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ORIGINAL ARTICLE

The impact of surgical delay on resectability of colorectal cancer: An international prospective cohort study

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Abstract

Aim: The SARS-CoV-2 pandemic has provided a unique opportunity to explore the impact of surgical delays on cancer resectability. This study aimed to compare resectability for colorectal cancer patients undergoing delayed versus non-delayed surgery.

Methods: This was an international prospective cohort study of consecutive colorectal cancer patients with a decision for curative surgery (January–April 2020). Surgical delay was defined as an operation taking place more than 4 weeks after treatment decision, in a patient who did not receive neoadjuvant therapy. A subgroup analysis explored the effects of delay in elective patients only. The impact of longer delays was explored in a sensitivity analysis. The primary outcome was complete resection, defined as curative resection with an R0 margin.

Results: Overall, 5453 patients from 304 hospitals in 47 countries were included, of whom 6.6% (358/5453) did not receive their planned operation. Of the 4304 operated patients without neoadjuvant therapy, 40.5% (1744/4304) were delayed beyond 4 weeks. Delayed patients were more likely to be older, men, more comorbid, have higher body mass index and have rectal cancer and early stage disease. Delayed patients had higher unadjusted rates of complete resection (93.7% vs. 91.9%, $P = 0.032$) and lower rates of emergency surgery (4.5% vs. 22.5%, $P < 0.001$). After adjustment, delay was not associated with a lower rate of complete resection (OR 1.18, 95% CI 0.90–1.55, $P = 0.224$), which was consistent in elective patients only (OR 0.94, 95% CI 0.69–1.27, $P = 0.672$). Longer delays were not associated with poorer outcomes.

Conclusion: One in 15 colorectal cancer patients did not receive their planned operation during the first wave of COVID-19. Surgical delay did not appear to compromise resectability, raising the hypothesis that any reduction in long-term survival attributable to delays is likely to be due to micro-metastatic disease.

KEYWORDS
colorectal cancer, coronavirus, COVID-19, SARS-CoV-2, surgery, surgical delay

*Collaborating authors are listed in Appendix A.

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INTRODUCTION

Globally, colorectal cancer is the third most commonly diagnosed cancer type and the second largest cause of cancer death [1]. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has affected all aspects of healthcare and has led to variable delays to the delivery of colorectal cancer surgery across the globe [2,3]. It is estimated that over 28 million operations were cancelled in the initial 3 months of disruption alone [4,5]. This creates a unique 'natural experiment' to explore the effects of treatment delay on outcomes of colorectal cancer surgery.

Although there is no international guidance on the optimal timing for colorectal cancer resection, it is generally perceived as a time critical intervention. In the UK, the National Health Service sets a target of 4 weeks from a treatment decision to definitive treatment in cancer care, but global practice and policy varies significantly. A number of modelling studies and systematic reviews have explored the impact of delays on long-term survival in colorectal cancer, but it is unclear whether this is related to poorer initial cancer control (i.e., lower rates of complete resection) or micro-metastatic disease spread [6].

Understanding the effects of surgical delay during the SARS-CoV-2 pandemic will help inform future prioritization of surgical waiting lists during post-pandemic recovery and postoperative surveillance by the multidisciplinary team.

This study aimed to explore the association between delayed surgery for colorectal cancer in patients not undergoing neoadjuvant therapy and surgical resectability during the SARS-CoV-2 pandemic.

What does this paper add to the literature?

This was a prospective cohort study of 5453 patients with a decision for curative colorectal cancer surgery. Surgical delays of up to 12 weeks were not associated with worse rates of complete resection. Any reduction in long-term survival attributable to delays is likely to be due to micro-metastatic disease and should be the focus of postoperative surveillance programmes.

METHODS

Study design and setting

This was an international prospective cohort study which included consecutive patients with a decision for elective curative surgery from the multidisciplinary team meeting, tumour board or equivalent. Any hospital worldwide undertaking elective colorectal cancer surgery was eligible for inclusion in this analysis. Each participating site recruited consecutive eligible patients for a period of 3 months following the emergence of COVID-19 in their local area (first notification of SARS-CoV-2 ranging between January and April 2020). Each site obtained ethical approval according to local regulations, and the COVIDSurg-Cancer study (overall inclusion by cancer type available in Table S12) was pre-registered with ClinicalTrials.gov (identifier NCT04384926).

Patient inclusion, pathways and follow-up

All patients with a decision for curative cancer surgery or who would normally have been offered curative surgery in the pre-pandemic setting but an alternative treatment was offered due to COVID-19 were included. Patients were excluded from this study if they had (1) planned palliative surgery, (2) a suspected cancer that was later found to be benign on histopathology, (3) a suspected benign tumour that was later found to be cancerous or (4) received endoscopic treatment only (e.g., transanal endorectal microsurgery).

