Original Article

Effects of the COVID-19 Pandemic on Colorectal Cancers in Taiwan: A Retrospective Study

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Key Words
COVID19;
Colorectal cancers;
Obstruction;
Perforation;
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CA-199

Introduction. The novel coronavirus disease in 2019 had spread rapidly worldwide and had a strong impact to health care society. After the first case of COVID19 in Taiwan, decrease activities of healthcare systems put colorectal cancer patients in greater risk. We conduct a retrospective study of a tertiary hospital and investigate the impacts of COVID19 for CRC.
Methods & Materials. All patients age greater than 18 years old diagnosed with colorectal cancers from our hospital since 2016 to 2021 were included. Final pathology of non-adenocarcinoma diseases was excluded. We divided the patients into two groups (group A: 2016-2019; group B: 2020-2021) according to the date of initial diagnosed.
Results. There were no statistical significance in between age, sex, tumor locations, and treatment methods. Group B presented with higher percentage of local advanced disease in clinical stage. 31 patients (14.8%) with T1 stage and 56 patients (26.8%) were presented with T2 stage. Clinical presentation of obstruction was found in 191 (34.9%) patients and 92 (43.8%) patients in each group respectively (p-value = 0.023). Initial visit of hospital with colon perforation were found in 18 (3.3%) patients and 15 (7.1%) patients in each group (p-value = 0.020).
Discussion. Despite a retrospective study and many limitations, we illustrate delay diagnosis; postpone treatment, and more patients present with more severe symptoms. Incidentally, we also found CEA elevate in colon cancers but not rectal cancers.
Conclusion. COVID19 pandemic had great impact on the screening and diagnosis of CRC. In consequence of more advance disease occasionally combine with more severe clinical symptoms.

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COVID-19 spread quickly across the globe and caused major disruptions to health-care services.[1,2] In Taiwan, although the first COVID-19 case was diagnosed on January 28, 2020, the virus did not spread widely enough to cause an outbreak until May 2021, at which point the government locked down the country to control the spread of the disease. Citizens and health-care providers turned their attention to COVID-19 and neglected to consider other diseases. Because health-care providers were operating at reduced capacities and the general population was reluctant to seek medical help during the pandemic, individuals with colorectal cancer (CRC) were at an increased risk of not receiving essential medical support.[3]

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CRC is the fourth most deadly cancer worldwide, causing nearly 900,000 deaths annually.[4] CRC is the second most prevalent cancer in Taiwan. In 2018, 4300 patients received a diagnosis of CRC, and the prevalence rate was 18.25 per 100,000 individuals.[11] Among men, CRC is the most prevalent cancer and is the third leading cause of cancer-related death. Among women, CRC is the third most prevalent cancer and is the fourth leading cause of cancer-related death. Since 2000, the Health Promotion Administration has provided free fecal occult blood tests for citizens aged 50-75 years. The tests can be undergone for free once every 2 years. Over the past 2 decades, CRC-related death rates have decreased by 23%. Early detection and early treatment have likely contributed to this decrease.

During the COVID-19 pandemic, screening for CRC was challenging, and after the pandemic, a higher number of patients presented with locally advanced tumors and more severe disease status at the emergency department. Most patients do not seek medical help until they experience severe symptoms, such as obstruction, bleeding, or perforation. This retrospective study at a tertiary hospital explored how the COVID-19 pandemic affected patients' initial presentation, severity of the disease, distribution in locations, treatment types that patient received and the correlation of tumor markers with CRC.

Methods & Materials

Inclusion and exclusion criteria

Patients aged > 18 years who received a diagnosis of CRC at our hospital between 2016 and 2021 were identified. A total of 800 patients were initially identified. Patients whose final pathology was a neuroendocrine tumor, liposarcoma, signet-ring cell carcinoma, lymphoma, a gastrointestinal stromal tumor, or Ewing sarcoma or who did not complete cancer imaging tests before treatment were excluded. Patients who did not complete cancer imaging tests but who underwent polypectomy for malignant colonic polyps were included. Finally, 758 patients were included for analysis and divided into two groups on the basis of whether the date they received their initial diagnosis was before or during the COVID-19 pandemic. Group A received their initial diagnosis in 2016-2019, and group B received their initial diagnosis in 2020-2021.

