

# Resilience in Rectal Cancer Treatment: Lessons from the COVID-19 Era in Czech Republic

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**Introduction:** The management of patients with COVID-19 infection has placed great pressure on the healthcare systems around the world. The aim of this study was to investigate the impact of the COVID-19 pandemic on the treatment outcomes of patients with rectal cancer by comparing them to those of patients with the same diagnosis in the pre-pandemic period.

**Methods:** Retrospective data analysis of patients undergoing multimodal treatment for rectal cancer at the four university hospitals during the COVID-19 pandemic (2020–2021) and the 2-year pre-pandemic period (2018–2019).

**Results:** A total of 693 patients (319 in the pre-pandemic period and 374 in the pandemic period) with rectal cancer were included in the study. The demographic and clinical characteristics of patients in both study periods were comparable, as was the spectrum of surgical procedures. Palliative surgery was more common in the pandemic period (18% vs 13%,  $p=0.084$ ). The proportion of patients undergoing minimally invasive surgery was higher during the COVID-19 pandemic ( $p=0.025$ ). There were no statistically significant differences between the study periods in the incidence/severity of post-operative complications, 30-day mortality and length of hospital stay. The number of positive resection margins was similar (5% vs 5%). Based on these results, COVID-19 had no effect on the postoperative morbidity and mortality in patients undergoing surgery for rectal cancer. Neoadjuvant treatment was more common in the pre-pandemic period (50% vs 45%). Long-course RT was predominantly offered in the pre-pandemic period, short-course RT during the pandemic. Significantly shorter “diagnosis-surgery” intervals were observed during the pandemic (23 days vs 33 days,  $p=0.0002$ ). The “surgery-adjuvant therapy” interval was similar in both analysed study periods ( $p=0.219$ ).

**Conclusion:** Our study showed, that despite concerns about the COVID-19 pandemic, multimodal treatment of rectal cancer was associated with unchanged postoperative morbidity rates, increased frequency of short-course neoadjuvant RT administration and shorter “diagnosis-surgery” intervals.

**Keywords:** rectal cancer, COVID-19, multimodal treatment, complications, morbidity, neoadjuvant radiotherapy

## Introduction

The coronavirus disease 2019 (COVID-19) pandemic has had a major impact on the healthcare services worldwide. Healthcare providers responsible for the management of cancer, had to make changes to their usual diagnostic and treatment procedures in an effort to prevent infection and accommodate the limited medical resources resulting from the pandemic.<sup>1,2</sup>

As a result, elective surgical procedures (including rectal cancer surgery) have been greatly reduced to ensure sufficient treatment capacity for COVID-19 patients and to reduce the burden on intensive care units during period of high COVID-19 caseloads.<sup>3–5</sup> Several expert committees have issued guidelines recommending to postpone non-urgent cancer surgery. It has been suggested to prefer open surgery over laparoscopic/robotic surgery because of concerns about the increased risk of aerosol spread of coronavirus 2(SARS-CoV-2) during the laparoscopic/robotic surgery.<sup>6–9</sup> This had raised concerns about delayed diagnosis, treatment and poorer outcomes of cancer patients during the COVID19 pandemic.<sup>10,11</sup>

The multimodal management of patients with rectal cancer differs significantly from the management of patients with colorectal cancer. In the available literature, there are many retrospective studies analysing the impact of COVID-19 on the outcomes of patients undergoing major abdominal surgery or surgery for colorectal cancer. However, data regarding multimodal treatment of patients with rectal cancer during the COVID-19 pandemic are very limited.

Therefore, the aim of the present study was to investigate the impact of the COVID-19 pandemic on the management and outcomes of rectal cancer patients by comparing them with those of patients with the same diagnosis in the pre-pandemic period.

## Materials and Methods

### Design and Setting

The study was conducted at four university hospitals in the Czech Republic (University Hospital Ostrava, University Hospital Olomouc, University Hospital Brno and University Hospital Královské Vinohrady), and was conducted according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) recommendations for observational studies. The study was approved by the Ethics Committee of the University Hospital of Ostrava (reference number 964/2021).

The Czech Republic was exposed to two waves of COVID-19 in 2020, one in April/May and a second starting in October. In response to both waves, national lockdowns were implemented from April to June, and then from October to the following June. The retrospective clinical study from four university hospitals was aimed to analyse data from the 2-year COVID-19 pandemic period (2020–2021) and the 2-year pre-pandemic period (2018–2019).

All patients with newly diagnosed rectal cancer who were treated at one of the participating university hospitals within the study period (1st January 2018–31st December 2021) were included in the study. Exclusion criteria were rectal cancer recurrence, multiple cancers (cancer duplicity/triplicity), early rectal cancer resected using transanal endoscopic techniques (endoscopic mucosal resection, endoscopic submucosal dissection, transanal endoscopic microsurgery), and patients with incomplete data.