From all the included patients, some of them did receive their planned curative surgery but some ended up not receiving it during the study period. For patients who were operated, follow-up data were collected at 30 days after surgery. For patients who remained non-operated, their last known status was recorded. All follow-up was completed by 31 August 2020 with a minimum follow-up of 3 months for all included patients. The characteristics of non-operated patients were described and reasons for the non-performance of the planned surgery were reported. This allows a comprehensive understanding of the whole sample and an informed discussion on how treatment pathways that were in place during the study influenced the patient groups that we are comparing.

Of all the operated patients, some required surgical resection alone and some required neoadjuvant therapy (chemotherapy and/or radiotherapy prior to surgery). Due to differences in disease biology, and potential effects of treatment intervals in patients undergoing neoadjuvant therapy, the patients who received neoadjuvant therapy were excluded from the main analysis as their disease behaviour is expected to be fundamentally different. However, tumour location and the type of neoadjuvant treatment are reported in the supplement for completeness.

Delay to surgery

The main analysis on surgical delays focused on patients who received their planned surgery with curative intent, without having received neoadjuvant therapy. Delay to surgery was defined according to the number of weeks from the date of the decision for curative surgery to the date when the patient received surgery. For the primary analysis, patients who were operated more than 4 weeks after their decision for surgery were classified as delayed and those who were operated within 4 weeks were defined as non-delayed. This 4-week cut-off was informed by UK National Institute for Clinical Excellence guidance and standards for timely delivery of cancer care [7].

Outcomes

The primary outcome measure for the study was complete resection, defined as disease amenable to surgical removal at the time of surgery with a negative circumferential resection margin (R0, no microscopic or macroscopic disease within 1 mm of the circumferential resection margin). Patients whose disease became unresectable during the study period or whose surgical resection was achieved with positive resection margins (R1 or R2) were classified as having an incomplete resection.

Secondary outcomes were also compared between patients undergoing delayed and non-delayed surgery. These included the 30-day postoperative mortality rate, 30-day major postoperative complication rate (defined as Clavien–Dindo Grade III–V complications) [8], stage change from baseline (clinical) to pathology (according to the American Joint Committee on Cancer [AJCC] 8th edition of the TNM staging system [9], defined as upstaged for any increase in stage, downstaged for any decrease in stage and no change for patients remaining at the same stage group), detection of new metastatic disease (clinically, intra-operatively or on radiological imaging that was not present at the time of decision for surgery) and the rate of emergency surgery (i.e., as all patients had an initial plan for elective surgery at study entry, emergency surgery can be interpreted as a cancer-related complication requiring emergency intervention). The indications for emergency surgery are presented.

Data variables

Baseline information was collected for each patient at the point of entry to the study. This included age, sex, American Society of Anesthesiologists (ASA) physical status classification, Eastern Cooperative Oncology Group (ECOG) performance score, Revised Cardiac Risk Index (RCRI), body mass index (BMI) (defined as underweight if <18.5 kg/m^2, normal if 18.5–24.9 kg/m^2, overweight if 25–29.9 kg/m^2 or obese if ≥30 kg/m^2), clinical (based on imaging and clinical observation at the time of decision for surgery) and pathological TNM stage groups collected according to the AJCC 8th edition, country income (grouped as high, upper middle and low/low middle income, as per the World Bank index classification based on gross national income per capita), surgical approach (open, laparoscopic or converted), anastomotic performance (with or without defunctioning stoma) and anastomotic method (handsewn or stapled).

Data handling and statistics

All the data collected were non-identifiable and uploaded to a secure online server hosted by the University of Birmingham, using the Research Electronic Data Capture (REDCap) system. Data management and analysis used RStudio version 4.0.3 with the 'readr', 'tidyverse', 'dplyr', 'gmodels', 'Hmisc' and 'finalfit' packages (R Foundation for Statistical Computing). Unadjusted categorical data were compared using the chi-squared test with Fisher's exact modification where required. A P value <0.05 was considered statistically significant. Logistic regression models were used to explore the association between delay to surgery and complete resection, adjusting for clinically plausible patient and disease factors selected a priori. All missing data were recorded and are reported in the tables and figures.

Reflecting differences in treatment timelines and capacity across different resource settings, we performed a sensitivity analysis exploring longer delays of 6, 8 and 12 weeks from treatment decision to surgery, and the primary outcome measure.

