with CRC were included in this study. Patient characteristics, preoperative, intraoperative, and postoperative clinicopathological findings were compared between groups.*
RESULTS: *The waiting times before admission increased in CG (Pre-CG [5.34±2.55] vs CG [18.13±9.11]; p<0.001). After admission, the waiting time before surgery was longer in CG (Pre-CG [2.04±1.34] vs CG [5.53±6.00]; p<0.001). There were no significant difference between the groups in terms of operation method (laparoscopic/open), operation type (emergency/elective), surgical procedure, combine organ resection, intraoperative blood transfusion requirment, operation time (p values, respectively; p=0.082; p=0.474; p=0.317; p=0.656; p=0.617; p=0.696). In this study, no significant difference was found between the groups in terms of postoperative complications (p=0.357) and mortality (p=0.826). It was found that the ICU stay was significantly shorter in CG (Pre-CG [11.63±2.22] vs CG [1.48±0.76]; p=0.008).*
CONCLUSIONS: *In this study, it was seen that the COVID-19 pandemic did not affect morbidity and mortality in CRC surgery, but it prolonged admission waiting and operation waiting times. Since there is very little data in the literature regarding the effect of COVID-19 on CRC surgery, our study will guide future studies on this subject.*

KEY WORDS: Colorectal Cancer, Coronavirus disease 2019, COVID-19, Surgery

Introduction

The rapid spread of the novel coronavirus disease 2019 (COVID-19), which appeared first in Wuhan, China, has caused a worldwide pandemic that has reached Turkey. COVID-19 disease caused by SARS-CoV-2 is mainly characterized by infected respiratory symptoms, including fever, dry cough, dyspnea and infiltrate on chest radiograph.

Facing the SARS-CoV-2 pandemic outbreak, the medical environment for Turkish surgeons has changed dramatically, presenting unprecedented challenges to their routine clinical practice [1,2]. Making decisions about performing surgery on non-cancerous patients is easy and

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can be postponed to the post-epidemic conditions. On the other hand, patients requiring emergency surgery such as colorectal cancer (CRC) patients should be treated with the some measures. Today, CRC, with 11% of cancer diagnoses, is the third most common and the second fatal cancer with annually 1.8 million new cases worldwide [3]. As a wasting disease, CRC itself and its corresponding treatment may weaken the immune response and makes patients more susceptible to SARS-CoV-2 infection. A recent Chinese study showed that about 1% COVID-19 infected patients had a history of cancer, which seemed to be higher than the overall incidence (0.29%) of cancer in the Chinese population [4]. SARS-CoV-2 infected patients who accompanied with cancers may in turn make the COVID-19 worse and the case-fatality rate is reported higher in those with pre-existing comorbid conditions. Besides, patients with both SARS-CoV-2 infection and cancer have a 5.6% case-fatality rate, which is more than 2 times higher than the overall case-fatality rate (2.3%) [5]. Therefore, there is anurgent need to assess its impact on cancer diseases and the treatment of colorectal cancers.

There are very few studies in the literature investigating the effect of the COVID-19 pandemic process on CRC surgery [3,6]. The aim of this study is to investigate the effect of the COVID-19 pandemic on CRC surgery.

