### ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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# CHANGES IN THE DEMOGRAPHIC AND CLINICAL FEATURES OF COLORECTAL CARCINOMA CASES FOLLOWING THE COVID-19 PANDEMIC

COVID-19 PANDEMİSİNİ TAKİBEN KOLOREKTAL KARSİNOM VAKALARININ DEMOGRAFİK VE KLİNİK ÖZELLİKLERİNDE MEYDANA GELEN DEĞİŞİKLİKLER

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#### Amaç

Bu çalışma, Covid-19 pandemisinden önce ve sonra başvuran kolorektal karsinomlu hastaların demografik, klinik ve patolojik özelliklerini karşılaştırmayı amacladı.

#### Gereç ve Yöntem

Pandemiden 9 ay önce ve ilk 9 ay içinde başvuran olgular çalışmaya dahil edildi. Bu çalışmanın birincil sonuç ölçütü, iki dönem boyunca invaziv kolorektal karsinomlu hastaların klinik ve patolojik özelliklerindeki farklılıktı.

#### Bulgular

Pandemi öncesi ve pandemi sonrası hastalar yaş, cinsiyet, tümör yerleşimi, tümör boyutu, lenf nodu invazyonu, farklılaşma, senkron tümör varlığı, radyal ve distal cerrahi sınır pozitifliği, perinöral ve lenfovasküler invazyon, TNM evresi, karaciğer metastazı ve nüks bakımından benzerdi. Pandemi öncesi döneme göre fark istatistiksel olarak anlamlı olmasa da, pandemi sonrası hastalarda ileuslu 3 hasta (%4,7) ve tümör perforasyonu olan 2 hasta (%3,2) belirledik.

Sonuç: Bulgularımız, pandemi sonrası dönemde kolorektal karsinom nedeniyle ameliyat olan hasta sayısında, muhtemelen hastanelerdeki sağlık organizasyonundaki yapısal değişiklikler ve hastaların SARS-CoV-2 ile olası enfeksiyon nedeniyle sağlık hizmetine başvuruda tereddüt etmesi nedeniyle pandemi öncesi döneme göre hafif bir azalma olduğunu göstermektedir. Sağlık sistemlerinin, Covid-19 salgını sırasında maligniteler gibi ciddi klinik durumları yönetmenin yeni yollarını bulmaya çalışması gerektiği açıktır.

**Anahtar Kelimeler:** Covid-19, Erteleme, Kolorektal karsinomlar, Sağlık hizmeti,

#### **Abstract**

#### Objective

This study aimed to compare the demographic, clinical and pathological features of patients with colorectal carcinomas presenting before and after the Covid-19 pandemic.

#### **Material and Method**

Subjects presenting from 9 months prior to and those

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presenting within the first 9 months of the pandemic were included in the study. The primary outcome measure of this study was the difference in the clinical and pathological features of the patients with invasive colorectal carcinomas during the two periods.

#### Results

Pre-pandemic and post-pandemic patients were similar with respect to age, gender, tumor location, tumor size, lymph node invasion, differentiation, presence of synchronous tumor, radial and distal surgical margin positivity, perineural and lymphovascular invasion, TNM stage, and liver metastasis and recurrence. Although the difference was not statistically significant when compared to the pre-pandemic period, we identified 3 patients (4.7%) with ileus and 2 patients with tumor perforation (3.2%)

among post-pandemic patients.

#### Conclusion

Our findings show a slight decrease in the number of patients undergoing surgery for colorectal carcinomas in the post-pandemic period compared to the prepandemic period, probably due to the structural changes in health-care organization in hospitals and patients' hesitation to apply for healthcare due to possible infection with SARS-CoV-2. It is evident that healthcare systems should strive to find new ways to manage serious clinical conditions such as malignancies during the Covid-19 pandemic.

