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RESEARCH ARTICLE

The Effect of the COVID-19 Pandemic on the Clinical and Pathological Stages of Colorectal Cancer Patients

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ABSTRACT

Aim: Coronavirus disease-2019 (COVID-19) appeared in Wuhan, China in December 2019 and the World Health Organization declared it a pandemic the following March. Colorectal cancer (CRC) is the third most common cause of cancer-related deaths worldwide, but the impact of the global pandemic on health services has severely affected the delivery of health care, including the diagnosis and treatment of CRC. The aim of this study was to investigate the effect of the COVID-19 pandemic on the clinical and pathological stages of CRC patients at the time of operation.

Method: Our study evaluated CRC patients who underwent surgery in a 6-month (May-October 2020) period during the COVID-19 pandemic and patients operated due to CRC in the same period of 2019, before the pandemic. Data collected included time of admission, complaints at admission, cancer stage and clinical characteristics, length of hospital stay, and complication and mortality rates.

Results: The study included 47 patients operated during the pandemic and 83 patients operated in the corresponding period, one year earlier. The number of cancerous lymph nodes, rates of lymphovascular and perineural invasion, and complication and mortality rates were significantly higher in patients operated during the pandemic, while the pathological stage and the rate of receiving adjuvant treatment were higher.

Conclusion: During the COVID-19 pandemic CRC patients presented with delayed diagnosis or more advanced cancer, leading to a significant increase in morbidity and mortality. Adjustment of health care provision during crises, such as the COVID-19 pandemic, should be planned to minimize the impact on emergency, cancer and infectious disease services.

Keywords: COVID-19, colorectal cancer, delay, increased mortality, pathological stage

Introduction

Coronavirus disease-2019 (COVID-19) emerged in Wuhan-China in December 2019 and the World Health Organization (WHO) declared it a pandemic on 11th of March the following year. COVID-19, which is caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), can cause asymptomatic infection, severe pneumonia, multiple organ failure and death. The pandemic had a major impact on the provision of health services, worldwide, leading to re-assignment of health services to COVID-19 treatment, shortages of healthcare staff and delay in patient presentations as populations sought to avoid infectious contact. Colorectal cancer (CRC) is the third most common cause of cancer-related deaths worldwide. The impact of the pandemic also affected cancer services, and has been shown to result in delays in hospital admission and diagnosis of CRC patients, resulting in increased morbidity and mortality. Complications such as obstruction, perforation, bleeding and peritonitis in CRC patients require emergency intervention, while a 6-week delay in treatment may lead to complications in early-stage CRC patients.[1,2] CRC patients are also at risk of COVID-19 but delay in seeking treatment and consequent progression of the cancer stage may occur due to later diagnosis and treatment.[2]

After the first COVID-19 case was detected in Turkey on 11.03.2020, the Turkish Ministry of Health recommended

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postponing all elective surgery on 17.03.2020 to ease the workload in hospitals and to prevent the interruption of healthcare services that would be required to deal with the pandemic. Due to the global decrease in hospitals and healthcare professionals working in a non-COVID setting, access to healthcare services became more limited for cancer patients.[3]

The aim of this study was to assess the clinical and pathological parameters of CRC patients admitted to our clinic during the COVID-19 pandemic and to examine the effect of the pandemic on these parameters by comparison with the same period of the previous year.

Materials and Methods

This study included CRC patients who underwent surgery in the General Surgery Department of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine between May 2020 and October 2020 (a 6-month period) during the COVID-19 pandemic (group B) and patients operated due for CRC (group A) in the same period of 2019 (May-October 2019). Information about the time of admission, complaints at admission, cancer stage, length of hospital stay, complication rate and peri-operative mortality were retrieved from patient files and follow-ups, and evaluated. Perioperative mortality estimation included deaths occurring within 30 days of surgery or before discharge.

Patients aged <18 years, with benign pathologies, tumors other than adenocarcinoma, and patients with recurrence were excluded from the study.

Tumor location in the patients was determined according to preoperative colonoscopy, abdominal computed tomography (CT), and perioperative findings. Patients who were operated within 24 hours due to massive bleeding, perforation and obstructive tumor were evaluated under emergency admission. Postoperative complications were scored according to the Clavien-Dindo classification.[4]

All patients who were operated during the COVID-19 pandemic were tested for the SARS-CoV-2 virus using a polymerase chain reaction method within the 48 hours before operation and all had negative results.