Materials and Methods

This study was approved by the Ministry of Health, General Directorate of Health Services and Ethics Committee of Ankara University Medical Faculty (Decision number: İ10-640-20). The data of 109 patients, who underwent surgery for colorectal cancer in the Surgical Oncology Clinic of Ankara University Medical Faculty in the period between August 2019 and August 2020, were retrospectively studied. According to the official statement of the Ministry of Health of Turkey description first case of coronavirus in Turkey was detected on March 11. Taking this into consideration, the patients were categorized into two groups: "pre-COVID-19" (Pre-CG; 66 cases; period from 01-08-2019 to 10-03-2020) and "COVID-19" (CG; 43 cases; period between 12-03-2020 and 31-08-2020). The operations were performed by 2 surgeons and same team. The criteria for inclusion in the study were as follows: patients with a preoperative diagnosis of histologically proven CRC adenocarcinoma; there was no missing patient data. On the other hand, the exclusion criteria were as follows: patients diagnosed with other malignant tumors such as lymphoma, neuroendocrine tumors, squamous cell carcinoma, stromal tumors in the preoperative or postoperative pathological examination; having a history of comorbid malignant tumors; and missing data. Patient characteristics, preoperative, intraoperative and postoperative clinicpathological findings were compared between the two groups. Patient characteristics were included age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) scores, comorbidity, tumor localization, neoadjuvant treatment status. The evaluation of preoperative clinicopathological findings included the analysis of admission waiting time (day), operation waiting time (day), AFP, CEA, CA 19-9, Hb and Clinical TNM staging. The following intraoperative findings were evaluated: operation type (elective / emergency), operation method (laparoscopic or open), surgical procedure performed (right hemicolectomy, total colectomy, left hemicolectomy, low anterior resection, abdominoperineal resection), combined organ resection, operation time (minute), requirment for blood transfusion. On the other hand, the following postperative findings were evaluated: 30-day postoperative complications, mortality, presence of postoperative fever, total hospital stay, intensive care unit (ICU) stay and postoperative blood transfusion requirment. Finally, all findings were compared between the two groups.

Statistical Analysis

SPSS 25.0 software was used in the analysis of the data. For descriptive analysis, quantitative variables mean ± standard deviation and median (minimum-maximum), and qualitative variables were presented as number of patients (percentage). The mean distributions of the quantitative data were tested with the Shapiro-Wilk test and histogram curves. In terms of the quantitative variable, the difference between the categories of the qualitative variable with two categories was examined using the Mann-Whitney U test for those who provided normal distribution assumptions and those who did not provide the Student-t-test. The Chi-squared test was used to evaluate the relationship between two qualitative variables. The statistical significance level was accepted as 0.05.

Results

During the pandemic period, polymerase chain reaction (PCR) test was performed for COVID-19 by taking combined nasal and throat swabs from all patients 24-48 hours before surgery. The operation of three patients was delayed due to PCR positivity and was performed at a later date. No PCR test positivity was found in any patient in the postoperative period.

109 patients who were operated for colorectal cancer were included in the study. Sixty six (60.6%) of 109 patients were operated before the pandemic (Pre-CG), and 43 (39.4%) during the pandemic period (CG). Fifty four (49.5%) of the patients were male, 55 (50.5%) were female and mean ± standard deviation and median (minimum-maximum) values of the patients' age were respec-

TABLE I - *Comparison of patient characteristics.*

Variables		Groups				
		Pre-CG (66 cases)		CG (43 cases)		
		N	%	N	%	P
Gender	Male	35	53.0	19	44.2	0.815a
	Female	31	47.0	24	55.8	
NeoadjuvantStatus	No	50	75.8	29	67.4	0.903a
	Yes	16	24.2	14	32.6	
Comorbidity	No	49	74.2	28	65.1	0.307a
	Yes	17	25.8	15	34.9	
ASA	1	49	74.2	28	65.1	0.513a
	2	11	16.7	11	25.6	
	3	6	9.1	4	9.3	
Tumor Location	Right	13	19.7	9	20.9	0.745a
	Transvers	2	3.0	3	7.0	
	Left	14	21.2	7	16.3	
	Rektum	37	56.1	24	55.8	
Age	Mean±SD	59.92±13.44		62.25±13.55		0.916b
BMI (kg/m^2)	Mean±SD	26.36±3.42		26.18±3.54		0.625b

a) Ki-kare; b, Student-t; c, Mann Withney U; SD, standart deviation.