Data definition

Tumor locations were classified as ascending, transverse, descending, sigmoid colon, and rectum based on imaging or colonoscopy. Tumor sizes were confirmed by the final pathological result or from imaging conducted on patients who did not receive surgical management. Clinical presentations of obstruction or perforation and tumor markers carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) at initial presentation were used to assist in making a diagnosis. Obstruction was defined by clinical presentation, imaging, or inability to pass a scope through the luminal narrowing. Perforation was defined by clinical presentation, imaging and final pathological report. Emergent enterostomy procedures for bowel obstruction and protective enterostomy after radical surgery were also investigated in this study. The treatment methods included local resection (polypectomy or transanal excision), radical treatment with or without neoadjuvant therapy (right hemicolectomy, transverse colectomy, left hemicolectomy, anterior resection, low anterior resection, abdominal-perineal resection, or Hartmann's procedure), chemotherapy, radiotherapy, chemoradiotherapy, palliative enterostomy, or palliative care and were selected on the basis of the disease status. Several patients completed CRC staging but sought second opinions for further treatment and were lost to follow-up. Such patients were included in this study as the loss group. Preoperative imaging was conducted by expert radiologists from our hospital and clinical staging was performed. Pathological staging was confirmed by a pathologist from our hospital.

Data collection and statistical analyses

Patient characteristics, including epidemiological information, laboratory findings, imaging findings, and pathological findings, were collected from patient

medical records. In a subgroup analysis, patients were divided into three groups according to their CEA levels: < 5, 5-199, and ≥ 200. Similarly, the patients were divided according to their CA19-9 levels: < 37, 37-199, and ≥ 200.

All statistical analyses were performed in SPSS 24.0 (Armonk, NY: IBM Corp.) by a specialist who was not involved in the data collection. Categorical variables are presented as frequencies and percentages; continuous variables are defined using means and standard deviations. The independent sample *t* test was used for continuous variables and the chi-square test or Fisher's exact test was used for categorical variables. A two-tailed p value < 0.05 was considered statistically significant.

Result

A total of 758 patients (548 patients in group A and 210 patients in group B) were included in this study. The mean age was 68.1 ± 13.0 in group A and 67.1 ± 13.6 years in group B. No significant difference was observed in the ages of the groups (p = 0.297) in Table 1. The sex distribution was not significantly different between the two groups (p = 0.599).

The clinical presentation of bowel obstruction was more prevalent in group B (92 patients, 43.8%) than in group A (191 patients, 34.9%; p = 0.023). However, no difference in emergent enterostomy for bowel obstruction was observed between group A (48 patients, 9.5%) and group B (15 patients, 7.1%; p = 0.101). Bowel perforation at initial visit was more prevalent in group B (15 patients, 7.1%) than in group A (18 patients, 3.3%; p = 0.018) shown in Table 1. These findings indicate that the patients who presented during the COVID-19 pandemic presented with more severe symptoms than those who presented before the COVID-19 pandemic.

More patients in group A had a CEA level of < 5 (62.2%) compared with those in group B (55.8%; p = 0.022), and more patients in group B had a CEA level of 5-199 (40.7%) compared with those in group A (31.0%; p = 0.022) in Table 2. However, no significant differences in CA19-9 levels were observed between the two groups. We divided patients according to whether their tumor was in the colon or rectum. For the patients whose tumor was in the colon, the CEA levels were higher in group B than in group A (p = 0.024); however, no significant difference was observed among the patients whose tumor was in the rectum. For the patients whose tumor was in the colon, the CA19-9 levels were not different between the groups; however, for the patients whose tumor was in the rectum, no patient in group B had a CA19-9 level > 200 shown in Table 2.

Discussion

Various studies have identified that diagnoses of CRC were often delayed until after the COVID-19 pandemic. In addition, the incidence of emergent diagnoses among patients who presented with severe symptoms, such as perforation, obstruction, and bleeding, was higher during the pandemic than before the pandemic. Surgical plans and chemotherapy regimens were changed.[5,6] Health-care providers and staff were exhausted due to the COVID-19 pandemic. Resources were reallocated to prioritize treatment of patients with COVID-19. Screening programs were postponed or canceled. Early diagnosis of CRC became challenging, and patients began presenting at emergency departments with severe symptoms at a greater rate. In addition, the waiting times for admission and hospitalization increased. All of these factors contributed to delays in diagnosing and interrupted treatment of CRC. In the present study, we demonstrated that a higher percentage of patients had T2-stage tumors at initial diagnosis during the COVID-19 pandemic compared with before the pandemic. In addition, a higher percentage of patients presented at our hospital with acute symptoms (obstruction or perforation) requiring emergency treatment during the pandemic than before the pandemic. Screening programs should be continued regardless of whether a pandemic occurs. Screening programs should be taken seriously.

