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Review

The impact of COVID-19 pandemic in the diagnosis and management of colorectal cancer patients

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María José Domper-Arnal*, Gonzalo Hijos-Mallada* and Ángel Lanas

***Abstract*:** The novel coronavirus disease 2019 (COVID-19) pandemic has posed an unprecedented challenge to healthcare systems worldwide, causing downscaling of almost all other activities, especially in its early stages. Currently, the availability of vaccines along with the spread of new viral variants has modified the epidemiology of the disease, and the previous activity is being gradually resumed in most healthcare facilities. In this review, we have summarized the influence of the COVID-19 pandemic in the diagnosis and management of colorectal cancer (CRC) patients. Population-based screening with either colonoscopy or fecal occult blood tests has proven to reduce CRC incidence and mortality, so screening programs have been implemented in most western countries. However, during the first COVID-19 wave, most of these programs had to be disrupted temporarily. In this review, we have thoroughly analyzed the consequences of these disruptions of screening programs as well as of the forced delays in diagnostic and therapeutic services on CRC prognosis, although its exact impact cannot be exactly measured yet. In any way, strategies to minimize its effect, such as catch-up strategies expanding the colonoscopy capacity or using fecal occult blood concentration and other risk factors to prioritize patients, are urgently needed. The COVID-19 pandemic has also led to a change in CRC patient presentation, with an overall temporary decreased incidence due to postponed diagnoses, but with more patients presenting in need of an emergency admission or with symptoms. Finally, changes in treatment approaches in CRC patients have been reported during the pandemic, namely a drop in the proportion of laparoscopic surgeries or a rise in short-term radiotherapy courses. We have therefore aimed to summarize the available evidence to guide the healthcare professionals treating CRC patients to choose the best treatment options in the current pandemic situation.

Keywords: colorectal cancer, COVID-19, prognosis, screening

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Correspondence to:
María José Domper-Arnal
Service of Digestive Diseases, University Clinic Hospital, San Juan Bosco AV 15, Zaragoza 50009, Spain

Aragón Health Research Institute (IIS Aragón), Zaragoza, Spain

CIBERehd, Madrid, Spain
mjdomperar@salud.aragon.es

Gonzalo Hijos-Mallada
Service of Digestive Diseases, University Clinic Hospital, San Juan Bosco AV 15, Zaragoza 50009, Spain

Aragón Health Research Institute (IIS Aragón), Zaragoza, Spain
gonzahijos@gmail.com

Ángel Lanas
Service of Digestive Diseases, University Clinic Hospital, Zaragoza, Spain

Aragón Health Research Institute (IIS Aragón), Zaragoza, Spain

CIBERehd, Madrid, Spain

University of Zaragoza, Zaragoza, Spain

*These authors are both first authors and corresponding authors of this article.

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, with almost 2 million new cases estimated to be diagnosed in 2020, and the second in terms of mortality.[1] The highest rates are seen in developed countries, whereas the incidence is rising in developing countries in parallel with economic progress, so its global incidence is projected to increase in the following years (around 60% by 2030).[2,3] CRC screening has been proven to reduce its incidence and mortality in average-risk population (asymptomatic population of 50–70 years without other risk factors).[4] Several screening strategies may be used, but most countries have implemented screening programs based on fecal occult blood test, followed by colonoscopy if positive. Randomized controlled trials have proven a reduction of CRC mortality by 9–22% among patients screened by guaiac-based fecal occult blood tests,[4–6] being a cost-effective strategy.[7] The quantitative fecal immunochemical test (FIT) is the most used method for CRC screening in most western countries, forasmuch as it has demonstrated greater adherence[8] and observational data strongly suggest