TABLE II - *Comparison of preoperative clinicopathological findings.*

Variables		Groups				
		Pre-CG (66 cases)		CG (43 cases)		
		N	%	N	%	P
Clinical TNM stage	1	8	12.1	7	16.3	0.552a
	2	38	57.6	24	55.8	
	3	16	24.2	7	16.3	
	4	4	6.1	5	11.6	
AFP	Normal	66	100	41	95.3	0.077a
	High	0	0	2	4.7	
CEA	Normal	24	36.4	23	53.5	0.078a
	High	42	63.6	20	46.5	
CA 19-9	Normal	48	72.7	34	79.1	0.453a
	High	18	27.3	9	20.9	
Operation waiting	Mean±SD	2.04±1.34		5.53±6.00		<0.001c
Hb	Normal	37	56.1	29	67.4	0.235b
	Low	29	43.9	14	32.6	
Admission waiting	Mean±SD	5.34±2.55		18.13±9.11		<0.001c

a) Ki-kare; b, Student-t; c, Mann Withney U; SD, standart deviation.

tively 60.84±13.47 62.00 (26.00-90.00). Tumor localization in pre-CG was right colon in 13 (19.7%) patients, transvers colon in 2 (3%) patients, left colon in 14 (21.2%) and rectum in 37 (56.1%) patients. In CG, 9 (20.9%) patients had right colon, 3 (7%) patients had transvers colon, 7 (16.3%) patients had left colon and 24 (55.8%) patients had rectum tumors, and there was no statistically significant di Iference between the two groups (p=0,745). Comparisons of patient characteristics are shown in (Table I).

The waiting times before admission increased in CG (Pre-CG [5.34±2.55] vs CG [18.13±9.11] ; p<0.001). After admission, the (Table II).

Thirty-five (%53) patients in pre-CG and 30 (%69.8) patients in CG were operated by laparoscopic method. There was no significant difference between the groups in terms of operation method (p=0.082). At the same time, no significant difference was detected between the groups in terms of operation type (emergency / elective), surgical procedure, combine organ resection, intraoperative blood transfusion requirment, operation time (p values, respectively; p=0.474; p=0.317; p=0.656; p=0.617; p=0.696). Although there was no significant difference between the two groups in terms of creating an ostomy (p=0.283), there was a significant difference in terms of ostomy type (p=0.030). More ileostomies were created in pre-CG. Intraoperative findings are summarized in (Table III).

TABLE III - *Comparison of intraoperative clinicopathological findings.*

Variables		Groups				
		Pre-CG (66 cases)		CG (43 cases)		
		N	%	N	%	P
Type of surgery	Elective	61	92.4	38	88.4	0.474a
	Emergency	5	7.6	5	11.6	
Operation time	Mean±SD	138.18±36.97		126.39±37.62		0.696b
Surgical procedure	Diagnostic Lap.	0	0	2	4.7	0.317a
	Right Hemicolectomy	13	19.7	9	20.9	
	Anterior Resection	8	12.1	7	16.3	
	Left Hemicolectomy	5	7.6	0	0	
	Low Anterior Resection	36	54.5	21	48.8	
	APR	0	0	1	2.3	
	Subtotal Colectomy	1	1.5	1		
	Loop Colostomy/ leostomy	2	3	2	4.7	
	Pelvic Egsenteration	1	1.5	0	0	
Operation method	Open	31	47.0	13	30.2	0.082a
	Laparoscopic	35	53.0	30	69.8	
Combine organ res.	No	53	80.3	33	76.7	0.656a
	Yes	13	19.7	10	23.3	
Intraoperative blood transfusion	No	53	91.4	38	88.4	0.617a
	Yes	5	8.6	5	11.6	
Ostomy	No	41	62.1	31	72.1	0.283a
	Yes	25	37.9	12	27.9	
Ostomy Type	Ileostomy	22	33.3	6	14.0	0.030a
	Colostomy	3	4.5	6	14.0	

a) Ki-kare; b, Mann Wtihney U; SD, standart deviation; lap, laparoscopy; APR, abdominoperineal resection