All study patients were treated according to NCCN guidelines. Neoadjuvant radiochemotherapy was offered to patients with rectal cancer classified as cT3-4 and/or N1-2 (as assessed by magnetic resonance imaging).

Data were extracted from the hospital information systems of the participating centres; anonymised data were stored in a secure database. Data collection included demographic and clinical information (sex, age, BMI, and ASA classification) and tumour characteristics (histopathology, cancer stage). Data on treatment (neoadjuvant therapy, elective/emergency surgery, curative/palliative surgery) and time intervals between treatment modalities (indications to surgery, surgery to adjuvant therapy) were extracted from the patients' medical records.

Perioperative and postoperative data included type of surgery, length of hospital stay, postoperative 30-day mortality, 30-day morbidity (complications classified according to Clavien-Dindo classification), and COVID in the postoperative course.

### Statistical Analysis

Descriptive statistics (mean, standard deviation, median, IQR, and relative frequencies) were used to characterize the data sets. Student's *t*-test, Mann–Whitney *U*-test according to probability distribution (Kolmogorov–Smirnov test), and  $\chi^2$  tests were used for statistical comparison of continuous variables. A *p*-value less than 0.05 was interpreted as a statistically significant result.

## Results

During the study period, a total of 756 patients with rectal cancer were treated at our participating hospitals. 18 patients with recurrent rectal cancer, 8 patients with multiple cancers, 35 patients treated with transanal endoscopic resection and 2 patients with incomplete data were excluded from the study. Data from a cohort of 693 patients with rectal cancer were analysed.

## Demographic and Clinical Data

Demographic and clinical data of our study patients (319 patients in the pre-pandemic period, 374 patients in the COVID-19 pandemic period) are shown in Table 1. Both study subgroups were comparable with respect to age, sex, BMI and ASA classification. Tumour characteristics (tumour distance from anal verge and cancer stage) were also similar in both study subgroups. Neoadjuvant therapy was given to 50% of study patients in the pre-pandemic period and 45% of patients in the pandemic period ( $p < 0.001$ ). Long-course radiochemotherapy was predominantly used in the pre-pandemic period (97%). During the COVID-19 pandemic, short-course radiotherapy was preferred (59% of patients receiving neoadjuvant treatment during the pandemic).

## Surgical Procedures

The basic characteristics of the surgical procedures performed are shown in Table 2. Elective procedures clearly predominated in both study subgroups; palliative surgery was performed in 13% of patients in the pre-pandemic period and in 18% of patients in the pandemic period (the difference was not statistically significant). The spectrum of surgical

**Table 1** Demographics and Clinical Data

	2018–2019 (n = 319)	2020–2021 (n = 374)	p
<b>Sex</b> Male/female (%)	218 (68%) / 101 (32%)	234 (63%) / 140 (37%)	0.112
<b>Age (years)</b> Mean, ±SD Median, IQR	64±11.7 66, 57–74	66±10.5 68, 58–73	0.203
<b>BMI (kg/m<sup>2</sup>)</b> Mean±SD Median, IQR	27±4.1 27, 24–29	27±5.0 27, 24–30	0.646
<b>ASA</b> I/II/III/IV (%)	8% / 59% / 32% / 1%	9% / 65% / 24% / 2%	0.199
<b>Tumour distance from anal verge (cm)</b> Mean, ±SD	8.1±3.8	7.8±3.6	0.756
<b>Cancer stage (clinical)</b> I/II/III/IV (%)	33% / 31% / 32% / 12%	29% / 26% / 36% / 8%	0.719
<b>Neoadjuvant therapy (%)</b> Long-course Short-course	160 (50%) 155 (97%) 5 (3%)	167 (45%) 68 (41%) 99 (59%)	<0.001

**Table 2** Surgery

	2018–2019 (n = 319)	2020–2021 (n = 374)	p
<b>Elective/Emergency surgery (%)</b>	307 (96%) / 12 (4%)	356 (95%) / 18 (5%)	0.241
<b>Curative/Palliative surgery (%)</b>	278 (87%) / 41 (13%)	307 (82%) / 67 (18%)	0.084
<b>Surgical procedure (%)</b> AR/LAR/APR/Hartmann	29% / 45% / 21% / 5%	30% / 43% / 24% / 3%	0.858
<b>Surgical Technique (%)</b> Open/Miniinvasive (laparo, robot)	242 (76%) / 77 (24%)	255 (68%) / 119 (32%)	0.025

**Abbreviations:** AR, anterior resection; LAR, low anterior resection; APR, abdominoperineal resection.

procedures was similar in both analysed study periods. Positive resection margins were found in 17 (5%) patients in the pre-pandemic period and 19 (5%) patients in the pandemic period. The proportion of patients who underwent laparoscopic/robotic surgery was significantly higher during the COVID-19 pandemic period compared to the pre-pandemic period ( $p=0.025$ ).