Given that patients undergoing emergency surgery could have shown distinct clinical features at the time of decision for surgery that made them more likely to receive an urgent intervention, a pre-planned subgroup analysis was performed for patients undergoing planned (elective) surgery only. Further subgroup analyses were performed looking exclusively at colon cancers, rectal cancers, early disease and advanced disease. For this purpose, early disease stage was defined as organ confined, non-nodal, non-metastatic (T1–3 N0 M0) and advanced disease was defined as reaching the serosa, nodal or metastatic disease (T4, N+ or M1). A sensitivity analysis of the adjusted and unadjusted results was conducted to explore the impact of longer delays in resectability: 0–4, 5–8, 9–12 and more than 12 weeks from decision to surgery.

RESULTS

In total, 5453 patients eligible for elective curative colorectal cancer surgery were included from 304 hospitals in 47 countries. This corresponds to 24.4% of all the patients included in the COVIDSurg-Cancer study (the remaining being patients with other cancer types) [10]. Of these 66.3% (3616/5453) had colon cancer and 33.7% (1837/5453) had rectal cancer. The clinical colorectal cancer stage was advanced in 63.6% (3466/5453) of the patients and early in 36.4% (1987/5453). Around two-thirds of the patients were ASA grade 1–2 (66.7%, 3619/5453) and one-third were ASA grade 3–5 (33.2%, 1809/5453). The majority of the patients were from high income countries (84.3%, 4599/5453), with 9.2% (500/5453) being from upper middle income countries and 6.4% (351/5453) from lower middle or low income countries.

Non-operated patients

From all the included patients, 6.6% (358/5453) did not receive their planned operation during the study period (Figure 1), of whom 74.3% (266/358) were still planned to have curative surgery at the time of follow-up. Patients who were not operated were more likely to have rectal cancer (52.5% vs. 32.4%, P < 0.001), worse performance status (5.9% vs. 2.9% were ECOG 3–4, P < 0.001), lower BMI (9.3% vs. 3.5% were underweight, P < 0.001), higher stage disease (14.6% vs. 10.3% had clinical Stage IV, P = 0.004) and be from a low/lower middle

income country (18.2% vs. 5.6%, $P<0.001$) (Table S1). The reasons why patients did not receive their planned operation are detailed in Table S2, with the most common reasons being a multidisciplinary team decision to avoid surgery due to patient risk (72.6%, 260/358), disease progression (29.1%, 104/358) and patient being unable to travel to hospital during the pandemic (26.3%, 94/358).

Operated patients

Of the 5095 operated patients, 15.5% (791/5095) received neoadjuvant therapy and 85.4% (4304/5095) underwent surgery without neoadjuvant treatment. The majority of the patients receiving neoadjuvant therapy had rectal cancer (81.8%, 647/791). Neoadjuvant therapy regimens by cancer location are shown in Figure S1.

From the 4304 patients who received an operation without neoadjuvant therapy, 59.5% (2559/4303) had surgery within 4 weeks of treatment decision and 40.5% (1744/4304) were delayed beyond 4 weeks. Delayed patients were more likely to be older (53.0% vs. 46.3% aged over 70 years, $P<0.001$), men (58.7% vs. 54.6%, $P=0.008$), more comorbid (37.7% vs. 30.9% were ASA 3–5, $P<0.001$), have a lower performance status (46.4% vs. 53.4% were ECOG 0), be from a higher income country (90.1% vs. 83.7% were from high income countries), have a higher BMI (22.5% vs. 17.4% were obese) and have a rectal cancer (26.9% vs. 20.8%, $P<0.001$) and early stage disease (41.9% vs. 32.8% were clinical Stage I). Full demographics are shown in Table 1.

Outcomes of delayed surgery

Delayed patients did not have lower rates of complete resection, compared to non-delayed patients. In the unadjusted analysis, delayed patients were more likely to have resectable disease (93.7% vs. 91.9%, $P=0.032$) and less likely to develop new metastases (6.2% vs. 10.1%, $P<0.001$) than non-delayed patients. Changes in disease stage from baseline to pathological staging were more common in delayed patients, including both upstaging and downstaging (Table 2). Delayed patients were also less likely to have had emergency surgery (4.5% vs. 22.9%, $P<0.001$) whilst waiting for their planned surgery, mainly due to obstructive symptoms. Other indications for emergency surgery in this cohort are shown in Table S3. There were no significant differences in 30-day major postoperative complications (9.3% vs. 9.8%, $P=0.648$) or postoperative mortality rates (1.5% vs. 2.2%, $P=0.126$). After adjustment for case mix, delay was not associated with significantly lower rates of complete resection (OR = 1.18, 95% CI 0.90–1.55, $P=0.224$) (Figure 2). The full adjusted model can be found in Table S4.