TABLE IV - *Comparison of postoperative clinicopathological findings.*

Variables		Groups				
		Pre-CG (66 cases)		CG (43 cases)		
		N	%	N	%	P
Pathological TNM stage	0	3	4.5	0	0	0.192a
	1	14	21.2	7	16.3	
	2	17	25.8	6	14.0	
	3	25	37.9	23	53.5	
	4	7	10.6	7	16.3	
Complication	No	54	81.8	38	88.4	0.357a
	Yes	12	18.2	5	11.6	
Postop. mortality	No	64	97.0	42	97.7	0.826a
	Yes	2	3.0	1	2.3	
Postop. fever	No	56	84.8	34	79.1	0.437a
	Yes	10	15.2	9	20.9	
Postop. Blood transfusion	No	56	84.8	32	74.4	0.177a
	Yes	10	15.2	11	15.6	
Hospital stay	Mean±SD	11.52±11.14		10.02±5.08		0.730b
ICU stay	Mean±SD	1.63±2.22		1.48±0.76		0.008b

a) Ki-kare; b, Mann Withney U; postop, postoperative.

Although the hospital stay was shorter in CG, there was no significant difference between the groups (Pre-CG [11.52±11.14] vs CG [10.02±5.08]; p=0.730). It was found that the ICU stay was significantly shorter in CG (Pre-CG [11.63±2.22] vs CG [1.48±0.76]; p=0.008). Postoperative complications were atelectasis, postoperative urinary retention, wound infection, intraabdominal abscess, sepsis, bleeding, ARDS, anastomotic leak, deep vein thrombosis (DVT) and pleural effusion, and there was no statistically significant difference between the two groups (p=0.357). There was no significant difference between the two groups in terms of postoperative mortality (p=0.826) (Table IV).

Discussion

Individuals with cancer had a higher risk of SARS-CoV-2 infection due to poor immunity from tumor load and malnourishment [7,8]. Moreover, cancer patients infected with COVID-19 had a significantly higher mortality rate compared with noncancer patients 9, 10

The current recommendations for management of colorectal diseases are still evolving, due to the limited experience on COVID-19 pandemic.

There is a present understanding that the COVID-19 pandemic should change some traditional surgical practices. After the diagnosis of the first case of COVID-19 in Turkey on 11 March 2020, the Ministry of Health of the Republic of Turkey recommended to postpone all elective surgeries on 17.03.2020 to lower the work load in hospitals and to prevent the disruption of healthcare services that will be required in the future period. After these developments, the approach towards the surgical treatment of colorectal cancer patients has been the subject of debate among surgeons.

During the COVID-19 pandemic period, many measures were taken to prevent the spread of the virus all over the world. Accordingly, some important changes were made in the working order of our Surgical Oncology clinic.

Double-bed wards were turned into a single-bed service, visitor reception was restricted, some surgeries such as ostomy closure and benign breast tumor surgeries were postponed, operations were performed with a limited number of staff to prevent unnecessary crowd. In present study, admission waiting time in CG was significantly longer than in Pre-CG ($p<0.001$). This may be due to the decrease in the number of beds and the patients avoiding the hospital admission for fear of contamination during the COVID-19 pandemic.

There is study in the literature related to the increase in the number of patients diagnosed with advanced stage cancer and delayed cancer emergency admissions due to the fear of COVID-19 transmission [11]. In contrast with this, in our study, admisson waiting prolongation during the pandemic process did not cause an increase in the number of patients diagnosed with advanced clinical or pathological stage CRC (p values, respectively $p=0.552$; $p=0.192$). Some studies report different results regarding delay in colorectal cancer surgery. Lee et al. reported that the survival rates were significantly different across patient groups treated within 30 days, in the 31-150 days, and > 151 days of diagnosis [12].

Wanis et al. compared 908 stage I-III colon cancer patients with respect to disease-free survival and overall survival according to the time from diagnosis to surgery[13].

The comparison of those who had surgery earlier or later than 30 days revealed that there was no difference in overall survival or disease-free survival. In a retrospective study conducted by Kucejko et al., it was reported that the best survival values were in those operated between 3-6 weeks [14]. Considering all these studies, it may be thought that elective colon cancer surgery can be deferred for approximately 6 weeks.