The study was approved by the Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (approval number: 12846, date: 21.01.2021). Written informed consent was obtained from all participants.

Statistical Analysis

Statistical analyses were conducted using SPSS version 17.0 (IBM Inc., Armonk, NY, USA). The normality of the variables was analyzed using histograms and the Kolmogorov-Smirnov test. Descriptive analyses were presented using mean, standard deviation and median values. Categorical variables were compared using the Pearson's chi-square test. The Mann-Whitney U test was used to compare non-normally distributed (non-parametric) data sets between groups. A $p<0.05$ was considered to indicate statistical significance.

Results

The study included a total of 130 patients, 83 in group A and 47 in group B with a mean age of 64.6±11.6 years. There were 78 (60%) male and 52 (40%) female patients.

Gender, complaints, and urgency (emergency vs elective) status of the patients were compared between group A and group B. There was no difference in age and gender distribution between the two groups of patients. Despite the lack of a statistically significant difference in complaints at admission, the rates of abdominal pain, rectal bleeding, and emergency admission were higher in group B than in group A (Table 1).

Tumor location, previous oncological treatment, requirement for intensive care, colostomy, presence of complications, and perioperative mortality were compared between group A and group B (Table 2). The rate of rectal tumor location tended to be higher in group B but there

Table 1. Patient complaints at admission and comparison between the groups

		A		B		p
		n	%	n	%	
Sex	Male	49	59.0	29	61.7	0.766
	Female	34	41.0	18	38.3	
Abdominal pain	No	47	56.6	23	48.9	0.398
	Yes	36	43.4	24	51.1	
Constipation	No	59	71.1	35	74.5	0.679
	Yes	24	28.9	12	25.5	
Change in bowel habits	No	73	87.95	43	91.5	0.532
	Yes	10	12.05	4	8.5	
Rectal bleeding	No	67	80.7	34	72.3	0.270
	Yes	16	19.3	13	27.7	
Fatigue	No	76	91.6	44	93.6	0.673
	Yes	7	8.4	3	6.4	
Incidental	No	79	95.2	46	97.9	0.443
	Yes	4	4.8	1	2.1	
Other	No	78	93.4	46	97.9	0.309
	Yes	5	6.0	1	2.1	
Emergency admission	No	63	75.9	33	70.2	0.478
	Yes	20	24.1	14	29.8	

was no significant difference in tumor location or the rate of colostomy between the groups. Although the rate of receiving neoadjuvant chemotherapy was higher in group B, again the difference was not significant. The presence of complications and perioperative mortality were significantly different between the groups, with a higher rate in group B than in group A. Using the Clavien-Dindo classification, grade 2 and higher complications in group A were: wound site infection n=3 (3.6%); and intra-abdominal collection n=2 (2.4%). In comparison, in group B, complications were: wound site infection n=4 (8.5%): intra-abdominal collection n=3 (6.4%); anastomotic leak n=2 (4.25%); intra-abdominal bleeding n=1 (2.1%); and pulmonary embolism n=1 (2.1%). Of four (8.5%) patients who died in group B, three had a history of obstructive tumors and sepsis, and one had postoperative pulmonary embolism.

The TNM (tumor, lymph node, metastasis) stage, lymphatic invasion, vascular invasion, perineural invasion, histological grade, surgical margin positivity, distant metastasis, and need for adjuvant chemotherapy were compared between group A and group B (Table 3). Although there was a high rate of advanced stage (stage 3-4) patients in group B, the difference was not significant. The comparison of rates of lymphatic invasion, vascular invasion, perineural invasion, and the number of positive lymph nodes and the need for adjuvant chemotherapy found that these were significantly higher in group B.

Age, duration of complaints (months), length of hospital stay (days) and levels of tumor markers including carcinoembryonic antigen and carbohydrate antigen 19-9 were compared between group A and group B. Although the duration of complaints and length of stay was longer in group B patients, the differences were statistically insignificant. The comparison of tumor marker levels between the groups revealed no significant difference (Table 4).