**Keywords:** Covid-19, Colorectal carcinomas, Delay, Healthcare

#### Introduction

The first patients with coronavirus disease-2019 (Covid-19) in Wuhan, Hubei, China presented with various viral infection-related symptoms including fewer, shortness of breath, sore throat, and cough (1). A novel coronavirus was identified from the throat swab samples of these subjects, and the disease was found to cause severe pneumonia. It was later defined as Covid-19 and was deemed to be a pandemic by the World Health Organization (WHO) (2).

By January 2022, about 320 million people have been reported to be infected by SARS-CoV-2 and there are 5.5 million deaths globally caused by Covid-19. The disease primarily affects the lungs but accumulating evidence demonstrated that multiple organs and systems were involved by the disease. The initial phase of Covid-19 led to a significant workload on healthcare systems due to excessive burden on emergency departments and intensive care units (3, 4). A state of alarm against the increasing number of Covid-19 cases was declared by almost all countries globally to slow the increase in Covid-19 cases. Among the measures, many healthcare centers delayed elective interventions in order to concentrate on the management of Covid-19 cases. Retrospective data investigating patient behaviors concerning the first phase of the pandemic indicate that there was a significant decline in the number of individuals presenting to the emergency department -even for life-threatening diseases including acute coronary syndromes (5, 6). This was particularly explained by patients' and healthcare workers' fear of being infected by SARS-CoV-2 (7, 8). Although there is extensive data concerning the

impact of the pandemic itself and related restrictions on cardiovascular diseases, there is still limited information regarding other fields of medicine. For instance, data concerning the influence on patients with colorectal carcinoma, which is one of the leading causes of death globally, are very limited.

This study aimed to compare the demographic, clinical and pathological features of patients with colorectal carcinomas presenting before and after the Covid-19 pandemic.

#### **Material and Method**

This retrospective study included data concerning patients with invasive colorectal carcinomas who underwent surgery in Osmangazi University, Department of General Surgery, Eskisehir, Turkey. Subjects presenting from 9 months prior to the Covid-19 pandemic and those presenting within the first 9 months of the Covid-19 pandemic were included in the study as the comparative groups. All patients scheduled for surgery at our department underwent PCR testing for Covid-19 and those with positive PCR test results were excluded. All patients underwent thorax and abdominal computed tomography for definition of tumor stage. Additionally, pelvic Magnetic Resonance Imaging (MRI) was utilized for those with rectal carcinomas. Written informed consent was obtained from all subjects for inclusion into the study. The protocol of the present study was reviewed by the Non-Interventional Clinical Research Ethics Committee of Osmangazi University and was conducted in accordance with the Helsinki declaration. Data concerning tumor stage, histopathological results, demographics, clini-

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cal features, surgical methodology, surgical findings, and hospital stay of the subjects included in the study were retrieved from the institutional digital database. The primary outcome measure of this study was the difference in clinical and pathological features of patients with invasive colorectal carcinomas presenting in the pre- and post-Covid-19 era.

#### **Statistical Analysis**

The SPSS version 21 software (SPSS Inc., Chicago, IL, USA) was used for data collection and statistical analyses-which were subject to a p value of 0.05 for the determination of significance. Continuous variables were assessed with the Kolmogorov-Smirnov test to ascertain the presence/absence of normal distribution, and, with respect the results, descriptive values were given as mean ± standard deviation or median (1st quartile - 3rd quartile). The independent samples t-test or the Mann-Whitney U test, again with respect to normality results, were employed for the comparative analysis of continuous variables. Categorical data were recorded as absolute frequency (n) and depicted with both absolute and relative frequency (percentage). Categorical variables were analyzed with the chi-square tests or Fisher's exact tests. For the comparison of the number of cases before and after the pandemic, we employed the one-sample chi-square test under the equal probabilities null hypothesis (H0: p1=p2=0.5).