## Short-Term and Long-Term Outcomes

The short-term outcomes of rectal cancer surgery in our study patients are shown in Table 3. There were no statistically significant differences between the study subgroups in the incidence and severity of postoperative complications, 30-day mortality, and length of hospital stay. According to these Results, COVID-19 did not influence postoperative morbidity and mortality in patients undergoing surgical treatment for rectal cancer. Histopathological examination of resected rectal specimens showed comparable results in both study subgroups ( $p=0.369$  and  $p=0.587$ ).

The time intervals regarding management of our study patients are presented in Table 4. The “diagnosis-surgery” interval was significantly shorter in the COVID-19 pandemic (23 days vs 33 days,  $p=0.0002$ ). The difference was determined by a subgroup of study patients undergoing neoadjuvant radiochemotherapy. The much shorter “diagnosis-surgery” interval in the COVID-19 pandemic was clearly caused by the significantly higher proportion of patients receiving short-course radiotherapy (see Table 1). Patients without neoadjuvant treatment also had a shorter “diagnosis-surgery” interval during the COVID-19 pandemic, but the difference was not statistically significant ( $p=0.134$ ). The interval for starting adjuvant therapy (“surgery-adjuvant therapy” interval) was very similar in both study periods analysed ( $p=0.219$ ).

**Table 3** Short-Term Outcomes

	2018–2019 (n = 319)	2020–2021 (n = 374)	P
<b>30-day Mortality (%)</b>	6 (2%)	4 (1%)	0.372
<b>30-day Morbidity (%)</b>	126 (39%)	149 (40%)	0.700
<b>Postoperative complications (%)</b>			
Clavien-Dindo 0	193 (61%)	225 (60%)	0.205
Clavien -Dindo I–II	67 (21%)	95 (25%)	
Clavien-Dindo III–V	59 (18%)	54 (14%)	
<b>Length of hospital stay</b>			
Mean±SD,	12±8.1	12±4.2	0.097
Median, IQR (days)	10, 8–14	9, 8–13	
<b>Pathology staging/radicality</b>			
0/II/III/III/IV (%)	3%/29%/24%/31%/12%	2%/29%/24%/36%/8%	0.369
R0/R1/R2 resection	88% / 5% / 7%	90% / 5% / 5%	0.587

**Table 4** Treatment Time Intervals

	2018–2019	2020–2021	p
<b>Diagnosis – Surgery (All patients) median, IQR (days)</b>	33, 16–126	23, 13–45	0.0002
<b>Diagnosis – Surgery (Patients without neoadjuvant therapy) median, IQR (days)</b>	20, 11–28	17, 10–26	0.134
<b>Diagnosis – Surgery (Patients with neoadjuvant therapy) median, IQR (days)</b>	123, 462,152	53, 26–143	0.002
<b>Surgery – Adjuvant therapy median, IQR (days)</b>	44, 33–65	42, 34–50	0.219

## Discussion

The management of patients with COVID-19 infection placed great pressure on healthcare systems around the world due to the reallocation of healthcare resources and national lockdowns. While the possibility of COVID-19 infection was a concern, the inability to receive appropriate treatment as a part of routine cancer care put patients at increased risk of cancer-related morbidity.

Kamposioras et al published a synthesis of recommendations from 25 countries providing general guidance on how to provide oncological care during a COVID-19 pandemic. Reduced mobility and physical contact of medical staff within hospitals was recommended, but the provision of medical services and curative primary tumour resections should not be postponed. The authors advice that neoadjuvant and adjuvant treatment should not be delayed or omitted; the use of regimens with the longest cycle was recommended.<sup>12</sup>

In contrast to these recommendations, significant changes in the multimodal management of colorectal cancer patients during the COVID-19 pandemic have been reported in the available literature.<sup>13–15</sup> Changes in systemic anticancer therapy and its impact on survival outcomes were published by Kamposioras et al (data from a large tertiary cancer centre). More than half of the patients had their treatment changed (21% had their treatment delayed, 10% had their treatment cancelled). Neoadjuvant therapy was changed in 20% and adjuvant therapy in 50% of patients offered a neoadjuvant/adjuvant treatment plan. Treatment was more likely to be changed in older patients and in patients who had already received a higher number of cycles of systemic anti-cancer therapy.<sup>13</sup>