Table 2. Comparison of tumor location and complication rates between groups

		A		B		p
		n	%	n	%	
Ascending colon	No	63	75.9	39	83.0	0.346
	Yes	20	24.1	8	17.0	
Descending colon	No	74	89.2	43	91.5	0.670
	Yes	9	10.8	4	8.5	
Transverse colon	No	77	92.8	43	91.5	0.792
	Yes	6	7.2	4	8.5	
Sigmoid colon	No	47	56.6	30	63.8	0.422
	Yes	36	43.4	17	36.2	
Rectum	No	69	83.1	33	70.2	0.085
	Yes	14	16.9	14	29.8	
Previous oncological treatment	No	68	83.95	35	74.5	0.192
	Yes	13	16.05	12	25.5	
Need for ICU	No	60	73.2	36	76.6	0.668
	Yes	22	26.8	11	23.4	
Colostomy	No	54	65.1	30	63.8	0.888
	Yes	29	34.9	17	36.2	
Complications*	No	78	93.9	36	76.6	**0.015**
	Yes	5	6.1	11	23.4	
Perioperative mortality	No	83	100	43	91.5	**0.043**
	Yes	0	0	4	8.5	

*Grade 2 and higher complications according to the Clavien-Dindo classification, ICU: Intensive care unit

Discussion

With the COVID-19 pandemic, healthcare systems around the whole world encountered unexpected pressures. After

Table 3. Comparison of histopathological and clinical tumor characteristics between groups

		A		B		p
		n	%	n	%	
TNM stage	Stage 1-2	40	49.4	18	38.3	0.225
	Stage 3-4	41	50.6	29	61.7	
Lymphatic invasion	No	22	27.2	1	2.1	**<0.001**
	Yes	59	72.8	46	97.9	
Vascular invasion	No	41	50.6	4	8.5	**<0.001**
	Yes	40	49.4	43	91.5	
Perineural invasion	No	24	29.6	4	8.5	**0.005**
	Yes	57	70.4	43	91.5	
Histological grade	Low grade	59	86.8	38	90.5	0.606
	High grade	9	13.2	4	9.5	
Surgical margin positivity	Negative	78	94.0	42	89.4	0.343
	Positive	5	6.0	5	10.6	
Number of positive lymph nodes		2.19±5.70		4.21±7.17		**0.012**
Distant metastasis	No	73	87.95	42	89.4	0.809
	Yes	10	12.05	5	10.6	
Need for chemotherapy	No	23	27.8	7	12.8	**0.045**
	Yes	60	72.2	41	87.2	

TNM: Tumor, lymph node, metastasis

Table 4. Comparison of age, duration of complaints, length of stay, and tumor markers between groups

	A		B		p
	Mean ± SD	Median	Mean ± SD	Median	
Age	65.31±11.47	66.00	63.28±11.83	63.00	0.297
Duration of complaints (months)	2.20±2.44	1.00	3.36±5.06	1.00	0.699
CEA	23.23±81.95	3.00	25.46±71.76	3.52	0.741
CA19-9	28.62±71.63	11.00	15.77±17.16	8.76	0.956
Length of hospital stay (days)	13.45±7.04	12.00	11.68±7.33	10.00	0.093

CEA: Carcinoembryonic antigen

the WHO declared a pandemic, COVID-19 was prioritized by healthcare services across the world. By April 2021, a total of 150 million cases and 3.2 million deaths due to COVID-19 were reported worldwide.[5]

The bed capacity, healthcare workers and intensive care units of hospitals were redirected to deal with the pandemic. Non-emergency treatment was not provided by some centers, or postponed in a planned manner. In addition, patients also delayed consulting healthcare professionals due to the fear of the pandemic and consequently presented to hospitals when the complaints were worse than would have been likely in pre-pandemic conditions. The Turkish Ministry of Health declared most of the hospitals in the country as referral hospitals for COVID-19 on March 11, 2020, which then resulted in postponement of elective surgery in many centers.[2,3]

The delay in providing routine services because of the health service pressure caused by COVID-19 also included the treatment of cancer patients. Cancer patients have to leave their homes to be checked and treated or they have to violate quarantine requirements by receiving treatment at home or in palliative care units. Cancer patients are at high risk for COVID-19 because they are often elderly and mostly immunosuppressed due to their treatment.[6] The studies from China reported significantly higher rates of coronavirus infection (39% vs 8%) and severe infection (75% and 43%) in cancer patients presenting to hospitals for surgical therapy or chemotherapy than in the non-cancer population.[7]