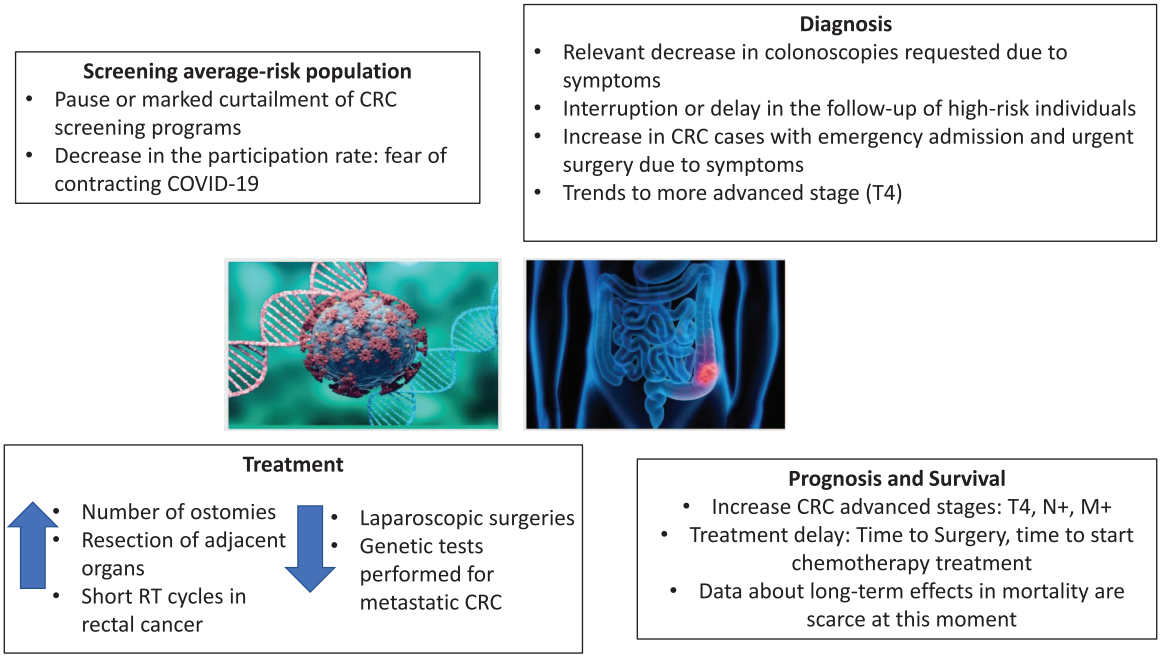

Figure 1. COVID-19 and CRC. Summary of the different interaction scenarios.
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CRC, colorectal cancer; RT, radiotherapy.

a higher reduction in CRC mortality compared with guaiac-based fecal occult blood tests.[9] However, the implementation of these screening programs had markedly increased the workload of most endoscopic units, with insufficient colonoscopy availability in many public health systems.[10]

In early December 2019, the first case of the novel coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, was reported in China.[11] COVID-19 has widely spread throughout the world, and it was declared a pandemic by the World Health Organization in March 2020. The spread of the pandemic has posed an unprecedented challenge to the healthcare systems worldwide, causing the downscaling of almost all other clinical activities,[12] including the already overwhelmed endoscopic units. The COVID-19 pandemic not only has strained endoscopic units involved in CRC diagnosis, but also surgical, anesthesiologist, and oncological teams implicated in CRC patient's treatment. Moreover, ensuring the safety of mostly immunocompromised cancer patients and minimizing transmission between healthcare workers have also become priorities in pandemic times. These facts have influenced the management of CRC patients, inducing changes in clinical practice, not always based on solid evidence.

This review aimed to report the impact of the COVID-19 pandemic in different aspects of the diagnosis and management of CRC patients (Figure 1), summarizing the available evidence to guide healthcare professionals treating CRC patients in the current pandemic situation.

Impact of COVID-19 pandemic in CRC screening

The COVID-19 pandemic initially forced a temporary pause or marked curtailment of CRC screening programs around the world.[13–16] As a result, average-risk population during this period were unable to participate in these programs or were subject to long delays after a positive FIT result, which is associated with an increased risk of advanced stage CRC.[13,17] Data regarding the effects of the discontinuation of CRC screening programs, reported by different health care systems worldwide, are summarized in Table 1.

After the first wave of the pandemic, and with the arrival of vaccination programs, the pressure posed by the COVID-19 pandemic to endoscopic

Table 1. Impact of COVID-19 on CRC screening programs worldwide.