#### Results

A total of 86 cases (mean age  $65.12 \pm 11.64$  years, 63.9% male) of invasive colorectal carcinoma were enrolled in the pre-pandemic period and 63 cases (mean age  $65.49 \pm 11.45$  years, 65.1% male) were enrolled in the post-pandemic period. Pre-pandemic and post-pandemic patients were similar with respect to age, gender, tumor location, tumor size, lymph node invasion, differentiation, presence of synchronous tumor, radial and distal surgical margin positivity, perineural and lymphovascular invasion, TNM stage, liver metastasis and recurrence (Table 1 and 2). We observed a slight decrease in the number of patients admitted and treated for colorectal cancer during the post-pandemic period; however, statistical analyses did not reveal a significant difference (p = 0.060).

Although statistical analyses did not reveal significant differences from the pre-Covid-19 period, there were 3 patients (4.7%) with ileus and 2 patients with tumor perforation (3.2%) among post-pandemic patients with invasive colorectal carcinoma. The mode of surgical intervention and length of hospital stay was similar between pre-and post-pandemic patients. The

number of open surgeries was significantly higher in post-pandemic patients compared to pre-pandemic patients (93.6% vs. 80.2%, p=0.037). Non-mucinous adenocarcinomas were more frequent among post-pandemic patients compared to pre-pandemic patients (85.7% vs. 60.4%, p=0.001).

#### **Discussion**

This study aimed to investigate the change in demographic, clinical and pathological features of patients with colorectal carcinomas prior to and following the Covid-19 pandemic. Our findings show that the preand post-pandemic colorectal carcinoma patients were similar with respect to demographic and clinical features. Tumor size and stage were also similar between pre- and post-pandemic patients. Interestingly, we found that post-pandemic patients more frequently underwent open surgery rather than laparoscopic surgery compared to pre-pandemic patients. Of note, a few of the post-pandemic patients had ileus, tumor perforation, and peritonitis carcinomatosa at presentation—none of which were identified among pre-pandemic patients.

Colorectal carcinoma is the fourth most frequently encountered cancer in the world and constitutes the third leading cause of cancer-related death globally, with an increasing prevalence particularly in developing countries (9). Dietary factors, particularly consumption of red and processed meat, abdominal obesity and physical inactivity, age, male sex, hereditary mutations, underlying inflammatory bowel disease, abdominal radiation exposure, cystic fibrosis, cholecystectomy, and androgen deprivation therapy are reported to be among the factors that contribute to the etiology of colorectal carcinomas (10). Although dietary changes, limitations in physical activity, and the resultant lifestyle changes due to pandemic-related restrictions must be considered in the future, there is unlikely to be any remarkable changes concerning these problems when considering the comparison of the patient groups included in this study.

Since colorectal carcinomas are potentially lethal unless diagnosed and managed early, the impact of the Covid-19 pandemic and related social isolation measures on the clinical findings of patients who had been treated for colorectal carcinoma within this period may be critical. Previous data including subjects with acute coronary syndromes, which is also potentially lethal, have shown dramatical decline in number of patients admitted to coronary care unit and scheduled for emergent coronary intervention following the Covid-19 pandemic (11, 12). Similarly, although mar-

