

The Impact of the COVID-19 Pandemic on Colorectal Cancer Patients in a Tertiary Center in Romania. Single Center Retrospective Study

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Rezumat

Impactul pandemiei COVID-19 asupra pacienților cu cancer colorectal într-un centru terțiar din Romania. Studiu retrospectiv, experiența unui singur centru

Introducere: Noul coronavirus, SARS-COV-2, a fost raportat pentru prima dată în Wuhan, China, la sfârșitul anului 2019. Pentru a reduce răspândirea virusului, au fost implementate măsuri de siguranță, care, din multiple motive, au condus la întârzieri în tratamentul cancerului colorectal. În prezent nu se știe încă, cum a influențat pandemia eficacitatea și rezultatele tratamentului cancerului colorectal în România.

Material și metodă: Am evaluat datele demografice, clinice, statusurile intraoperatorii și datele morfopatologice ale pacienților diagnosticați cu cancer colorectal în clinica noastră, 302 în total, în perioada 15.03.2019 - 14.03.2021. Pacienții din 2019 au fost încadrați în grupul de control, iar cei tratați în pandemie, în grupul de studiu.

Rezultate: Am observat o scădere cu 12% a spitalizărilor pentru tratamentul cancerului colorectal în perioada pandemiei, în primele șase luni această scădere a fost de peste 38%. Rata internărilor de urgență, procedurilor chirurgicale cu colo/ileostomie, rezecțiilor paliative și a metastazelor clinice a fost mai mare în grupul pandemic. S-a constatat invazie loco-regională mai

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avansată, a crescut numărul de pacienți, cu stadiu tumoral mai avansat, am constatat o rată mai mare de invazie vasculară și perineurală, am avut o rată mai mare de cazuri unde marginile de rezecție au fost pozitive, iar numărul de ganglioni limfatici excizați a fost considerabil mai mare la cazurile operate după implementarea restricțiilor.

Concluzie: Pandemia COVID-19, cu restricțiile în tratamentele chirurgicale, au avut un efect negativ major asupra eficacității tratamentului cancerului colorectal din țara noastră. Efectele pe termen lung sunt încă necunoscute, cercetări suplimentare în acest domeniu sunt necesare. Credem că tratamentul pacienților cu cancer colorectal, ar trebui să aibă o prioritate absolută.

Cuvinte cheie: cancer colorectal, pandemia COVID-19, impact, chirurgie, întârziere, stadializare patologică

Abstract

Background: The novel coronavirus, SARS-COV-2, was first reported in Wuhan, China in the end of 2019. To curb its spread, social distancing measures and new safety regulations were implemented which led to major disruptions in colorectal cancer care. It is however unknown how it influenced the Romanian colorectal cancer care.

Methods and material: We assessed the demographical, clinical, intraoperative and pathological data of our colorectal cancer patients, 302 in total, between 15.03.2019-14.03.2021. The first year's data was considered as the control group and the second one, the study (pandemic) group.

Results: We observed a 12% decrease in colorectal cancer hospitalizations in the first year, 38,6% in the first six months. The rate of emergency admissions, colo/ileostomy formatting procedures, palliative resections, clinical metastasis was higher in the pandemic group. More advanced loco-regional invasion, a higher tumor stage, higher rate of vascular, perineural invasion, positive resection margin, and a higher lymph node yield was seen after the restrictions were implemented.

Conclusion: The COVID-19 pandemic and the response against it had a major effect on the colorectal cancer care in our country. The outcomes of these worse clinical and pathological findings are unknown, but it is important to do further research in this field. We think colorectal cancer care should have an absolute priority in future pandemics.