Country and screening method	Design of the study	Data reported	Specifications and limitations
Italy, FIT (20 μg/g)[18]	➢ Retrospective study. Comparing colonoscopy results between March and May 2020 and the same period in 2019	➢ Decreased number of colonoscopies (3.9-fold) with low acceptation rate (43.8% of patients with positive FIT) ➢ More CRC (8% *versus* 1%) and high-risk adenomas (47% *versus* 25%) were detected in the lockdown group	➢ 'COVID-free' hospital: patients and staff with ongoing COVID-19 testing ➢ Limitation: low sample size ($n = 60$ in lockdown group, $n = 238$ in control group)
Netherlands, biennial FIT (47 μg/g)[19]	➢ Observational study comparing the outcomes of CRC screening program between 2020 and previous years	➢ Total number of FIT invitations sent decreased 23.5% ➢ Participation rates of FIT and colonoscopy in the months just before and during the disruption of the screening program were significantly lower but returned to normal levels afterwards ➢ 31.2% of patients with advanced neoplasia were estimated to be not diagnosed	➢ CRC screening program was disrupted from 16 March to 3 June ➢ Limitations: not individual data available (analysis could not be adjusted by age or screening round)
Australia, biennial two-sample FIT (20 μg/g)[20]	➢ Modeling study to estimate the long-term impact of the disruption of CRC screening on its incidence and mortality	➢ A 6-month disruption would result in 0.6% relative increase in incidence and 1% increase in mortality between 2020 and 2050	➢ Limitations: not reporting real outcomes, only model projections
Canada, biennial FIT (20 μg/g)[20]	➢ Modeling study to estimate the long-term impact of the disruption of CRC screening on its incidence and mortality	➢ A 6-month disruption would result in 0.3% relative increase in incidence and 0.4% increase in mortality between 2020 and 2050	➢ Limitations: not reporting real outcomes, only model projections
Belgium, biennial FIT (15 μg/g)[21]	➢ Observational study describing the effects of the two first COVID-19 waves (March–June 2020, August–December 2020) on participation and coverage of screening programs (CRC, breast and cervical)	➢ Invitation coverage remain stable (98.5% in 2020), as well as people screened within 40 days after invitation (−2.6%, not significant differences compared with 2019), used as an indicator of willingness to screen	➢ CRC screening program was disrupted from 22 March to 23 May 2020, and from 15 November to 28 November 2020. ➢ Limitations: not reporting data on CRC diagnosis, staging and outcomes
Spain, biennial FIT (20 μg/g)[22]	➢ Observational study comparing the outcomes of the CRC screening program between 2020 and 2019	➢ 43% of the target population did not receive the invitation in 2020. ➢ Participation rate decreased by 5.1% and colonoscopy adherence by 8.9% from January to March 2020. Both returned to normal levels afterwards. Time interval between a positive FIT and colonoscopy was longer in 2020 ➢ A lower number of CRC cases were diagnosed (85 *versus* 156), but the proportion of advanced stages increased in 2020 (43.5% *versus* 38.5%)	➢ CRC screening program was disrupted from 12 March to 1 September 2020 ➢ Limitation: only included population of an urban location (Barcelona)

(Continued)

Table 1. (Continued)

Country and screening method	Design of the study	Data reported	Specifications and limitations
Taiwan, biennial FIT (20 μg/g)[23]	• Observational study comparing the outcomes of the CRC screening program from December 2019 to April 2020, with previous periods	• Decreased screening uptake (88.8% *versus* 91.2–92.7%). • Significantly lower colonoscopy acceptance (66.1% *versus* 70.2–77.5%), with significantly higher rate of rescheduling or cancelation	• CRC screening was not disrupted in Taiwan • Limitation: single center study, external validity may be limited
United States, variable (FIT, colonoscopy)[24]	• Observational study comparing screening colonoscopies performed in January–April 2020 with the same period previous year	• CRC screening colonoscopies decreased by 5.6% in February 2020. This drop increased up to 39.4% and 84.5% in March and April 2020	• Multicenter study • Limitations: no data regarding previous use of FIT, or screening acceptance
Austria, variable (FIT, colonoscopy)[25]	• Retrospective study comparing screening colonoscopies performed between March and September 2020 with the same period previous year	• The mean rate of colonoscopies per week was significantly lower (594.5 *versus* 808.35). • No significant differences were found in the advanced adenoma or CRC detection rate. Significantly less non-advanced adenomas were detected	• Lockdown from 16 March to 9 April 2020. • Limitations: no data available regarding previous use of FIT or participation

COVID-19, coronavirus disease 2019; CRC, colorectal cancer; FIT, fecal immunochemical test.

units is diminishing. Therefore, CRC screening programs have been gradually resumed. In fact, a recently published European Society of Gastrointestinal Endoscopy guideline recommends a return to full gastrointestinal endoscopy procedure capacity in those areas with an ongoing vaccination policy, which applies to most western countries.[26] Indeed, prior to the vaccination era, solid evidence was available supporting that the risk of SARS-CoV-2 transmission in gastrointestinal endoscopic units was considerably low if personal protective equipment was properly used, suggesting that a full recovery of endoscopic units should be considered.[27,28]

