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How the COVID-19 pandemic has affected the colorectal cancer screening in Italy: a minireview.

COVID-19 and colorectal cancer screening in Italy

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Abstract

The COVID-19 pandemic has caused detrimental effects on many aspects of healthcare practice. Screening programs for the commonest malignancies, namely colorectal cancer (CRC), breast cancer and cervical cancer have been discontinued or interrupted since the beginning of restriction measures aimed to limit transmission of the new coronavirus infection. Robust evidence exists in favour of the role of screening campaigns in reducing mortality from CRC. In fact, the majority of pre-malignant lesions of the colon and rectum can be diagnosed with colonoscopy and treated by endoscopic or surgical resection. Besides, colonoscopy screening allows the diagnosis of CRCs in their pre-clinical stage. Italy was one of the first European countries where a high level of COVID-19 infections and deaths was observed, and one of the first where lockdowns and strict measures were adopted to reduce the risk of COVID-19 diffusion among the population. A systematic review of the literature was performed, including the PubMed, Scopus and Web of Sciences databases, with the aim of critically evaluating the impact of the COVID-19 pandemic on CRC screening in Italy. We found that reduction of CRC screening activity surpassed 50% in most endoscopic units, with almost 600,000 fewer CRC screening exams conducted in the first 5 mo of 2020 *vs* the same period of 2019. While the consequences of the discontinuation of endoscopy screening for the prognosis and mortality of CRC will be evident in the next few years, recent data confirm that CRC is currently treated at a more advanced stage than in the pre-COVID era. Since delays in CRC prevention and early diagnosis may translate to increased CRC-specific mortality, world healthcare systems should adopt strategies to maintain the regularity of CRC screening during subsequent peaks of the COVID-19 pandemic or future events that might hamper screening programs.

Key Words: COVID-19; Colorectal cancer screening; Italy

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the colorectal cancer screening in Italy: a minireview.. *World J Gastrointest Oncol* 2022; In press

Core Tip: Screening is a key component of colorectal cancer control. As in the rest of the world, the COVID-19 emergency has interrupted the regular delivery of cancer screening services in Italy. As a consequence, significant delays in the diagnosis and treatment of malignant and pre-malignant lesions have occurred, with possible effects on disease prognosis. Screening activity has gradually resumed after the first wave of the pandemic. The healthcare system is called on to be prepared to prevent the potential suspension of new rounds of screening during the COVID-19 pandemic or future extraordinary events that might hamper screening programmes.

INTRODUCTION

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Introduction

¹⁰ Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males, the second in females and the second leading cause of cancer death. Although incidence and mortality vary between countries, according to GLOBOCAN estimates, worldwide, the year 2020 saw ²² 1.93 million new CRC cases diagnosed and 0.94 million deaths caused

by CRC. The incidence of the disease is increasing in high-income countries, where it has traditionally been higher, as well as in middle- and low-income countries [1,2]. Robust evidence exists about the role of screening programmes in reducing mortality from CRC. CRC screening includes a faecal occult blood test (FOBT) to detect haemoglobin in blood that may originate from a neoplastic or pre-neoplastic lesion, as well as colonoscopy. The latter allows either biopsy of early CRC or lesion removal at the time of the test.

In the last 2 years, population screening programmes for the commonest cancers have been devastated by the spread of the COVID-19 pandemic [3-7]. In fact, screening has been deprioritized as healthcare resources have been reoriented toward treatment and prevention of the new coronavirus infection. Besides, many people have avoided hospitals and screening services for fear of contracting COVID-19.

Italy was one of the first countries in Europe to be affected by COVID-19, and measures taken to contain the spread of COVID-19 infection were more restrictive than those in other countries from the onset of the pandemic.

This review aims to critically evaluate the impact of the COVID-19 outbreak on CRC screening programmes in Italy. We also discuss projected effects of delayed CRC diagnosis and treatment due to discontinuation of screening.