Subgroup analysis

In the subgroup analysis of patients undergoing elective surgery only, delay was not associated with lower rates of complete resection (OR = 0.94, 95% CI 0.69–1.27, $P=0.672$) (logistic regression

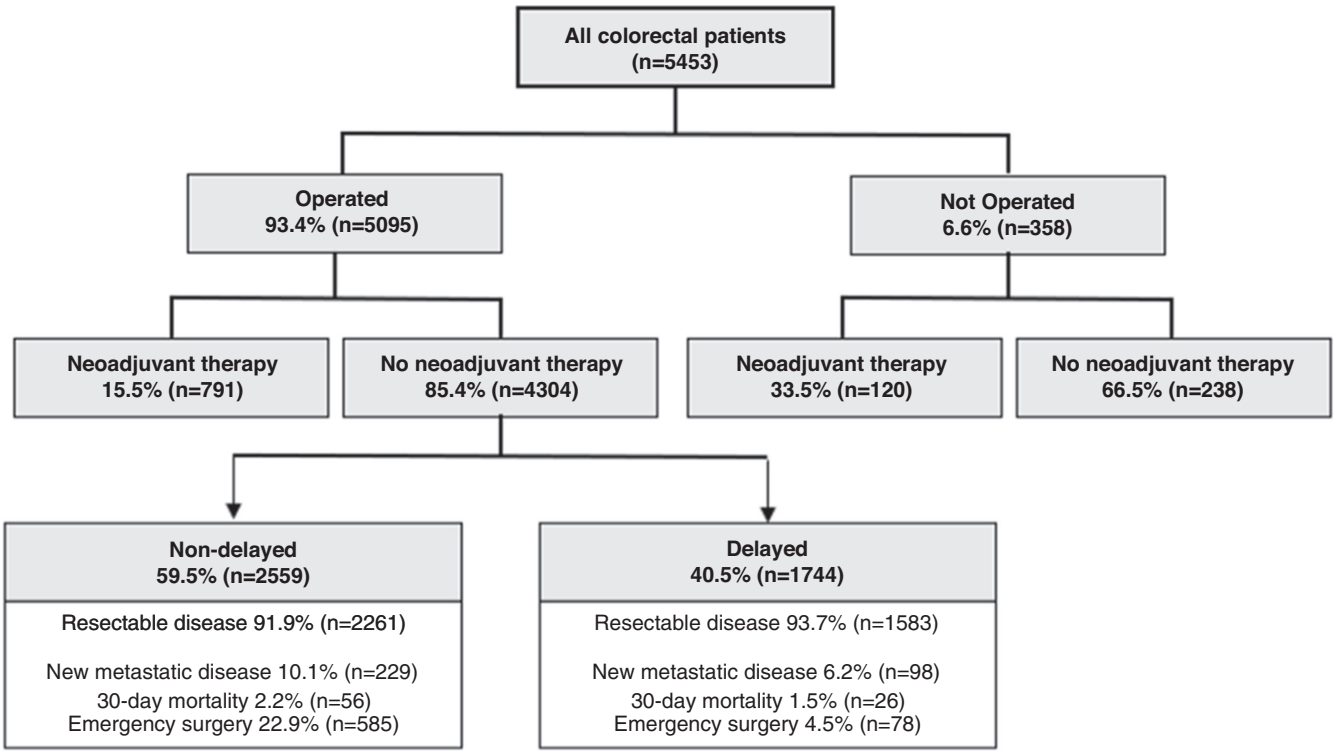


FIGURE 1 Flowchart of patient inclusion, with outcomes stratified by delay versus non-delay. Delay was defined as a time from decision to treat to surgery of >4 weeks