In any way, strategies to restructure these screening programs to mitigate the effects of its previous discontinuations on CRC staging and survival are still urgently needed.[29] To catch-up to this backlog of screening colonoscopies, it has been estimated that the colonoscopy capacity should be expanded up to 150%.[30] Indeed, in the Netherlands, after the CRC screening halt, colonoscopy availability was expanded up to 120%, achieving a catch-up effect in the second part of 2020.[31] However, increasing the colonoscopy capacity is not possible for every health system, so it has been suggested that increasing FIT cutoff or using specific risk factors (male sex and advanced age) could be an effective strategy to prioritize access to colonoscopies and reduced the number of CRC or advanced adenomas underdiagnosed in a CRC screening program, compared with randomly reducing the number of population screened.[32] Colon capsule endoscopy has also been advocated as an alternative for CRC screening after a positive FIT, as it can be performed as an out-of-clinic procedure, avoiding patients to attend medical facilities, and it has demonstrated a high diagnostic accuracy (area under receiver operating curve 0.963 for polyps at least 6 mm); hence, it may be used to filter patients in need of a colonoscopy.[33] In fact, current CRC screening guidelines recommend this technique as a valid alternative for individuals unable or unwilling to undergo colonoscopy.[34] Computed tomography colonography is also recommended in this setting. However, it provides a lower sensitivity compared with capsule endoscopy, especially for serrated and flat colorectal polyps diagnosis.[34,35] Be that as it may, some authors have also suggested this technique as a screening tool during the pandemic.[36] Another key point is the effect that the pandemic may have had on

participation in screening programs, as the asymptomatic population may be less willing to seek diagnostic care due to fear of contracting COVID-19.[13] It is crucial to ensure the participation rate returns to a similar figure as it was prior to the pandemic, as a 25% or 50% decrease in this rate has been estimated to increase CRC incidence by 0.2–0.9% and deaths by 0.6–1.6%, compared with data previous to the pandemic.[20]

Impact of COVID-19 pandemic in CRC diagnosis outside screening programs

Apart from the CRC screening programs, the COVID-19 pandemic has had a substantial impact on the timely diagnosis of CRC in all the other settings. In England, the '2-week wait' referral pathway has been established since 2000 so that patients with 'red-flag' symptoms suggestive of CRC could be evaluated within this period of time, to allow early diagnosis and treatment.[37] Data from this country comparing care in 2019 with that in the first 10 months of 2020 showed that patterns of referral for suspected CRC changed radically due to the COVID-19 pandemic, with a 63% relative reduction of 2 weeks wait referrals in April 2020, compared with the monthly average in 2019, along with a 66% reduction of the referrals meeting this timeframe target. Over the following months, there was a gradual recovery. However, a 23% reduction of 2-week wait referrals was detected considering the period from April to October 2020. In total, they calculated that across this 7-month period, 3500 fewer patients than in 2019 were diagnosed and treated for CRC in this setting.[38]

To mitigate the effects on CRC prognosis of the delays in the 2-week referral pathway, a modeling study performed in this same population suggested that the use of FIT with a cutoff of 10 μg/g (cutoff suggested by NICE guidelines for symptomatic patients,[37] although a higher cutoff of 20 μg/g has been proven to provide a similar diagnostic accuracy with less endoscopic procedures required[39]) would avoid the 89% of deaths attributable to diagnostic backlogs while reducing colonoscopy requirements by 80%.[40] However, investigations of all patients with results above that level would require a large number of examinations, so during COVID-19 waves it has been advocated to use higher cutoffs, with fecal hemoglobin concentrations higher than 100 μg/g warranting an urgent colonoscopy whereas values between 10 and 100 μg/g may have the endoscopic examinations deferred (not omitted),[41] as fecal hemoglobin concentration directly correlates with the risk of advanced neoplasia and CRC, both in screening and symptomatic patients.[42] Although it allows to prioritize high-risk patients and to avoid normal colonoscopies, it is important to highlight that an increase in the FIT positivity threshold also entails a risk of missing relevant pathology. In a recent meta-analysis evaluating the diagnostic yield of FIT in symptomatic patients, sensitivity and specificity for CRC diagnosis were 87.5% and 80.5% using a cutoff 10 μg/g cutoff. At higher positivity threshold of 100 μg/g, sensitivity decreased to 68.1% (which implies missing 20% of the CRC cases which would have been diagnosed with the 10 μg/g cutoff), along with an increase in specificity (93.4%).[43]