A multicentre study from northern Italy showed that patients with colorectal cancer who underwent surgery during the COVID-19 pandemic had an increased risk of advanced disease in terms of associated symptoms, clinical T4 stage and number of liver metastases.<sup>14</sup> A registry-based study in the Netherlands reported an increased number of colorectal cancer patients presenting with ileus during the pandemic.<sup>15</sup>

Our study investigated whether the COVID-19 pandemic affected the management of patients with rectal cancer in the Czech Republic. The results of the study showed that multidisciplinary treatment, radicality and postoperative morbidity/mortality during the pandemic were comparable to the results before the pandemic. The proportion of patients undergoing minimally invasive rectal surgery was higher during the COVID-19 pandemic and significantly shorter time intervals “diagnosis-surgery” were noticed during the pandemic. The shorter “diagnosis-surgery” interval in our study was determined by two main factors: a significantly higher proportion of patients undergoing short-course radiotherapy during the COVID-19 pandemic (see Table 1) and better availability of operating theatres. Elective surgery for patients with benign diagnoses (such as cholecystectomy, hernioplasty, varicose vein surgery, etc.) was not performed during the pandemic, resulting in increased availability and earlier times for rectal cancer surgery.

The importance of the time intervals between diagnosis and cancer surgery has been demonstrated by many authors – delays in surgery have a negative impact on patient prognosis.<sup>16,17</sup> One study from England estimated an increase in colorectal cancer deaths of approximately 1500 cases during the COVID-19 pandemic.<sup>18</sup> However, Clifford et al published data from a multicentre observational study focused on rectal cancer management during the COVID-19 pandemic in the UK (ReCaP). A total of 500 patients diagnosed at 42 sites were recruited into the study. A change in initial MDT outcome due to COVID-19 was reported in 22.3% of study patients. There was a significant shift from long-course to short-course neoadjuvant RT (short-course increased from 15.4% to 45.2%, long-course dropped from 56.3% to 14.0%). Surprisingly, 6 months after the last patient was recruited, only 225 patients (out of 500) underwent surgical resection (51.6% without any neoadjuvant therapy). Approximately 50% of operations were performed laparoscopically, with a 30-day re-operation rate of 5.8%. The 30-day postoperative mortality rate was 1.3%, with only two patients becoming COVID-19 positive within 30 days.<sup>19</sup>

Authors from Peking University Cancer Hospital (single-centre retrospective study) reported that during the COVID-19 pandemic, a significantly lower proportion of patients underwent surgical resection in comparison with the pre-pandemic period (60.3% vs 75.4%,  $p=0.009$ ). The number of postoperative complications was higher during the pandemic (27.6% vs 14.5%,  $p=0.041$ ). Open surgery was performed more often and the time interval between surgery and the last radiotherapy session was significantly longer (15.4 vs 13.8 weeks).<sup>20</sup>

According to a meta-analysis published by Pararas et al, the use of neoadjuvant radiochemotherapy for rectal cancer has increased significantly during the pandemic.<sup>21</sup> The increase in neoadjuvant treatment is likely to be the result of

guidelines issued by several colorectal societies/associations recommending to offer neoadjuvant radiochemotherapy for patients with rectal cancer as an alternative treatment to delay surgery.<sup>8,9,22</sup>

It has been suggested that short-course RT followed by delayed surgery (5–13 weeks) may be the best option for patients with rectal cancer during the COVID-19 pandemic.<sup>23,24</sup> This approach offers oncological outcomes comparable to more traditional treatment schedules and has the advantage of reducing patient exposure to the hospital environment during radiotherapy and of postponing surgery to a time when the pandemic is under control. The short-term outcomes of short-course neoadjuvant RF appear to be similar to those of long-course RT. However, the omission of systemic chemotherapy in many of these patients needs to be carefully monitored.

Our study results indicate that the COVID-19 pandemic was not associated with worse perioperative/postoperative outcomes in patients undergoing multimodal treatment for rectal cancer in the Czech Republic. The main strengths of the present study are its multicentre design, meticulous data collection and rigorous comparison of patient outcomes between the pre-pandemic and pandemic periods. The retrospective nature of the study, the lack of survival data and the heterogeneity of the data due to the multicentre design are potential biases.

## Conclusion

In Conclusion, our study demonstrated that despite concerns regarding perioperative COVID-19 infection and reduced availability of intensive care, multimodal treatment of rectal cancer was associated with unchanged postoperative morbidity/mortality rates, increased frequency of short-course neoadjuvant RT administration and shortened “diagnosis-surgery” intervals. As the world continues to grapple with the challenges posed by the pandemic, further research is needed to refine treatment strategies, improve patient safety, and optimise the use of healthcare resources in the context of cancer management during such crises.

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## Disclosure

The authors have no conflicts of interest to declare for this work.

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