Key words: colorectal cancer, COVID-19 pandemic, surgery, pathological staging, delay, impact

Introduction

The first cases of COVID-19 infectious disease, caused by the novel coronavirus SARS-COV-2, was reported in Wuhan, Hubei Province, China in the end of the year 2019 (1). Due to the high contagiousness and rapid spread of the disease around the globe, the WHO declared the COVID-19 outbreak a pandemic in 11th March of 2020 (2). Due to the fact that many key questions regarding this novel strain of the coronavirus family were unanswered, vaccines were unavailable and the

pressure on the ICU wards were mounting, guidelines were issued to help prevent the spread of the disease (3). In many countries severe restrictions were implemented, the non-emergency admissions in hospitals suddenly declined (4,5,6). The screening rate of the population plummeted resulting in huge delays in diagnosis and surgery resulting in fewer cancer operations in this period (5,7,8). In the UK, it is estimated that colon cancers deaths will have one of the biggest rise, between 15.3-16.6%, after 5 years from the diagnosis (8). On the 16th of March, the

Romanian government introduced harsh restrictions (social distancing, curfew, mandatory face covering) in order to curb rising infection rate and to help lower the mounting pressure on hospitals. Hospital bed capacity was limited, in many cases elective operations were halted completely, only emergency admissions were allowed (9,10).

Our objective was to study and quantify the effects of the COVID-19 restrictions in Romania, by analyzing the admission rate of colorectal patients in our facility. Our goal was to assess the clinical and pathological characteristics of our patients, whose treatment suffered major disruptions and delays because of the pandemic.

Material and Methods

In our single center retrospective cohort study, we included data of 302 patients admitted in our Clinic for colorectal carcinoma in a period of two years between 15.03.2019 and 14.03.2021. To compare surgical care during pandemic times with pre-pandemic times; we formed a study group, patients admitted while the COVID-19 restrictions were in effect, between 15.03.2020 and 14.03.2021; and a control group, patients hospitalized between 15.03.2019 and 14.03.2020.

We collected our data from H3 Healthcare Concept System, which is the medical database of our clinic, and from histopathological reports. For this study we created a database using the Microsoft Excel spreadsheet program and analyzed our data with IBM SPSS Statistics program.

Our criteria of exclusion were: patient younger than 18 years old, benign tumor diagnosis after histopathologic examination, positive COVID-19 RT-PCR test for elective patients (they were discharged for home quarantine immediately). In our inclusion criteria we used the ICD-10 (10th Edition of International Classification of Diseases) diagnosis system and selected our patients after the following diagnosis codes: C18, C19, C20. In case of D37.4, D37.5, D37.9 diagnoses we selected the case if the histopathological

examinations described a malignant tumor.

We assessed demographic, clinical, operative, postoperative and histopathological data to create our database. We additionally calculated the cancer stage of each case according to the AJCC 8th edition and DUKES classification.

Statistical Analysis

Quantitative variables were determined in mean $\pm$ standard deviation, whereas qualitative variables were expressed in integers and percentages. For identifying outliers we used the Grubbs test. Every variable was subjected to a normality test. Our variables were unpaired ones. For variables with Gaussian distribution we used student T test and for nonparametric ones we applied Mann-Whitney tests. For categorical variables Fisher's exact test and Chi squared test were applied. The level of significance was determined at $p=0.05$. Confidence interval of 95% was used.

Results

We found no significant differences between the study group (pandemic era) and the control group (prepandemic era) in demographic data (*Table 1*). The two studied population had similar average age ($p=0.670$), similar gender ratio ($p=0.139$). We assessed our patients addresses and found no significant differences between the rural and urban patients. The proportion of rural patients did not drop since the start of the pandemic, not even in emergency cases. Patients during and before the pandemic had similar tumor localization ($p=0.678$, *Fig. 1*) and had similar procedure types ($p=0.787$, *Fig. 2*) for these tumors. We had two similar, comparable colorectal cancer groups.