It has been reported that an increase in the incidence and stage of CRC may occur as a result of delayed diagnosis and treatment due to the pandemic, and the associated decrease in availability of cancer screening programs and endoscopic diagnostic tests. In Spain, Suárez et al.[8] compared the March-June period between 2019 and 2020, and reported restrictions in colorectal screening tests, a 48% decrease in numbers diagnosed with CRC, and a significant increase in the emergency diagnosis and treatment of CRC.[9]

Primary surgery should be performed within six weeks in early-stage CRC. Complications such as intestinal obstruction, bleeding, and perforation may occur when there is a potential delay in treatment or diagnosis. Such cases are a high priority for surgical intervention. Colorectal surgical procedures for reconstruction or syndrome, in turn, can be postponed in a planned manner. During the pandemic, patients were referred for neoadjuvant chemotherapy or short-term radiotherapy to reduce the risk of COVID-19 during CRC surgery. However, delayed surgical treatment may bring additional psychological problems, for which psychological support would be beneficial.[2] Our results showed a longer duration of complaints before seeking medical help and a higher rate of neoadjuvant chemotherapy during the COVID-19 pandemic.

An Italian study by De Vincentiis et al.[10] compared the quarantine periods in 2020 due to pandemic with 2019 and 2018. These authors reported that CRC (62%) was the third most common cancer, after prostate (75%) and breast (66%) among cancer diagnoses, but diagnostic/therapeutic delay would potentially have a greater effect on survival in CRC, considering the early diagnosis of prostate and bladder. To avoid delay, general provision of fecal occult blood tests, triage by family physicians, increased use of tumor marker or mutation analyses (KRAS, NRAS, BRAF), and use of diagnostic methods other than colonoscopy, such as CT colonography or double-contrast barium enema, were recommended.

It has been demonstrated with a moderate level of evidence that delayed surgical resection in CRC leads to poor outcomes. Delay in colon cancer surgery would result in delayed staging and chemotherapy administration in advance-stage patients. It was stated that neoadjuvant chemotherapy could be considered in all colon cancers in case of a delay for any reason. Maringe et al.[11] reported that the mortality rate due to CRC increased by 15.3-16.6% in UK due to delayed diagnosis as a result of the COVID-19 pandemic in.[8,12] Our results also indicate a significantly higher rate of peri-operative mortality during the pandemic increasing from 0% in group A to 8.5% in group B.

In CRC lymphovascular and perineural invasion are considered poor prognostic factors and also risk factors for aggressive biological behavior. Tumor behavior is adversely affected due to the delay in diagnosis and treatment of patients during the COVID-19 pandemic.[13,14] Unfortunately, the results of this study found significantly higher rates of lymphovascular and perineural invasion, higher numbers of involved lymph nodes, and a greater need for adjuvant chemotherapy in CRC patients operated during the COVID-19 pandemic. These findings are in line with earlier reports.

A paper published by the COVIDSurg Collaborative, with the participation of 190 countries, reported a 12-week delay in CRC surgery in 35.9% of responders.[15] The report stated that, based on this data, cancer surgery should be continued, despite the pandemic, to avoid delayed and increasing numbers of operations for CRC, an increase in emergency cases and, given the prevalence of CRC, an increased impact on public health.

Study Limitations

The limitations of our study were the single-center design and the absence of long-term follow-up and longer-term survival comparison between the patient groups.

Conclusion

Adjustments of health policies during the COVID-19 pandemic should consider not only the patients with COVID-19 patients, but also those with other urgent medical conditions. Patients without COVID-19 present with delayed diagnosis or more advanced cancer, leading to a significant increase in morbidity and mortality. Thus, healthcare systems should be planned in a way to ensure appropriate treatment for both infectious diseases and normal emergency or cancer patients during future crises affecting healthcare services.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (approval number: 12846, date: 21.01.2021).

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.E., E.T., Design: S.E., T.A., Ş.B., M.F.Ö., Supervision: S.E., N.K., S.S.U., Materials: S.E., E.T., T.A., Ş.B., Data Collection or Processing: E.T., T.A., Ş.B., S.S.U., Analysis or Interpretation: S.E., M.F.Ö., N.K., Literature Search: S.E., E.T., Writing: S.E., E.T., Ş.B., Critical Review: S.E., E.T., Ş.B., M.F.Ö.

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