TABLE 1 Demographic features of patients having delayed and non-delayed surgery

		Non-delayed ($n = 2559$)	Delayed ($n = 1744$)	*P* value
Site	Colon	2028 (79.2)	1274 (73.1)	<0.001
	Rectum	531 (20.8)	470 (26.9)	
Age	<70 years	1374 (53.7)	819 (47.0)	<0.001
	≥70 years	1185 (46.3)	925 (53.0)	
Sex	Female	1162 (45.4)	720 (41.3)	0.008
	Male	1397 (54.6)	1024 (58.7)	
ASA grade	1–2	1764 (69.1)	1084 (62.3)	<0.001
	3–5	789 (30.9)	657 (37.7)	
	Missing	6	3	
ECOG score	0	1343 (53.1)	795 (46.4)	<0.001
	1–2	1101 (43.5)	867 (50.6)	
	3–4	85 (3.4)	50 (2.9)	
	Missing	30	32	
Revised Cardiac Risk Index	1–2	2382 (93.1)	1598 (91.6)	0.086
	≥3	177 (6.9)	146 (8.4)	
Body mass index	Underweight	92 (3.7)	45 (2.6)	<0.001
	Normal	1,121 (44.7)	634 (37.1)	
	Overweight	858 (34.2)	646 (37.8)	
	Obese	437 (17.4)	385 (22.5)	
	Missing	51	34	
Stage group	Stage I	806 (32.8)	709 (41.9)	<0.001
	Stage II	560 (22.8)	365 (21.6)	
	Stage III	863 (35.1)	503 (29.7)	
	Stage IV	230 (9.4)	116 (6.9)	
	Missing	100	51	
Country income	High income	2143 (83.7)	1571 (90.1)	<0.001
	Upper middle income	259 (10.1)	116 (6.7)	
	Low/lower middle income	157 (6.1)	57 (3.3)	
Approach	Open	1203 (47.1)	800 (45.9)	0.733
	Minimally invasive	1216 (47.6)	850 (48.8)	
	Converted to open	137 (5.4)	92 (5.3)	
	Missing	3	2	
Anastomosis	Yes (with defunctioning stoma)	330 (13.1)	199 (11.6)	0.316
	Yes (without defunctioning stoma)	1716 (68.3)	1187 (69.1)	
	No	467 (18.6)	331 (19.3)	
	Missing	46	27	
Anastomotic method	Stapled	1646 (80.5)	1125 (81.2)	0.641
	Handsewn	398 (19.5)	260 (18.8)	
	Missing	515	359	

Notes: Delay was defined as a time from decision to treat to surgery of >4 weeks. Data reported as *n* (%). Percentages expressed of column total. *P* values calculated using chi-squared test.

Abbreviations: ASA, American Society of Anesthesiologists classification; ECOG, Eastern Cooperative Oncology Group.

model available in Figure S2). Demographic trends of delayed patients were also similar to the main analysis (Table S5). When looking at colon and rectal cancers in isolation, a delay of 4 weeks was not associated with a reduced rate of complete resection in colon (OR = 1.33, 95% CI 0.95–1.87, $P = 0.101$) or rectal cancer (OR = 0.91, 95% CI 0.58–1.44, $P = 0.692$). Delay was not associated with poorer

TABLE 2 Unadjusted outcomes compared between delayed and non-delayed patients

		Non-delayed ($n = 2559$)	Delayed ($n = 1744$)	*P* value
Resectability	Complete resection	2261 (91.9)	1583 (93.7)	0.032
	Incomplete resection	199 (8.1)	106 (6.3)	
	Missing	99	55	
Resection margins	Positive	107 (4.4)	74 (4.4)	1
	Negative	2310 (95.6)	1599 (95.6)	
	Missing	142	71	
Progression to unresectable disease	Yes	127 (5.0)	40 (2.3)	<0.001
	No	2432 (95.0)	1703 (97.7)	
	Missing	0	1	
New metastatic disease	Yes	229 (10.1)	98 (6.2)	<0.001
	No	2036 (89.9)	1472 (93.8)	
	Missing	294	174	
Stage change (from baseline to pathology)	Downstaged	393 (18.1)	335 (22.0)	0.001
	No change	1236 (56.9)	775 (50.8)	
	Upstaged	543 (25.0)	416 (27.3)	
	Missing	387	218	
30-day mortality	Died	56 (2.2)	26 (1.5)	0.126
	Alive	2502 (97.8)	1718 (98.5)	
	Missing	1	0	
30-day major postoperative complications	Yes	251 (9.8)	163 (9.3)	0.648
	No	2307 (90.2)	1581 (90.7)	
	Missing	1	0	
Urgency	Emergency	585 (22.9)	78 (4.5)	<0.001
	Elective	1973 (77.1)	1663 (95.5)	
	Missing	1	3	

Notes: Delay was defined as a time from decision to treat to surgery of >4 weeks. Data reported as *n* (%). Percentages expressed of column total. *P* values calculated using chi-squared test.

resectability in patients with early disease only (OR = 1.20, 95% CI 0.67–2.18, $P = 0.537$) or advanced disease only (OR = 1.11, 95% CI 0.81–1.52, $P = 0.517$). Full logistic regression models for the subgroup analysis are shown in Tables S6–S9.