Our data showed a 12% decrease in hospital admissions for colorectal cancer diagnosis in the first year of COVID-19 restrictions in comparison with the year before that. In the first six months the patient influx decrease was more substantial (-38.4%) (*Fig. 3*). A change in

Table 1. Demographical and clinical characteristics of colorectal patients

	Study Group n = 142 (%)	Control Group n = 160 (%)	p value
Age	67.08	67.66	0.670
Standard Deviation	10.90	12.25	
Sex			0.139
Female	55 (38.7)	49 (30.6)	
Male	87 (61.3)	111 (69.4)	
Adress			0.839
Urban	70 (49.3)	83 (51.9)	
Rural	72 (50.7)	77 (48.1)	
Adress – emergency presentation	n=58 (%)	n=44 (%)	0.424
Urban	31 (53.4)	20 (45.5)	
Rural	27 (46.6)	24 (54.5)	
Presentation			
Emergency	58 (40.8)	44 (27.5)	0.014
Chronic	84 (59.2)	116 (72.5)	0.014
Age distribution of patients			
<25	0 (0)	1 (0.6)	1.000
25-50	12 (8.5)	18 (11.3)	0.417
51-75	96 (67.6)	91 (56.9)	0.055
>75	34 (23.9)	50 (31.3)	0.157
Intervention type			
Palliative	74 (52.9)	58 (37.7)	0.009
Curative	66 (47.1)	96 (62.3)	0.009
Metastases			
Yes	38 (26.8)	20 (12.5)	0.002
No	104 (73.2)	140 (87.5)	0.002
Stoma			
Colo/ileostomy	62 (43.7)	51 (31.9)	0.035
Without	80 (56.3)	109 (68.1)	0.035
Approach			
Clasic	133 (93.7)	146 (91.3)	0.430
Laparoscopic	9 (6.3)	14 (8.8)	0.430
Hospital mortality			
Yes	16 (11.3)	12 (7.5)	0.259
No	125 (88.7)	147 (92.5)	0.259
Anastomosis			
Yes	67 (47.2)	80 (50)	0.625
No	75 (52.8)	80 (50)	0.625
Stappled	34 (50.7)	42 (52.5)	0.832
Hand sewn	33 (49.3)	38 (47.5)	0.823
Neoadjuvant therapy			
Yes	25 (17.6)	23 (14.8)	0.518
No	117 (82.4)	132 (85.2)	0.518
Length of hospital stay			
Mean	11.00	10.30	0.526
Standard deviation	7.659	5.066	
Length of ICU stay			
Mean	3.792	2.962	0.141
Standard deviation	3.922	2.676	

ICU – intensive care unit

some clinical variables was reported during the pandemic (*Table 1*). Between the two groups, there were no significant differences in number of patients, who received neoadjuvant therapy prior to the surgical intervention ($p=0.518$). Similar results were acquired if only the rectum

and rectosigmoid carcinomas were taken into account ($p=0.270$). The average hospitalization time in the pandemic group was similar to the year before the national lockdown ($p=0.526$). There were no changes reported in ICU stay between the two main groups ($p=0.141$). The in-