It should be noted that the COVID-19 pandemic has also affected the follow-up of high-risk individuals previously on a specific screening program, such as genetic predisposition syndromes.[44] FIT has also been proposed as a method of risk stratification in patients with Lynch syndrome, with a cutoff of 10 μg/g, during the periods of maximum strain to the endoscopic units.[45]

Impact of COVID-19 in CRC incidence and presentation

Overall, the incidence of cancer diagnosis (including all cancers) showed a statistically significant decrease of 17.2% in the first year after the declaration of the state of emergency in Spain (from 13 March 2020 to 13 March 2021), compared with the same period during previous year. Regarding only CRC cases, the incidence was 16.9% lower in this period. There were no differences in the incidence comparing previous years (2018–2019 and 2017–2019) so that decreased CRC incidence was attributed to the impact of the pandemic (disrupt of the screening program and lower endoscopic resources) implying underdiagnosed CRC cases, diagnostic delays and a worse prognosis.[46] Similarly, the incidence of CRC dropped 30% from March to May 2020 (corresponding to the lockdown period) and persisted a 9% lower from June to September 2020, compared with the average in 2018 and 2019 during the same period, in a cross-sectional study performed in an urban area of France.[47]

As a result of the temporary disruption of CRC screening programs, the proportion of CRC cases

diagnosed by presenting with abdominal symptoms increased during this period. This short-term effect of the COVID-19 pandemic on CRC patient presentation has been reported consistently by several studies. A retrospective study performed in Japan analyzed all CRC cases that underwent surgery during a 4-month period before and after the declaration of the state of emergency (17 April 2020), comparing the outcomes of CRC patients operated during the same period in the previous year. No significant changes were observed in the number of CRC patients undergoing surgeries (CRC incidence),[48] being this a surprisingly different finding compared with other studies which consistently report a decrease in CRC incidence during COVID-19 period.[46,47,49,50] This difference may be related to different COVID-19 policies (as Japan has had a low burden of COVID-19 cases compared with European countries) or with the study population, as other studies performed in this country have also reported a decreased CRC incidence in Japan during 2020.[51,52] Nevertheless, the number of patients who needed an emergency admission (38.7% *versus* 13–18%) and that of patients with obstructive CRC (39% of patients presented with complete obstruction, compared with 15% before the state of emergency) were significantly increased.[48]

Another study with an analogous design in Spain, which compared new CRC diagnosis between March and June 2020 and during the same time period in 2019, reported that the CRC incidence decreased by 38% in 2020 (111 *versus* 58 patients). Significantly more patients in the COVID-19 period were diagnosed in the emergency setting (12.1 *versus* 3.6%) and also most patients were diagnosed by presenting abdominal symptoms (94.8%), with only 5.2% diagnosed in a CRC screening setting (these figures were 66.7% and 33.3% in the pre-COVID period).[49] Data from the United Kingdom also compared outcomes of CRC cases diagnosed during 2020 with the same population in 2019 and 2018. This study concluded similarly that more patients with CRC presented at emergency rooms (36% *versus* 28.6%), with an increased rate of bowel obstruction (8.6% *versus* 4.3 %) and an increased frequency of T4 cases (34.5% *versus* 27.1%). Significantly more urgent surgeries were performed due to CRC in this period (28.1% *versus* 19.5%). Only a short delay (4 months) in referral and diagnosis was enough to detect an increase in the proportion of patients presenting with a large bowel obstruction in this population.[50] These are relevant data as CRC patients in need for an urgent surgery have a significantly worse prognosis when compared with those managed by elective surgeries.[53]

Impact of COVID-19 pandemic in CRC treatments

The COVID-19 pandemic has also affected CRC treatment trends. Clinical practice guidelines have been issued by Surgery[54] and Oncology Societies[55,56] with an effort to guide healthcare professionals treating CRC patients to prioritize interventions during the pandemic. A study previously mentioned,[38] conducted in England encompassing the first wave period of the pandemic, reported a marked change in surgical practice for CRC treatment. The proportion of laparoscopic surgeries fell from 59% in 2019 to 25% in April 2020. Likewise, the operations resulting in stoma formation increased from 44% in 2019 to 56% in April 2020.[38] Data from Korea similarly showed that a significantly lower percentage of patients underwent laparoscopic surgery (81.2%) from March to September 2020 compared with previous years (88%). Besides, a higher proportion of patients received stoma formation (4.1 *versus* 1.8%) and a higher number of patients requiring resection of adjacent organs (4.8% *versus* 2.8%) were detected during the COVID-19 period.[57] Conversely, studies with an analogous design performed in Italy[58] and Denmark[59] did not found differences in the use of laparoscopic surgery during the COVID-19 first wave. This decreased use of the laparoscopic approach has been a topic of outstanding controversy during the COVID-19 pandemic, as it was hypothesized that this approach may increase the risk of virus aerosolization and therefore transmission. Even though evidence supporting this statement is scarce, it has led to a decreased in laparoscopic surgeries in several areas (a 42.5% of respondents of an international survey, with participation of more than 80 countries, reported a change in their surgical approach to laparoscopic/robotic to open during the first COVID-19 wave[60]) depriving patients from the advantages of this approach. Recently published guidelines have addressed this area of contention, recommending that either laparoscopic or open approach may be used in COVID-19 patients, with a decision of the technique based on the usual clinical factors. In the same vein, the laparoscopic approach should be undertaken even in COVID-19 confirmed patients if consider the preferred option.[61]