Sensitivity analysis of longer surgical delays

In a sensitivity analysis exploring the association of longer delays and complete resection, 59.5% (2559/4304) of patients were operated in 0–4 weeks, 25.3% (1089/4304) in 5–8 weeks, 8.9% (384/4304) in 9–12 weeks and 6.3% (271/4304) in >12 weeks from decision to surgery (all demographics available in Table S10). Longer delays were not associated with worse resectability outcomes in unadjusted (Table S11) or adjusted analyses (Table 3). Compared to patients undergoing surgery within 4 weeks of treatment decision, the odds of complete resection were not significantly different at 5–8 weeks from treatment decision (OR = 1.16, 95% CI 0.86–1.59, $P = 0.344$), at 9–12 weeks (OR = 1.40, 95% CI 0.85–2.41, $P = 0.206$) or beyond 12 weeks (OR = 1.03, 95% CI 0.62–1.80, $P = 0.920$).

DISCUSSION AND CONCLUSIONS

During the first wave of the SARS-CoV-2 pandemic, one in 15 patients did not receive their planned operation for colorectal cancer. In those who did undergo surgery, delays of more than 4 weeks did not appear to be associated with reduced rates of complete resection. This was robust to several sensitivity and subgroup analyses. Although there are inherent biases in this study design, including selection bias in those that were exposed to treatment delay, this study represents a unique natural experiment to better understand the pathobiology of survival after colorectal cancer surgery.

Whilst long-term oncological outcome data are not yet available for this cohort, these data provide important insight into the potential mechanism for the relationship between long-term survival and treatment delay. Although the previous studies show controversial findings on the impact of delay to oncological outcomes [11–14], a systematic review looking at long-term survival for patients undergoing colorectal cancer surgery 1 month and 3 months after the diagnosis showed a reduction in overall and disease-free survival with surgical delays [15]. Another multi-specialty review of delays