Table 1

## Summary of patients' and some tumor characteristics with regard to before and after pandemic

	Period		
	Before pandemic	After pandemic	р
Number of cases	86	63	0.060
Age	65.12 ± 11.64	65.49 ± 11.45	0.845
Sex			
Female	31 (36.05%)	22 (34.92%)	1.000
Male	55 (63.95%)	41 (65.08%)	
Tumor localization			
Right colon	27 (31.40%)	17 (26.98%)	0.952
Transverse colon	8 (9.30%)	8 (12.70%)	
Descending colon	5 (5.81%)	4 (6.35%)	
Sigmoid colon	9 (10.47%)	6 (9.52%)	
Rectum	37 (43.02%)	28 (44.44%)	
Pathological diagnosis			
Non-mucinous adenocarcinoma	52 (60.47%)	54 (85.71%)	0.001
Mucinous adenocarcinoma	34 (39.53%)	9 (14.29%)	
Tumor size, mm	44 (25 - 60)	45 (30 - 60)	0.429
Number of lymph nodes	23 (18 - 32)	27 (15 - 38)	0.663
Number of pathological lymph nodes	0 (0 - 2)	0 (0 - 2)	0.727
Differentiation	'		
Poor	8 (9.30%)	4 (6.35%)	0.658
Moderate	69 (80.23%)	50 (79.37%)	
Well	9 (10.47%)	9 (14.29%)	
Synchronous tumor	1 (1.16%)	5 (7.94%)	0.083
Radial surgical margin positivity	4 (4.65%)	0 (0.00%)	0.138
Distal surgical margin positivity	0 (0.00%)	0 (0.00%)	N/A
Perineural invasion	24 (28.24%)	21 (33.33%)	0.627
Lymphovascular invasion	41 (47.67%)	34 (53.97%)	0.553
T stage			
T1	3 (3.49%)	3 (4.76%)	0.854
T2	12 (13.95%)	6 (9.52%)	
Т3	51 (59.30%)	39 (61.90%)	
T4	20 (23.26%)	15 (23.81%)	
N stage			
N0	49 (56.98%)	35 (55.56%)	0.964
N1	26 (30.23%)	19 (30.16%)	
N2	11 (12.79%)	9 (14.29%)	
Stage			
Stage 1	8 (9.30%)	9 (14.29%)	0.564
Stage 2	30 (34.88%)	18 (28.57%)	
Stage 3	35 (40.70%)	23 (36.51%)	
Stage 4	13 (15.12%)	13 (20.63%)	

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables

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Table 2

#### Summary of tumor characteristics with regard to before and after pandemic

Neoadjuvant radiotherapy	22 (25.58%)	9 (14.29%)	0.141
Chemotherapy	10 (11.63%)	12 (19.05%)	0.304
Liver metastasis	15 (17.44%)	13 (20.63%)	0.779
Recurrence	1 (1.16%)	1 (1.59%)	1.000
Peritonitis carcinomatosa	0 (0.00%)	2 (3.17%)	0.177
lleus	0 (0.00%)	3 (4.76%)	0.074
Tumor perforation	0 (0.00%)	2 (3.17%)	0.177
Type of surgery			
Laparoscopy	17 (19.77%)	4 (6.35%)	0.037
Open surgery	69 (80.23%)	59 (93.65%)	
Operation			
Right hemicolectomy	22 (25.58%)	11 (17.46%)	0.269
Transverse hemicolectomy	6 (6.98%)	3 (4.76%)	
Left hemicolectomy	5 (5.81%)	5 (7.94%)	
Anterior resection	10 (11.63%)	12 (19.05%)	
Low anterior resection	29 (33.72%)	20 (31.75%)	
Abdominoperineal resection	13 (15.12%)	7 (11.11%)	
Other	1 (1.16%)	5 (7.94%)	
Length of stay in hospital, days	6 (5 - 8)	7 (5 - 9)	0.210
Leakage	5 (5.81%)	2 (3.17%)	0.699
Infection	14 (16.28%)	18 (28.57%)	0.109
Other complications	1 (1.16%)	1 (1.59%)	1.000
Mortality	1 (1.16%)	1 (1.59%)	1.000

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables

ginally non-significant, our findings suggest a decline in the number of patients with invasive colorectal carcinomas who were scheduled for surgery in the post-pandemic period compared to the pre-pandemic period. The decline in number of patients presenting with colorectal carcinomas is probably a consequence of the strict containment measures and the 'state of alarm' declared by almost all governments along with the public-health messages encouraging individual isolation against the spread of Covid-19. These may have resulted in a population-wide reluctance to seek medical care for relatively-mild symptoms or conditions. Despite the enormous impact of self-isolation measures on patient behavior, our results did not show a significant change. This may be easily

explained by statistical limitations, but our center is a tertiary healthcare provider which would have increased the likelihood of referrals from other centers that could not schedule such surgeries regardless of their urgency. We did not analyze data regarding the referral status of patients that underwent surgery during the post-pandemic period which is an evident limitation of the study; however, it is evident that university hospitals such as ours would experience a relatively lower level of decrease regarding such surgeries.