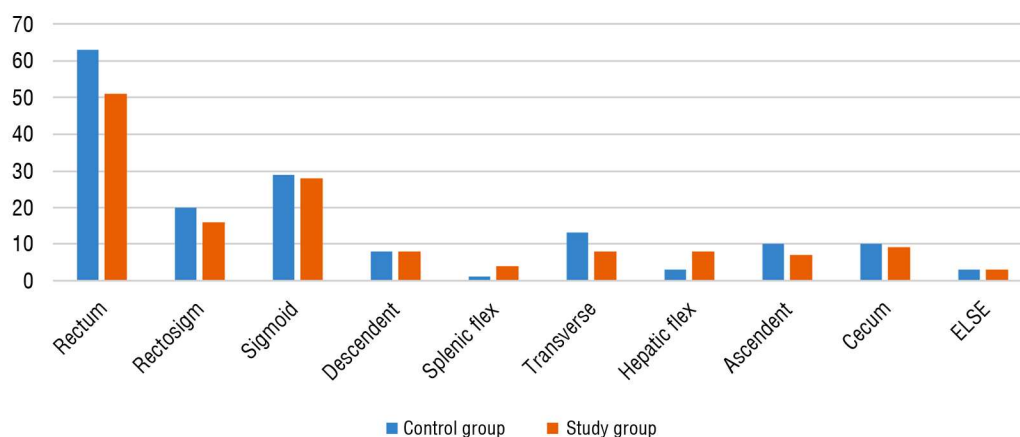


Figure 1. Tumor localization

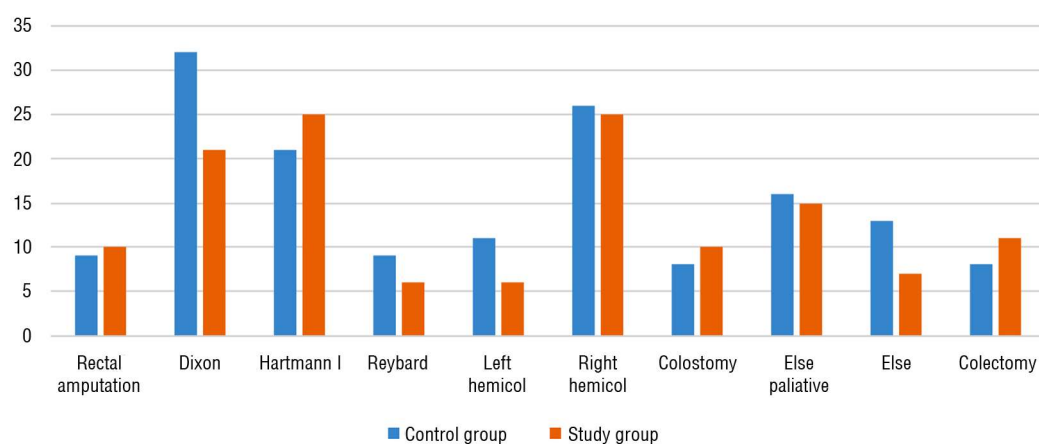


Figure 2. Type of procedures preformed for colorectal patients

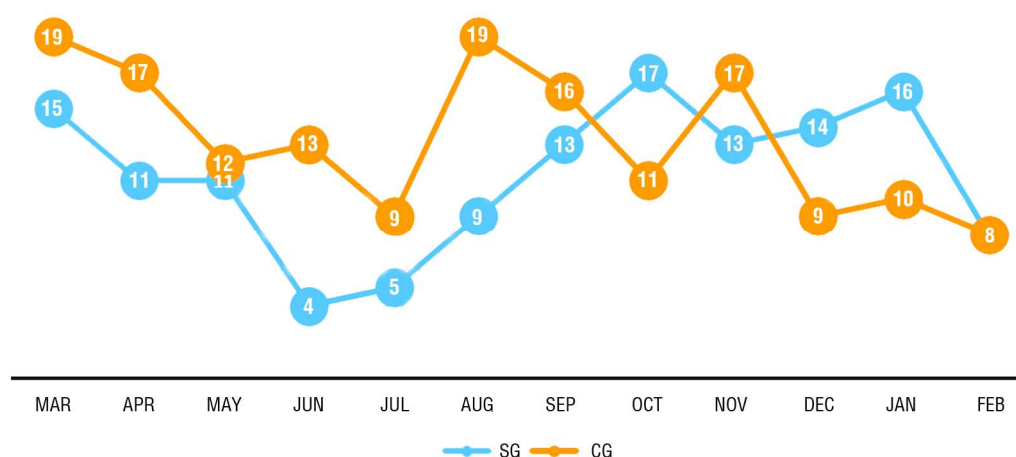


Figure 3. Monthly admission rate of colorectal cancer patients
SG – study (pandemic) group, CG – control group