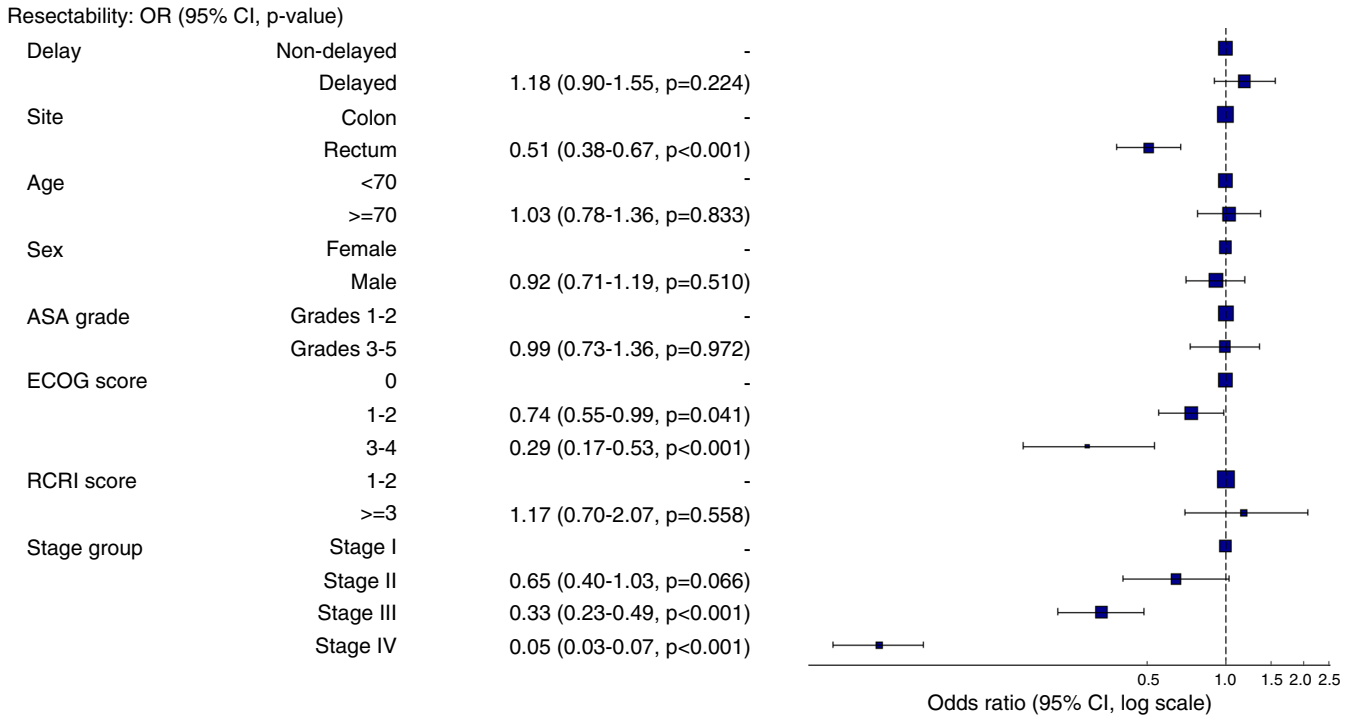


FIGURE 2 Multivariate logistic regression model exploring the association between delay to surgery and resectability, adjusting for patient and disease factors. Number in dataframe 3966, number in model 3966, missing 0, Akaike information criterion 1786.9, *C* statistic 0.776. Full model presented in Table S4. Delay was defined as a time from decision to treat to surgery of >4 weeks. Data reported as odds ratio (95% confidence interval, *P* value). OR >1 means higher odds of resectability for delayed patients, OR <1 means lower odds of resectability for delayed patients. ASA, American Society of Anesthesiologists classification; ECOG, Eastern Cooperative Oncology Group; RCRI. Revised Cardiac Risk Index

in multimodal cancer treatment showed a negative impact on long-term oncological outcomes [6]. This study suggests that a delay to surgery does not affect short-term patho-oncological outcomes. It raises the hypothesis that any decrease in long-term survival observed is unlikely to be due to initial cancer control and may be related to micro-metastatic disease spread. Patients whose surgery is delayed might therefore benefit from closer follow-up strategies for early detection of relapse and metastatic disease. Further research is required to understand the effectiveness of enhanced follow-up pathways on long-term survival, alongside their performance in different tumour biology patterns (not captured in this study).

The clinical features of non-operated patients suggest clinical selection based on a perceived high risk of surgical complications, given that these patients had worse performance status, were more likely to be underweight and had more advanced disease. Although these decisions probably aimed to protect frail patients from the additional risk conveyed by perioperative SARS-CoV-2 infection, they might have exposed some patients with advanced disease to a risk of progression to palliative disease. Changes in the management of colorectal cancer during the COVID-19 pandemic have been described by several research groups, including reduction of the number of patients receiving surgery and shorter treatment regimens [16–18]. This study provides further insight on the drivers of these clinical decisions and on which patients might have been more impacted by them.

Advanced (non-organ confined) and rectal cancers were also more likely to be operated promptly, as opposed to early and colon cancers which were more likely to be delayed. This suggests that additional features of the disease were perceived by surgical teams as justifying early surgery, which might explain why non-delayed patients had higher non-adjusted rates of progression to unresectable disease and new metastasis. Changes in disease stage observed in this study include higher rates of both upstage and downstage with increased delay. As delayed patients were more likely to have advanced disease, this might reflect lower reliability of clinical staging and imaging studies in advanced cancers, particularly when nodal disease is present [19].

The performance of elective colorectal cancer surgery within 4 weeks of treatment decision might not be feasible in many settings worldwide, even in a pre-pandemic setting [20,21]. Additionally, there might be variation in the usual timeframes from decision to surgery across settings, depending on local practices and pathways (e.g., preoperative assessment efficiency, existence of routine prehabilitation programmes). This study looked at longer delays of 8 and 12 weeks which showed no association with resectability impairment either, ensuring the generalizability of the findings.

Symptoms of obstruction, perforation or bleeding in patients awaiting elective surgery might have prompted earlier surgery, explaining why emergency surgery was more common in non-delayed patients (undergoing surgery within 4 weeks of treatment decision).

TABLE 3 Multivariate logistic regression model exploring the association between stratified delay to surgery and resectability, adjusting for patient and disease factors