The acute burden of Covid-19 on the healthcare system led to some infrastructural changes in organization of medical staff in hospitals (13-15). Pulmonary disease specialists and ICU physicians were first as-

signed to the management of patients with Covid-19; however, with increasing number of patients with Covid-19, physicians from other field were requested to take a role in the management and care of patients with Covid-19. During the initial phase of disease spread the majority of the outpatient clinics admitted less patients with less staff and the physicians and surgeons of these clinics were assigned to work in the care of Covid-19 patients. These structural changes concerning healthcare organization in hospitals may have a role in diagnostic and treatment delays of patients with other critical disorders such as cardiovascular disorders and malignancies (16, 17).

In this study, the acute complications of colorectal carcinomas including ileus and tumor perforation were non-existent in the pre-pandemic period. A total of 5 cases suffering from the aforementioned complications were identified in the post-pandemic patient group, indicating delays in hospital application, referral or diagnosis, ultimately resulting in delayed treatment and complications. This finding also supports our consideration that the structural change in healthcare organization complicated patients' optimal managements and delayed their diagnosis and treatment. The current study shows a particular reduction in the frequency of mucinous adenocarcinoma. This subtype is relatively rare (up to 20% of colorectal cancers) and is usually accepted to demonstrate considerably worse prognosis (18). A very recent study from Turkey showed that mucinous adenocarcinomas comprised 10.5% of all cases during an 8-year period in a relatively small center (19). Due to the tertiary status of our center and the fact that our hospital serves a greater population in central Anatolia, a relatively higher frequency for surgeries involving patients with relatively severe disease may be expected due to referrals, as demonstrated by the pre-pandemic data. However, the significant reduction of such patients could indicate missed diagnoses, referral chain problems, and possibly, transfers to larger institutions (which may have been relatively less effected by staff/physician limitations) during the pandemic. The fact that we cannot obtain data that could elucidate the causes of this change is an unavoidable limitation, and indicates the need for nationwide studies aimed at determining alterations in healthcare delivery and disease burden.

Apart from the previously-mentioned limitations, this study has several other limitations to be noted. The cross-sectional design of the study, relatively small sample size, and short study period complicate the interpretation of data. The lack of definitive information regarding patients' interpretation of isolation measures/restrictions must also be considered when evalu-

ating the impact of pandemic-related restrictions on patients' behavior regarding application to healthcare institutions. However, the findings of this study provide a baseline for larger studies and may attract the attention of healthcare professionals and policy makers on regarding decisions about the management of patients with malignancies, particularly those with colorectal carcinomas.

#### Conclusion

Our findings show a slight decrease (albeit, non-significant) in the number of patients undergoing surgery for colorectal carcinomas in the post-pandemic period compared to pre-pandemic period, probably due to the structural changes in health-care organization and patients' reluctance to seek healthcare for the fear of contracting SARS-CoV-2. The healthcare system should not only focus on Covid-19; policy makers must find ways to enable sufficient management of other serious clinical conditions including malignancies. Any delay in diagnosis and management of patients with colorectal carcinomas not only will increase mortality and morbidity but also will increase the effort and costs required to manage advanced stage cancer.

#### **Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

#### **Ethical Approval**

The protocol of the present study was reviewed and approved by the Non-Interventional Clinical Research Ethics Committee of Osmangazi University (Date: 01.06.2021, No: 04). The study was conducted in accordance with the Helsinki declaration.

#### **Consent to Participate and Publish**

Written informed consent to participate and publish was obtained from all individual participants included in the study.

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#### **Availability of Data and Materials**

Data subject to third party restrictions

#### **Authors Contributions**

DBÖ: Conceptualization; Data curation; Formal analysis; Investigation; Methodology;

Validation; Writing-original draft

AK: Conceptualization; Formal analysis; Writing-review & editing

HD: Investigation; Validation; Writing-original draft

BÜ: Methodology; Supervision; Writing-review & editing

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