hospital mortality was alike between the two groups ($p=0.259$). Emergency presentations were significantly more common in the study group ($p=0.014$). Cases were considered acute and operated in emergency setting if the patient presented massive hemorrhage, bowel obstruction due to stenotizing tumor, acute abdomen caused by perforated bowel with localized or generalized peritonitis. In the pandemic group more patients had procedures that ended with permanent or temporary stoma formation ($p=0.035$). Hartmann's procedures, colostomies without resection, abdominoperineal rectum resections were the interventions which resulted in colo/ileostomy. After the implementation of COVID-19 restrictions the proportion of palliative surgical care has increased according to our first year results ($p=0.009$). We had a lower rate of curative resections in the study group in comparison with the control group ($p=0.009$). We observed more clinical metastasis during the procedures, in cases operated after March of 2020 ($p=0.002$), mainly hepatic metastases. We did not find a statistically significant difference between the two groups regarding postoperative complications that needed reintervention of inpatients. Similar ratio of surgical approach was seen, same laparoscopy/laparotomy ratio. ($p=0.430$). We did not detect any differences in use of mechanical stapler for bowel anastomosis, same hand sewn/stappled anastomosis ratio ($p=0.823$). Same results when the analysis was narrowed to elective ($p=0.765$) and emergency operations ($p=0.264$).

Histopathological results shed light on some major differences between the study and the control group (*Table 2*). Patients from the study group had a more advanced loco-regional tumor spread ($p=0.026$). We saw the same tendency in case of the vascular and perineural invasion. From the total of 200 cases where perineural invasion was measurable, in the study (pandemic) group 40 (43%) and in the control group (prepandemic) 30 (28%) had positive perineural invasion in their histopathological report ($p=0.027$). Similarly, the patients from the study group had more chance of developing a vascular invasion.

Whilst in the control group only 30.2% of the patients had vascular invasion, this was more frequent in the study group with 47.5% of the cases ($p=0.011$). We did not observe important differences though, in lymphatic invasion between the groups ($p=0.411$). In cases where the tumoral resection was possible the resection margins of the specimens were examined. To achieve an R0 resection it is key that the edges of the resected specimens are completely clear of cancerous cells (negative resection margin). In our study, amongst the patients who were treated while the pandemic restrictions were in place the share of the positive resection margin on histopathological reports were significantly higher ($p=0.032$). We measured the differences in tumor progression of cases by grouping them into stages. For colorectal cancer staging we used, the AJCC's 8th Edition, and the now less frequently utilized Dukes classification. According to these classifications, more advanced tumor advancement was observed in the pandemic group (AJCC $p=0.003$, DUKES $p<0.001$). According to the AJCC classification, we found in the study group 34.6% of the cases with stage IV tumor (only 17.1% in the control group). The number of resected lymph nodes were higher in the pandemic ($p<0.001$). Though, the average lymph node resection number is highly influenced by the type of procedure. Although we did not observe any statistical differences between the two groups in metastatic lymph node count ($p=0.257$) and lymph node ratio (LNR) ($p=0.525$), it is important to state that in the pandemic group we had on average more metastatic lymph nodes and the also the LNR was higher.

Discussion

The global pandemic brought a lot of uncertainties into the colorectal cancer care. In the beginning of the pandemic severe restrictions were implemented in cancer care which led to a major disruption in the colorectal cancer care (11). A general fear of the rapidly spreading virus discouraged the