After admission, the patients were hospitalized in a single bed room. In addition to the routine preoperative examinations of the patients, the COVID-19 polymerase chain reaction (PCR) test was performed in all patients 24-48 hours before surgery.

At the same time, after admission, the patient was observed for 2 days preoperatively for high fever and suspicious findings for SARS-CoV-2. During this observation period, patients with negative PCR tests and no suspicious findings for SARS-CoV-2 were operated. Factors such as preoperative examinations, a longer observation period (2 days) and a decrease in the number of beds caused a prolonged operation waiting time in the CG ($p<0.001$). In line with this, Yu-xuan Li et al. reported that the admission waiting and operation waiting time was long in the pandemic group [15].

During the pandemic period, the operation of 3 patients was delayed due to the positivity of the preoperative PCR test and was performed at a later date. Although ileus was present in one of these patients, ileus regressed as a result of nasogastric decompression and intravenous medicamentous treatment. After the symptoms of COVID-19 regressed and the PCR test was negative, an elective surgery (low anterior resection and protective loop ileostomy) was performed.

CRC treatment for patients who are COVID-19 positive should be as conservative as possible, using stent placement for stenosing cancer and performing surgery after the resolution of infection. Hartmann's procedure should be recommended for left-sided occlusion or perforation [16] SARS-CoV-2 complicates the postoperative course with diagnostic challenges and a potentially high mortality. Aminian et al. reported in their study the development of acute respiratory distress syndrome (ARDS) after surgery in two of the four patients, and three patients died during the perioperative period [17]. In contrast, Cai et al reported that eight patients underwent abdomi [18]

In the present study, no significant difference was found between the two groups in terms of intraoperative findings such as operation time, operation type, surgical method, surgical procedure, combined organ resection, creating an ostomy and intraoperative blood transfusion. In the first 2 months of the pandemic, considering the viral transmission risk of laparoscopy, open surgery was mostly performed in our clinic.

In the following months, necessary precautions were taken and CRC surgeries were performed by laparoscopic method. In this study, the effect of COVID-19 on the surgical method (open / laparoscopic) was not observed ($p=0.082$). Although there are concerns regarding SARS-COV-2 release into CO2 during laparoscopic surgery, there is no clear evidence to support open surgery over

laparoscopic surgery. Yu et al. have reported their experience on the surgical method in colorectal cancer patients during the COVID-19 pandemic [8]. According to the authors, in laparoscopic surgery, the surgeons contact with the abdominal cavity will decrease and the aerosol emission overcome by electrical equipment will also decrease. On the other hand, compared with total laparoscopic surgery, laparoscopic surgery with an auxiliary incision can reduce the operation time and thus the exposure time.

Taking these issues into account, Yu et al. recommends laparoscopy-assisted radical surgery for colorectal cancer patients during the pandemic but they highlight that the aerosols need to be strictly managed. There are very few publications on transmission of SARS-CoV-2 in open and minimally invasive surgery, and their level of evidence is low [19,20]. There are points where laparoscopic and open surgery provide advantages and disadvantages to each other and there is no consensus in this regard. However, all efforts should be made to eliminate the risk of staff exposure to aerosolized particles. This can be achieved by minimizing the creation of a plume (reduce power setting) through the use of electrocautery or ultrasonic scalpels, limiting CO2 release into the operating room by lowering the pneumoperitoneum pressure, reducing the Trendelenburg position, or deflating the abdomen before retrieving a specimen or before removing the trocars [20]. We tried to follow these recommendations while performing laparoscopic surgery in our clinic.

In the present study, no significant difference was found between the groups in terms of postoperative complications (p=0.357) and mortality (p=0.826). Although it was not statistically significant, it was observed that the length of hospital stay was shorter during the pandemic period (p=0.730). It was found that the ICU stay was significantly shorter in CG (p=0.008). This results can be explained by the efforts of patients to be discharged as soon as possible to reduce the risk of transmission of COVID-19.