CEA is an oncofetal protein that is elevated in the serum of patients with a variety of cancers, including CRC. CEA is a recommended prognostic marker of

Table 1. Patient characteristics

	2016-2019 (n = 548)	2020-2021 (n =210)	*p* value
	n (%)	n (%)	
Age (years), mean ± SD	68.2 ± 13.0	67.1 ± 13.6	0.297
Sex			0.599
Male	335 (61.1%)	124 (59.0%)	
Female	213 (38.9%)	86 (41.0%)	
Location			0.749
Ascending colon	109 (19.9%)	49 (23.3%)	
Transverse colon	58 (10.6%)	24 (11.4%)	
Descending colon	44 (8.0%)	13 (6.2%)	
Sigmoid colon	194 (35.4%)	69 (32.9%)	
Rectum	143 (26.1%)	55 (26.2%)	
Pathology			0.168
Adenocarcinoma	523 (95.4%)	205 (97.6%)	
Mucinous adenocarcinoma	25 (4.6%)	5 (2.4%)	
Obstruction			0.023[1]
No	357 (65.1%)	118 (56.2%)	
Yes	191 (34.9%)	92 (43.8%)	
Perforation			0.020[2]
No	530 (96.7%)	195 (92.9%)	
Yes	18 (3.3%)	15 (7.1%)	
Ostomy			0.106
No	418 (82.6%)	167 (88.4%)	
Complete obstruction	48 (9.5%)	15 (7.9%)	
Protective enterostomy	40 (7.9%)	7 (3.7%)	
Treatment			0.727
Local excision	74 (13.5%)	23 (11.0%)	
Radical resection	362 (66.1%)	143 (68.1%)	
Ostomy only	14 (2.6%)	6 (2.9%)	
C/T and or R/T only	26 (4.7%)	9 (4.3%)	
Best supportive care	30 (5.5%)	8 (3.8%)	
Loss treatment	42 (7.7%)	21 (10.0%)	
Tumor size (mm)	44.9 ± 24.5	44.2 ± 26.3	0.723
Clinical stage T			0.002[3]
1	131 (25.4%)	31 (14.8%)	
2	88 (17.1%)	56 (26.8%)	
3	221 (42.9%)	88 (42.1%)	
4	75 (14.6%)	34 (16.3%)	
Clinical stage N			0.502
0	256 (49.7%)	106 (50.7%)	
1	128 (24.9%)	44 (21.1%)	
2	131 (25.4%)	59 (28.2%)	
Clinical stage M			0.529
0	398 (77.3%)	166 (79.4%)	
1	117 (22.7%)	43 (20.6%)	
Clinical stage			0.850
1	170 (33.0%)	70 (33.5%)	
2	72 (14.0%)	27 (12.9%)	
3	156 (30.3%)	69 (33.0%)	
4	117 (22.7%)	43 (20.6%)	

Table 1. Continued

	2016-2019 (n = 548)	2020-2021 (n =210)	*p* value
	n (%)	n (%)	
Pathological stage T			0.057
0 + IS	90 (20.6%)	21 (12.4%)	
1	26 (6.0%)	16 (9.4%)	
2	47 (10.8%)	26 (15.3%)	
3	205 (47.0%)	77 (45.3%)	
4	68 (15.6%)	30 (17.6%)	
Pathological stage N			0.127
0	248 (56.9%)	88 (51.8%)	
1	76 (17.4%)	42 (24.7%)	
2	112 (25.7%)	40 (23.5%)	
Pathological stage M			0.615
0	359 (82.3%)	137 (80.6%)	
1	77 (17.7%)	33 (19.4%)	
Pathological stage			0.141
0	89 (20.4%)	21 (12.4%)	
1	64 (14.7%)	34 (20.0%)	
2	83 (19.0%)	31 (18.2%)	
3	123 (28.2%)	51 (30.0%)	
4	77 (17.7%)	33 (19.4%)	

[a] Fisher's Exact test.

[1] Perforation colon cancer was observed more in the COVID pandemic.

[2] Colon cancers cause symptoms of obstructions were more in the COVID pandemic.

[3] More clinical T stage 1 was seen in pre COVID pandemic and clinical T stage 2 in COVID pandemic.

Table 2. Correlation of tumor markers and tumor size before and after COVID pandemic

Colon and rectum	2016-2019 (n = 548)	2020-2021 (n = 210)	*p* value
	n (%)	n (%)	
CEA (ng/mL)			0.022
< 5	331 (62.2%)	111 (55.8%)	
5-199	165 (31.0%)	81 (40.7%)	
≥ 200	36 (6.8%)	7 (3.5%)	
CA199			0.738
< 37	385 (76.5%)	136 (73.9%)	
37-199	67 (13.3%)	26 (14.1%)	
≥ 200	51 (10.1%)	22 (12.0%)	

CEA: carcinoembryonic antigen; CA199: carbohydrate antigen 19-9.