Literature search and study selection

The present review focused on the literature covering the topic of CRC screening in Italy during the COVID-19 era. ²¹ A systematic literature search using the PubMed, Scopus and Web of Science databases was conducted in February 2022. The following keywords were used and combined for the search: 'colorectal', 'colon', 'rectal', 'cancer', 'carcinoma', 'malignancy', 'screening', 'screening program', 'COVID', 'COVID-19', 'SARS-CoV-2', 'coronavirus', 'Italy' and 'Italian'. Articles published in English from 1 January 2020 to 31 January 2022 were retrieved, screened and selected by two independent authors. Relevant data were extracted into a standardized data collection ²⁰ sheet by three authors. The Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA) ^[8] guidelines were used to create a flowchart, which is shown in Figure 1.

The final inclusion criteria were observational retrospective studies, surveys or national and regional database-based studies that presented numerical analyses and comparisons of CRC screening results between the COVID-19 and pre-COVID-19 eras.

At the time of this review, a total of seven articles had been finally selected from a comprehensive number of 563 published studies ^[6,7,9-13]. The included articles are briefly summarized in Table 1. The outcomes were defined as percentages or overall proportions. Due to the nature of the work (minireview), no formal statistical analyses were conducted. Most of the studies (71%) focused their attention on the first semester of 2020, coinciding with the first COVID-19 burst in Italy ^[7,9,11,12,13]. The remaining two articles (29%) analysed a broader time frame of almost the entire year of 2020 ^[6,10]. No articles were found concentrating on the 2021 situation, even though the pandemic was ongoing in its third and fourth waves. The studies ranged from single-unit experiences ^[7] to nation-wide surveys including all Italian regions ^[9] or evaluating more than 100 units across the country ^[12]. All of them focused on the reduction of endoscopic screening exams for CRC and the decrease in CRC new diagnoses in the analysed period with respect to the same temporal window in the previous years, namely 2018 and 2019.

Epidemiology of CRC and screening programmes in Italy

According to the Italian Minister of Health, in the year 2020, about 43,700 people were diagnosed with CRC (20,282 women and 23,420 men), and about 20,000 died from the disease ^[14]. The 5-year survival rate for CRC in Italy is 65.3% in men and 65.3% in women ^[15]. CRC is one of the most preventable of all cancers, and regular screening is one of the most powerful preventive tools. Screening is the process of looking for cancer or precancerous lesions in people asymptomatic for the disease. The key usefulness of screening is that most CRCs develop following the so called 'adenoma-carcinoma sequence'. Benign adenomatous polyps usually take several years to develop into CRC.

With regular screening, most polyps can be detected and safely removed before they turn into forms of invasive carcinoma. Besides, screening can permit the diagnosis and treatment of early forms of CRC, thus increasing the possibility of a cure. The main aim of CRC screening is to decrease mortality from the disease ^[15-17]. There is evidence that the introduction of CRC screening programmes in the early 2000s has substantially reduced mortality rates in European countries ^[18-21]. In Italy, CRC screening programmes organized by the public health system cover the population of the entire country. In most regions, a FOBT by the immunochemical technique is offered **is-offered** every 2 years to all men and women aged 50–69 years, who are at the highest risk of developing the disease. In some regions, such as Piedmont, flexible sigmoidoscopy or FOBT are offered once in a time to people aged 58–69 years. The widespread use of FOBT in Italy has led to a progressive reduction in the incidence and mortality from CRC, the latter thanks to detection of CRC in its early stage. Data from 48 cancer registries from 17 Italian regions reported a reduction in the CRC incidence rate from 104.3 and 64.3 per 100.000 in the year 2003 to 89.9 and 58.4 per 100,000 in 2014 in men and women, respectively. Besides, in the same time frame, mortality rates decreased from 41.1 to 39.2 per 100,000 in men and from 24.6 to 23.1 per 100,000 in women ^[15]. Data from randomized studies have demonstrated that both FOBT and flexible sigmoidoscopy have proven efficacy in reducing mortality from CRC by 22% and 28%, respectively ^[15,22]. In Italy, the most often used approach to CRC screening is to invite the target population by mail to undergo FOBT. Men and women with negative FOBT are recalled to repeat the test 2 years later. Those who do not respond to the first call are contacted by mail a second time within 6 mo. Patients with positive FOBT are contacted by phone to undergo a total or virtual colonoscopy (CT colonography) in the case of incomplete colonoscopy ^[15]. When colonoscopy or sigmoidoscopy detects neoplasms, patients are directed to surgery or endoscopic surgery and enrolled in a follow-up programme. Despite being a less tolerated and operator-dependent examination, colonoscopy leads to a complete exploration of the entire colorectal lumen and is much

more sensitive than flexible sigmoidoscopy, based on indirect evidence and observational studies [23].