Table 2. Pathological data of the colorectal patients

	Study group n (%)	Control Group n (%)	p value
Local invasion (T)			0.026
Mean	3.75	3.41	
SD	0.87	0.90	
T1=1	2 (1.9)	2 (1.8)	
T2=2	4 (3.8)	12 (10.6)	
T3=3	32 (30.2)	50 (44.2)	
T4a=4	48 (45.3)	35 (31)	
T4b=5	20 (18.9)	14 (12.4)	
Lymphatic invasion (L)			
Yes	64 (64.6)	62 (59.0)	0.411
No	35 (35.4)	43 (41.0)	0.411
Vascular invasion (V)			0.011
No	52 (52.5)	74 (69.8)	
Yes	47 (47.5)	32 (30.2)	
Perineural invasion (Pn)			
Yes	40 (43.0)	30 (28.0)	0.027
No	53 (57.0)	77 (72.0)	0.027
Rezection margins			
Positive	20 (19.8)	10 (9.3)	0.032
Negative	81 (80.2)	97 (90.7)	0.032
AJCC Stadiation			0.003
Mean	5.64	4.53	
SD	2.385	2.381	
I =1	4 (3.8)	9 (8.1)	
Ila=2	12 (11.5)	24 (21.6)	
Ilb=3	16 (15.4)	17 (15.3)	
Ilc=4	2 (1.9)	5 (4.5)	
IIla=5	0 (0.0)	2 (1.8)	
IIlb=6	23 (22.1)	32 (28.8)	
IIlc=7	11 (10.6)	3 (2.7)	
IV=8	36 (34.6)	19 (17.1)	
DUKES stadiation			<0.0001
Mean	4.37	3.59	
SD	1.54	1.43	
A = 1	2 (1.9)	2 (1.8)	
B1=2	14 (13.6)	31 (27.9)	
B2=3	19 (18.4)	22 (19.8)	
C1=4	13 (12.6)	31 (27.9)	
C2=5	19 (18.4)	6 (5.4)	
D=6	36 (35.0)	19 (17.1)	
Lymph node yield			
Mean	23.26	14.93	<0.0001
Standard deviation	13.984	8.231	
Metastatic lymph node (+L)			
Mean	2.20	1.61	0.257
Standard deviation	3.722	3.751	
LNR			
Mean	0.116	0.998	0.525
Standard deviation	0.195	0.181	

LNR – lymph node ratio, SD – standard deviation

patients of contacting their general practitioner while experiencing symptoms (12). Delays of surgical treatment leads to a sharp increase in mortality and morbidity (6). Worldwide surgical wards saw a serious decrease in colorectal

cancer operations (13,14). Colorectal cancer screening programs suffered major setbacks, thus early cancer diagnosis declines (15). According to M. Abdellatif et al, 57.4% of their patients had a delay in the treatment plan

because of the pandemic (16). Giulio A Santoro et al reports that almost half of cases (48.9%) had a change in the original treatment plan and 26.3% of elective patients had emergency operation while waiting for appointment (5).

As in our case, many hospitals reported a more severe decrease in operations in the first half of the pandemic year. As the total number of admissions plummeted, the proportion of emergency operations for complicated colorectal cancer was on the rise (11). Some authors recommended stoma-forming procedures over anastomosis to reduce the duration of hospital stay and the incidence of anastomotic leakage. The combination of anastomotic leakage and SARS-COV-2 infection results in soaring mortality rates (17). Our data shows also a growth in stoma operations, but probably the reason is that, more tumors were not resectable, and more patients were operated under emergency conditions, when preoperative preparation of the bowel is not possible for primary anastomosis.

Minimal invasive procedures suffered a decline in the pandemic times. In our clinic the laparoscopic approach is not widespread yet, and only a few very selected cases are operated this way. If it had not been for the low number of laparoscopic colorectal resections, most likely the decrease in our facility would be significant. Stapled anastomosis rates has seen a growth in pandemic times which reflects the efforts of minimizing the length of hospitalization (17). Our trends of using stapled anastomosis is seriously restricted by the lack of resources our institution has. International studies matches our data: more palliative procedures were performed in the COVID-19 pandemic than before, with parallel decrease of curative resections. Some authors also concluded that the resection of adjacent organs was more common in that period (13). We categorized as palliative operations the following: colostomy or ileostomy without resection, laparotomy plus biopsy, palliative resection, cytoreductive surgery. The demographic and clinical characteristics of the patients, included in our study, were typical of those observed in colorectal cancer

patients treated at our institution.