After surgery, in patients with fever of unknown cause, appropriate ward isolation measures were taken and postoperative blood routine, C-reactive protein, procalcitonin, chest CT, and SARS-CoV-2 PCR tests were done. As a result of these examinations, COVID-19 disease was not detected in patients in the postoperative period in our clinic.

Limitations

The limitations of our study are the following: it is not randomized, and it is a retrospective and single-center study. Besides, since the pandemic process is not yet over, our study includes a early phase of pandemic. It is necessary to consider all these factors when interpreting the results of this study.

Conclusions

In conclusion, this study is one of the few studies in the literature investigating the effect of COVID-19 on CRC surgery. In this study, it was observed that the pandemic prolonged the admission waiting and operation waiting times. The effect of COVID-19 on the morbidity and mortality of CRC surgery was not observed. Despite the full impact of COVID-19 on CRC surgery is still unknown, this will only be evident in the long run. Although our study sheds light on this issue, further studies with larger sample size are needed.

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Riassunto

COVID-19 è stato visto per la prima volta in Cina alla fine di dicembre 2019. La malattia si è diffusa rapidamente ed è stata dichiarata pandemia dall'Organizzazione mondiale della sanità (OMS) l'11 marzo 2020. Solo casi chirurgici urgenti e interventi oncologici che non possono essere rimandati sono stati eseguiti durante questo processo pandemico. Essendo una malattia da deperimento, il cancro del colon-retto (CRC) stesso e il trattamento corrispondente possono indebolire la risposta immunitaria ai batteri respiratori, rendendo i pazienti più suscettibili alle infezioni virali. Inoltre, i malati di cancro del colon-retto sono immunosoppressi a causa degli effetti collaterali della chemioterapia e / o della radioterapia assunte. La scelta delle procedure chirurgiche e la gestione perioperatoria dei pazienti con CRC è diventata ancora più importante nella pandemia COVID-19. L'impatto sulla chirurgia CRC è sconosciuto. In questo studio, abbiamo mirato a valutare gli effetti della pandemia COVID-19 sui risultati preopartivi, intraoperatori e postoperatori dei pazienti operati per cancro del colon-retto nella nostra clinica.

Metodi e Materiali: abbiamo definito come periodo "COVID-19" quello compreso tra il 12-03-2020 e il 31-08-2020. Tutti i pazienti arruolati sono stati divisi in due gruppi, gruppo pre-COVID-19 (Pre-CG; 66 casi) e gruppo COVID-19 (CG; 43 casi). In questo studio sono stati inclusi un totale di 109 pazienti con CRC. Le caratteristiche del paziente, i risultati clinicopatologici preoperatori, intraoperatori e postoperatori sono stati confrontati tra i gruppi.

Risultati: tempi di attesa prima del ricovero sono aumentati in CG (Pre-CG [5,34 ± 2,55] vs CG [18,13 ± 9,11]; p <0,001). Dopo il ricovero, il tempo di attesa prima dell'intervento chirurgico è stato più lungo in

CG (Pre-CG [2,04 ± 1,34] vs CG [5,53 ± 6,00]; p <0,001). Non c'erano differenze significative tra i gruppi in termini di metodo di operazione (laparoscopica / aperta), tipo di operazione (di emergenza / elettiva), procedura chirurgica, resezione d'organo combinata, requisito di trasfusione di sangue intraoperatoria, tempo di intervento (valori p, rispettivamente; p=0,082; p=0,474; p=0,317; p=0,656; p=0,617; p=0,696). In questo studio, nessuna differenza significativa è stata trovata tra i gruppi in termini di complicanze postoperatorie (p=0,357) e mortalità (p=0,826). È stato riscontrato

CONCLUSIONI**:** in questo studio, si è visto che la pandemia COVID-19 non ha influenzato la morbilità e la mortalità nella chirurgia CRC, ma ha prolungato i tempi di attesa del ricovero e dell'operazione. Poiché in letteratura sono disponibili pochissimi dati sull'effetto del COVID-19 sulla chirurgia CRC, il nostro studio guiderà gli studi futuri su questo argomento.

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