CRC that is used for tumor diagnosis and monitoring responses to therapy.[7] CA19-9 is another established serum marker for a variety of cancers. CA19-9 is mainly

used to identify biliary tract and pancreatic disease but also plays a role in CRC. Proctologists generally differentiate between colon and rectal cancer because they have differing clinical presentations and therapeutic strategies. There was one retrospective study showed CEA and CA19-9 combined in correlation with diagnostics and prognosis. Overall and recurrence-free survival were significantly shorter in patients with a CEA or CA19-9 level ≥ 200 compared to patients with an increased, but less than 200 or normal level. According to this study, we subgroup patient's CEA level to ≥ 200, 5-199 and < 5 and subgroup CA-199 level to ≥ 200, 5-37 and < 37. In our study, there was more colorectal cancer patient with initial diagnosed CEA level > 5 after year 2020 ($p = 0.022$). This may indicate more severe disease after year 2020. In other words, CEA might be an effective biomarker for evaluate the severity of CRC. However, this trend cannot found in CA-199 group.[12]

Further studies with larger sample sizes are warranted to validate this hypothesis. A study proposed a novel method for detecting CRC that involves screening of serum oxysterol biomarkers.[8] Serum metabolomics were also identified as potential early biomarkers of CRC.[9] Despite these new methods having been proposed, CEA and CA19-9 continue to be the most commonly used biomarkers for detection of CRC and monitoring of responses after treatment.

A nationwide analysis observed that the number of screenings for CRC decreased by more than 15% during the COVID-19 pandemic.[10] This finding indicated that patients would present with a more advanced disease stage during this time; however, few studies have verified this hypothesis. Our study revealed that the symptoms at initial diagnosis were more severe for patients presenting after the start of the COVID-19 pandemic. In addition, the decrease in screening numbers was more pronounced in cities than in the countryside, which reflected the correlation between the severity of the COVID-19 outbreak in a specific region and the willingness of patients in that region to undergo screening. Our study revealed that patients in eastern Taiwan, where only a few cases of COVID-19 were confirmed, were more likely to undergo screening. These findings demonstrate that citizens were afraid to seek medical services because they feared potential exposure to COVID19. This phenomenon were also found in other countries and a large systemic review.[13,14] This fear led to later diagnoses and more advanced disease stages of CRC occurring after the COVID-19 pandemic. Another study from Netherlands also showed that there is no effect on the treatment of colorectal cancer during COVID-19 pandemic; however, more severe symptoms at presentation was shown.[15] All these studies from worldwide showed similar result as our study.

This study has several limitations. First, this is a retrospective study. The retrospective design was employed because conducting an investigation during the COVID-19 pandemic would have been challenging. In addition, data was collected from a single tertiary hospital. Therefore, the findings may not be generalizable to the rest of the country. Bias relating to the reluctance of patients in this region to seek medical help may be present. Second, our analysis did not include patients who underwent preoperative neoadjuvant chemoradiotherapy because this may have caused regression of pathological staging, leading to possible underestimation of results. Third, we collected data on only patient characteristics, initial clinical status, treatment, and short-term outcomes. Research with a long-term follow-up is required to gain further insights into the effects of the COVID-19 pandemic on CRC.

Conclusion

The COVID-19 pandemic resulted in increased incidence of patients presenting at hospitals with more advanced T stages that occasionally occurred in combination with more severe clinical symptoms, such as bowel obstruction or perforation. Establishment of better management strategies is warranted to prevent similar problems from occurring during subsequent worldwide outbreaks of a disease.

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原　著

新型冠狀病毒大流行對於台灣大腸直腸癌的影響，回溯型研究

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介紹　2019 年新型冠狀病毒疫情在全球迅速蔓延，對醫療社會產生了強烈影響。台灣出現首例新冠肺炎病例後，醫療系統活動的減少使大腸直腸癌患者面臨更大的風險。我們針對一家三級醫院進行回顧性研究，調查新冠肺炎對大腸癌的影響。

方法與材料　納入 2016 年至 2021 年期間在本院確診的所有年齡大於 18 歲的大腸直腸癌患者。排除非腺癌疾病的最終病理。我們根據初次診斷日期將患者分為兩組 (A 組：2016-2019 年；B 組：2020-2021 年)。

結果　年齡、性別、腫瘤部位和治療方法之間沒有統計意義。B 組臨床階段局部晚期疾病的比例較高。31 名患者 (14.8%) 為 T1 期，56 名患者 (26.8%) 為 T2 期。每組分別有 191 例 (34.9%) 和 92 例 (43.8%) 患者出現阻塞臨床表現 (p = 0.023)。各組首次就診的結腸穿孔患者分別為 18 例 (3.3%) 和 15 例 (7.1%) (p = 0.020)。

討論　儘管進行了回顧性研究並存在許多局限性，但我們仍說明了延遲診斷；延後治療，更多患者出現更嚴重的症狀。順便說一句，我們還發現結腸癌中 CEA 升高，但直腸癌中則沒有升高。

結論　新冠肺炎疫情對大腸直腸癌的篩檢和診斷產生了很大影響。由於病情進展，有時會出現更嚴重的臨床症狀。

關鍵詞　新型冠狀病毒、大腸直腸癌症、腸阻塞、腸穿孔。