The present study was designed to evaluate how COVID-19 restrictions affected colorectal cancer patient care. We would like to mention that in our region, of the three major clinics which treat colorectal cancer, one was completely repurposed for fighting the coronavirus pandemic. Therefore, the patient load usually treated there was redistributed in the remaining two surgical clinics. This can be an explanation why our admission numbers decreased with only 12% in a year.

According to our data we treated more advanced cancers, several of which was emergency. The fact that there was no substantial difference between the duration of hospitalization of these patients in comparison with the pre-pandemic ones, shows our intention to discharge as quickly as possible our patients in order to limit the chance of nosocomial infection (with COVID-19). Yun Xu however reports a longer length of stay of inpatients for palliative and curative resections alike (13).

In our institute an important chunk of the ICU ward and staff was repurposed for treating COVID-19 patients, thus limiting the capacity to a small number of beds where post-operative cancer patients could be admitted. This can be an explanation why we had similar admission rate to the ICU ward, and why patients benefited intensive care for the same amount of time during the pandemic. Because of the bed shortage, a lot of seriously ill patients were treated on the surgical ward.

Pathological Results

From our patient sample almost every variable showed a more advanced cancer in the pandemic group. We would like to point out that in Romania the colorectal cancer screening program is somewhat inexistent, thus limiting the opportunity to diagnose the disease in early stages. The limited number of cases admitted to this study, and fact that there was no screening program in place to be disrupted, could explain why some parameters did not show significant differences. We

believe, that before the COVID-19 restrictions, in comparison to countries with developed medical systems, we already treated more advanced cancers, therefore limiting the extent of the situation to worsen. In international literature, few studies were published that focused on the pathological upstaging of the colorectal cancer in this period with conflicting results. We report significantly more advanced tumor cases (higher stages) in the pandemic if we group our data according to AJCC and the less used DUKES classification. We had more locally advanced cancer (T) in the COVID-19 group. E. Williams et al and M Schinkwin et al found more T2, T3, T4 patients during the pandemic (18,19). Other authors claim that no difference in TNM stages and/or metastatic lymph node yield was found (13,20,21). J.Y.Choi's data shows significantly more lymph node metastasis and lymphovascular invasion but similar overall TNM staging and perineural invasion in the pandemic (13). A study from Brazil measured the clinical (preoperative) staging distribution of the patients and found similar local invasion and metastasis but more patients with clinically positive lymph nodes, and a higher proportion of clinically advanced cancers in the pandemic (22). We also had significantly more metastases, higher lymph node yield, more vascular and perineural invasion, higher proportion of positive resection margin but similar lymph node ratio and lymphatic invasion in this time. Some authors expect a rise of pathological advanced cancers (colorectal and other) in the following months, years (23-25).

When interpreting the results of this study, the following limitations should be considered. First, the data entered in our archives, at the moment of discharge, relies on several individuals and therefore we cannot exclude inherent bias. Second, this is a single institution's experience and must be interpreted accordingly. It is unclear yet as to whether these results will be reproducible across other Romanian tertiary clinics.

Conclusion

The COVID-19 pandemic and the measures to contain the spread of the virus had major effects on the colorectal cancer treatment pathways. Fewer diagnosis and surgical interventions were made in this period in Romania and around the world. Delays in treatment could seriously impact the clinical and pathological characteristics of the patients, with possibly worse short and long term outcomes. We do not have enough evidence to exactly quantify the impact of the pandemic, but this study should raise awareness about this particular population of colorectal cancer patients, who should benefit from a very close follow-up. It is important to repeat more similar studies on large samples in order to gain solid evidence. It is quintessential to have precise guidelines in place for future pandemics otherwise colorectal cancer patients could become "collateral damage".

Conflicts of Interest and Source of Funding

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Ethics Approval

The present study was approved by the institution's ethics committee.

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