In rectal cancer, radiotherapy alone or in combination with chemotherapy or surgery represents part of the gold standard of treatment, especially in the early stages. During COVID-19 waves, clinical practice guidelines advocated for short-course radiotherapy (5 sessions in 5 consecutive days) instead of a long course, with the aim of reducing the hospital admissions without harming the effect of radiotherapy.[55,56] Timing of surgery is recommended to be delayed until 4–8 weeks after radiotherapy, as it was associated with a reduction in postoperative morbidity and around 10% of patients may be offered an organ preservation strategy, avoiding surgery if complete response is achieved.[56] In England, a 44% relative increase in radiotherapy courses was registered in April 2020 compared with the same month in 2019, although falling by July below the 2019 average. This increase was justified by short-course radiotherapy treatments delivered, representing 63% in April 2020 (in contrast with 20% in April 2019). In the following months until October 2020, the use of short-term radiotherapy prescriptions remained above 2019 average.[38]

Adjuvant chemotherapy has an impact on survival rates of high-risk stage II and stage III CRC patients.[62] Current guidelines recommend that the start of the treatment should not be postponed more than 6 weeks and the interval between cycles should not be prolonged, even during COVID-19 waves.[55] It is important to continue performing microsatellite instability testing, as for CRC cases with high microsatellite instability, the benefits from a 5-fluorouracil based adjuvant therapy are limited and capecitabine may be a valid option.[55] Moreover, RAS testing should be carried out in every patient diagnosed with metastatic CRC, as it is a negative predictive biomarker for EGFR antibodies therapy, as well as BRAF mutational status.[63] It has been reported that during both the first wave of COVID-19 pandemic and the first months after it, the number of genetic tests performed for metastatic CRC was significantly reduced (by more than 40%) in the reference center for cancer center and high-risk individuals in Serbia.[64]

Impact of COVID-19 pandemic in CRC prognosis and survival

CRC survival relies mainly on the stage of the disease at diagnosis as well as on the timely and prompt treatment, and the COVID-19 pandemic is having a negative impact in both aspects. A retrospective study previous to the COVID-19 pandemic showed that the interval between diagnosis and start of treatment has a negative effect in CRC survival, with a progressively increased risk of death in parallel with the length of this period [hazard ratio (HR): 1.51 if more than 30 days; HR 1.64 if more than 150 days delay compared with those who received treatment within 30 days following CRC diagnosis).[65] Likewise, a systematic review found that a delayed elective CRC surgery was associated with poorer overall survival, with an HR of 1.13 for 1-month delay and an HR of 1.53 for a 3-month delay.[66] Moreover, a meta-analysis showed that a delay of more than 8 weeks between surgery and adjuvant chemotherapy is associated with increased mortality (HR: 1.2),[67] being the benefit minimal or completely lost if this delay progress up to 6 months.[62]

After the onset of COVID pandemic, several studies have brought to spotlight the negative influence of the pandemic in this setting. A Japanese retrospective study compared the stage at diagnosis among patients diagnosed with several gastrointestinal cancers, between March and December 2020 and a pre-COVID period (January 2017–February 2020). Significant differences were found both in the incidence of CRC (13.47% lower in the pandemic period) and in the CRC stage at diagnosis, with a decreased incidence of stages 0-II (32–35% reduction compared with the pre-COVID period) along with an increase in stage III CRC cases (68.4% increase).[52] In the same way, a recently published Italian multicentric study found that CRC patients undergoing surgery in 2020 presented more frequently T4 stages and multiple liver metastases compared with the same cohort from 2019.[68] A modeling study performed in Canada estimated that only a 3 or 6 months interruption of the CRC screening program would lead to 1100 or 2200 more CRC cases, with over 60% at an advanced stage, implying an increase in CRC mortality in the 2020–2029 period whose magnitude would be determined by the timing of resumption of the screening program (from 0.49% excess of CRC mortality if immediate restoration to 1.2% assuming a 2-year transition period).[69] Conversely, a multicentric study performed in the Netherlands tried to approximate the impact of CRC screening disruption using real-life data, monitoring the incidence and stage distribution of CRC cases diagnosed in individuals aged 55–75 years (irrespective of the indication) before and after the