		Non-resectable ($n = 297$)	Resectable ($n = 3669$)	OR (univariable)	OR (multivariable)
Delay	0–4 weeks	193 (8.2)	2154 (91.8)	–	–
	5–8 weeks	66 (6.5)	955 (93.5)	1.30 (0.98–1.74, $P = 0.079$)	1.16 (0.86–1.59, $P = 0.344$)
	9–12 weeks	19 (5.3)	338 (94.7)	1.59 (1.01–2.67, $P = 0.060$)	1.40 (0.85–2.41, $P = 0.206$)
	>12 weeks	19 (7.9)	222 (92.1)	1.05 (0.66–1.76, $P = 0.855$)	1.03 (0.62–1.80, $P = 0.920$)
Site	Colon	200 (6.6)	2846 (93.4)	–	–
	Rectum	97 (10.5)	823 (89.5)	0.60 (0.46–0.77, $P < 0.001$)	0.51 (0.38–0.68, $P < 0.001$)
Age	<70	158 (7.9)	1850 (92.1)	–	–
	≥70	139 (7.1)	1819 (92.9)	1.12 (0.88–1.42, $P = 0.358$)	1.03 (0.78–1.36, $P = 0.828$)
Sex	Female	127 (7.3)	1604 (92.7)	–	–
	Male	170 (7.6)	2065 (92.4)	0.96 (0.76–1.22, $P = 0.749$)	0.91 (0.70–1.18, $P = 0.491$)
ASA grade	1–2	187 (7.1)	2437 (92.9)	–	–
	3–5	110 (8.2)	1232 (91.8)	0.86 (0.67–1.10, $P = 0.226$)	0.99 (0.73–1.36, $P = 0.964$)
ECOG grade	0	129 (6.4)	1874 (93.6)	–	–
	1–2	144 (7.9)	1690 (92.1)	0.81 (0.63–1.03, $P = 0.090$)	0.74 (0.55–0.98, $P = 0.039$)
	3–4	24 (18.6)	105 (81.4)	0.30 (0.19–0.50, $P < 0.001$)	0.29 (0.17–0.53, $P < 0.001$)
RCRI grade	1–2	278 (7.6)	3387 (92.4)	–	–
	≥3	19 (6.3)	282 (93.7)	1.22 (0.77–2.03, $P = 0.421$)	1.18 (0.71–2.08, $P = 0.544$)
Stage group	Stage I	39 (2.7)	1418 (97.3)	–	–
	Stage II	35 (4.0)	838 (96.0)	0.66 (0.41–1.05, $P = 0.078$)	0.65 (0.40–1.03, $P = 0.066$)
	Stage III	102 (7.8)	1205 (92.2)	0.32 (0.22–0.47, $P < 0.001$)	0.34 (0.23–0.49, $P < 0.001$)
	Stage IV	121 (36.8)	208 (63.2)	0.05 (0.03–0.07, $P < 0.001$)	0.05 (0.03–0.07, $P < 0.001$)

Notes: Number in dataframe 3966, number in model 3966, missing 0, Akaike information criterion 1790.1, *C* statistic 0.776. Delay was measured from decision to treat to surgery. Data reported as odds ratio (95% confidence interval, *P* value). OR >1 means higher odds of resectability for delayed patients, OR <1 means lower odds of resectability for delayed patients.

Abbreviations: ASA, American Society of Anesthesiologists classification; ECOG, Eastern Cooperative Oncology Group; RCRI, Revised Cardiac Risk Index.

Although we presented the reasons for emergency surgery in this cohort of patients awaiting planned resection, some could have had symptoms of obstruction or other acute complication at the time of treatment decision, to whom a delay beyond 4 weeks would not be clinically acceptable. To address the selection bias that these clinical findings might have had in the length of delay from decision to surgery, we performed a subgroup analysis of patients undergoing elective surgery only, that again showed no difference in resectability with surgical delays.

This study has several important limitations. Longer-term follow-up of this cohort will be required to explore the true clinical impact of treatment delay for these patients. The second is the risk of selection bias in the comparison of delayed and non-delayed patients. We attempted to overcome this through multivariable modelling and several subgroup and sensitivity analyses, but the analysis may still be subject to residual bias from unmeasured confounders. Third, patients who remained non-operated may have had a poorer prognosis at baseline and/or may have been subject to disease progression and other cancer-related sequelae which could lead to underestimation of the impact of delay (7% of the cohort overall). Fourth, we were unable to explore the impact of treatment delay in patients with prior neoadjuvant therapy, who pose a biologically distinct treatment group. Finally, histological data were not collected and therefore we were unable to explore whether molecular subtypes or mutational status differed between the groups, and whether this impacted resection.

SARS-CoV-2 waves are not the only pressure that health systems face, and many factors can cause delays in the delivery of surgical care. These findings can inform clinical decision making, management of surgical waiting lists and patient informed consent before surgery. Guidance on management of colorectal cancer should also take these findings into account when designing follow-up strategies for patients who are operated for colorectal cancer. The possibility of performing cancer resection with a few weeks of delay without a negative impact on local control could be important for patients who may benefit from longer periods of pre-habilitation and pre-conditioning before surgery, in order to achieve a better fitness status and optimize perioperative outcomes.

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AUTHOR CONTRIBUTION

Individual contributions to this paper are listed in the appendix. The writing group and statistical analysis group have analysed, interpreted and drawn conclusions from the data. The COVIDSurg operations team, international cancer leads and dissemination committees led the conduct of the study and contributed to data curation. The listed collaborators have contributed with patient level data from their sites.

CONFLICT OF INTEREST

There are no conflicts of interest to declare.

ETHICAL STATEMENT

This study was approved in every participating country and hospital as per local requirements. National and hospital leads were responsible and guaranteed the necessary approvals ahead of data upload.

DATA AVAILABILITY STATEMENT

Data-sharing requests will be considered by the management group upon written request to the corresponding author. If agreed, de-identified participant data will be available, subject to a data-sharing agreement.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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