pandemic. CRC incidence in this population decreased from April to June 2020 (being this drop as high as 42% in April 2020), albeit this was partially compensated in the second half of the year (in December 2020, new CRC cases were 24% higher than expected). Regarding the staging, 48% of the incidence decrease was due to stage I CRC, in contrast to stage IV cases which remain stable, so the authors conclude that this temporary suspension of the Dutch CRC screening program would have a minimal long-term effect on CRC mortality.[31]

Circulating tumor DNA (ctDNA) is a new surrogate marker of disease burden. In non-metastatic CRC, the detection of ctDNA after surgery or after adjuvant chemotherapy has been associated with minimal residual disease, resulting in high recurrence rates and a lower survival.[70] In a recently published randomized control trial, ctDNA measurement was compared with standard clinicopathological features to decide which patients with stage II CRC should be treated with adjuvant chemotherapy. A ctDNA approach significantly reduced the proportion on patients treated with adjuvant chemotherapy (15% *versus* 28%) without compromising recurrence-free survival (93.5% *versus* 92.2% at 2 years).[71] Repeated measurements of this biomarker after CRC treatment have been suggested to detect recurrence earlier that radiology or laboratory examinations.[72] Its measurement before surgery to identify high-risk stage II or III patients has also been studied, although currently available evidence is not strong enough to make recommendations.[73] In the same line, in metastatic CRC, ctDNA concentration harbors prognostic information, helping clinicians to predict response to systemic therapies.[74] A cohort study including 80 patients with metastatic CRC (half diagnosed prior the first COVID-19 lock down in France – March to May 2020) reported that the median ctDNA was significantly higher in patients who were diagnosed after the lockdown. Patients with higher ctDNA concentration had lower median survival (14.7 *versus* 20 months).[75]

Regarding the influence of treatment delays, a study analyzing all the CRC cases diagnosed in two hospitals within 2020 ($n = 107$) reported that 53% of patients suffered from treatment delay (defined as more than 2 months from the first specialized visit to the start of oncologic therapy). Almost 40% of patients with treatment delay were diagnosed with cancer upstaging at the moment of start treatment (odds ratio: 3.27) compared with patient who received timely treatment.[76] A modeling study performed in England estimated the effect of a 3–6 months delay of the oncologic surgery on the survival (age specific and stage specific) of different cancers, balancing it with the outcomes of an equivalent volume of COVID-19 hospitalizations. For CRC, the survival was markedly affected even by these modest delays to surgery, with a reduction in the 5-year net survival around 30% for stage III CRC in all age groups. Nevertheless, it should be mentioned that only in the specific group of older patients (aged >70 years) with early stage CRC, the hypothetical impact of COVID-related mortality was higher than the impact of 3–6 months surgical delay. They concluded that cancer diagnostic and surgical pathways must be resumed with rapid catch-up to the backlog accrued.[77]

Therefore, the adjournments in diagnosis (in both screening and symptomatic populations) and access to treatments would have a detrimental impact in CRC prognosis, although the magnitude of this impact is still not completely known. Regarding the effect of the disruption of CRC screening programs, a study performed in Italy analyzed the effect of mortality due to up-stage CRC patients associated with different delay spans of the screening program. They conclude that delays up to 4–6 months do not affect the performance of screening programs, but a sustained backlog beyond 6 months would significantly increase the CRC cases detected in advances stages, along with a significant increase in the total number of deaths at 5 years (12%) if the delay persists more than 1 year. This increase in mortality was 5.1% for 7–12 months delays, being not significant,[78] supporting the hypothesis of the previously mentioned Dutch study.[31] In symptomatic patients, a modeling study analyzing the effect of delays in the 2-week wait referral pathway on different cancer survivals reported that CRC was the cancer in which the impact of this delay was higher in terms of attributable lives lost, with a reduction in 10-year net survival ranging from 10–22% in the 30–39 age group to 16–36% in the >80 age group assuming a 3-month delay in this pathway.[79] Another modeling study considering all the cancer cases diagnosed of four major tumors (breast, colorectal, lung, and esophageal) estimated a 15.3–16.6% increase in the number of deaths due to CRC up to 5 years after diagnosis, considering different scenarios with variable availability of endoscopic resources.[80]

A multicentric study conducted in France recently published has reported real-life data of 1-year survival of CRC cases diagnosed within 2020 compared with 2018 and 2019 cases. The 1-year survival rates for CRC undergoing surgery were 94% in 2018–2019, 93% in 2020 in patients without SARS-CoV-2 infection, and 76% in 2020 patients with SARS-CoV-2 infection, being infection related to the SARS-CoV-2 virus an independent risk factor of increased mortality (HR: 3.78). The 1-year survival rates for CRC patients who received other treatments were 64%, 66%, and 27%, respectively. No significant differences were found regarding CRC staging or delay to treatment. The authors, therefore, concluded that the worse 1-year survival rate was attributable to the infection itself rather than to the impact of the pandemic on the health system or tumor stage.[81] However, real-life data with longer follow-up are needed to confirm this interesting finding as other studies previously mentioned have reported changes in CRC staging[52] and treatment delays[76] associated with the pandemic, so this finding may differ if analyzed in other populations.

Limitations

This review has focused on data from developed countries, as more compelling evidence on the effects of the COVID-19 pandemic on CRC patients is available. In these populations, CRC incidence is higher (around two-thirds of all cases occurring in cases with high or very high human development index), but it was stabilizing or declining prior to the COVID-19 pandemic forasmuch as the roll-out of population-based screening programs and changes toward healthier lifestyle choices.[1–3] Rapid increases in CRC incidence and mortality were being observed in low-income and middle-income countries prior to pandemic onset. Evidence regarding the influence of COVID-19 in CRC patients care in these areas is scarce and hence has almost not been mentioned in this review. Indirect evidence based on an international survey suggested that the pandemic has had a negative influence, especially in screening and diagnostic services in these areas. These health systems are likely less prepared to overcome this health crisis compared to high-income countries, so the consequences of the pandemic on the emerging number of CRC cases in these populations are still to be determined and may be devastating.[82]

Furthermore, the COVID-19 pandemic emerged 2 years ago, and its evolution is difficult to anticipate as it probably would be variable across different world areas regarding vaccination availability and spread of viral variants. Therefore, data regarding its long-term influence on CRC patients only can be based on modeling studies,[20,40,69,77,79,80] whose ability to predict the pandemic outcomes in this setting is still to be confirmed.

Conclusions

The COVID-19 pandemic is still active, and since the beginning of 2020 has led health systems worldwide to complex challenges. In this review, we have summarized its deleterious impact in CRC diagnosis both in population screening programs[13,14] and in symptomatic patients,[38] eliciting temporarily decreased incidence due to a postponed diagnosis in many CRC cases, as well as an probably increase in CRC mortality (not yet well established) in the following years.[80] Efforts to mitigate this survival decline are needed, mainly focusing on catching-up CRC screening programs and resuming at least the previous colonoscopy workload in the endoscopic units to meet the demands of screening and diagnostic colonoscopies backlog. Using surrogate biomarkers such as FIT, as well as stratification by other risk factors,[32,40] may be useful strategies to prioritize patients with higher risk while resuming the normal endoscopic activity, to minimize this forthcoming increase in CRC mortality by detecting the cases with a higher risk.

Regarding CRC treatment, although in the early stages of the pandemic it was believed that laparoscopic approach may increase the risk of transmission,[60] there is no evidence supporting this fact so the decision of the surgical technique should be based on the same clinical factors used prior the pandemic.[61] Elective surgery should not be delayed more than 4–6 weeks if possible.[55,66] Likewise, adjuvant chemotherapy should not be delayed more than 6 weeks if indicated[55] and short-course radiotherapy may be preferred for neoadjuvant therapy in rectal cancer.[56]

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication
Not applicable.

Author contribution(s)
María José Domper-Arnal: Conceptualization; Methodology; Supervision; Writing – review & editing.

Gonzalo Hijos-Mallada: Conceptualization; Investigation; Methodology; Writing – original draft.

Ángel Lanas: Conceptualization; Formal analysis; Methodology; Supervision; Writing – review & editing.

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ORCID iDs
María José Domper-Arnal https://orcid.org/0000-0002-2584-6614

Gonzalo Hijos-Mallada https://orcid.org/0000-0003-2743-9593

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