Epidemiology of COVID-19 in Italy

Italy was the first European nation to be affected by COVID-19. The first Italian cases of COVID-19 date back to 30 January 2020, when two tourists tested positive by nasopharyngeal COVID-19 Test in Rome. In February 2020, in the city of Codogno, located in the Northern region of Lombardy, a 38-year-old man was hospitalized for respiratory symptoms and tested positive; the day after, 60 cases of COVID in Codogno were diagnosed [24]. During this first COVID-19 wave, the Italian Healthcare Service was near collapse, registering in just 1 mo almost 40 000 total cases and 3000 deaths (March 2020) [25]. From then onwards, Italy underwent three further pandemic waves, like most other countries in Europe. In that period, the development of vaccines contributed dramatically to proper management of the pandemic crisis [26]. As of 14 March 2022, 13,402,905 positive cases were registered in Italy, including 12,242,669 discharged and healed people, 156 997 deaths and 1,003,239 active cases [27]. Italy ranks 9th in the world and 5th in Europe for the total number of cases, and 8th in the world and 3rd in Europe for the absolute number of deaths. Furthermore, Italy ranks 53rd in the world for total cases per capita and 25th for total deaths per capita [26].

Effects of the COVID-19 pandemic on CRC screening in Italy

The DECOR-19 DElayed ColoRectal cancer care during the COVID-19 Pandemic was a global perspective from an international survey, where the highest number of respondents (1051) were from Italy. Of note, endoscopic procedures for CRC were the diagnostic techniques most affected by the COVID-19 emergency (73.7% of respondents). Colorectal cancer surgery was delayed in 58.3% of institutions. For 90% of respondents, the delay was 5–8 wk beyond the normal wait time and for the remaining 10%, more than 8 wk [28].

The Italian National Screening Observatory reported on the accumulated delay experienced by organized screening programmes up to May 2020. In the first 5 mo of 2020 *vs* the same period of 2019, 585,287 fewer CRC screening exams were conducted, accounting for a 54.9% decrease ⁶ [9]. Based on these numbers, an estimated 1,168 colorectal cancers and 6,667 advanced adenomas would have been missed in the period from January 2020 to September 2020 ⁶ [29].

A survey was conducted by the National Centre for Screening Monitoring on cervical, breast and colorectal cancer screening activities conducted in 2020. Screening tests for CRC decreased by 45.5% in 2020 compared with 2019, with an estimated 1,299 CRC cases going undiagnosed. Interestingly, participation in CRC screening programmes decreased by 20%.

[30].

In a study investigating the Cancer Diagnostic Delay in Northern and Central Italy ⁵ During the 2020 Lockdown, ⁵ a comparison was made among the number of first pathologic diagnoses of malignancy made from weeks 11 to 20 (April and May) of 2018, 2019 and 2020 at seven pathology units serving secondary care hospitals in Northern-Central Italy. A consistent decrease of 46.6% in new colorectal cancer cases diagnosed by screening programmes (335 in 2018–2019 and only 178 in 2020) was observed ⁵ [11].

The number of people who responded to invitations for FOBT screening in the region of Veneto in 2020 was about 16,000 Less than ⁸ in the previous 2 years, with an adherence rate that decreased from 65.2% to 54.2%. Colonoscopies fell by 22.2% (67,138 in 2020 ⁸ *vs.* 86,298 for the period 2018–2019); the rate reached its lowest in April (-70.4%). There was a 13.1% reduction in screening colonoscopies following a positive FOBT and a 24.9% reduction in non-screening colonoscopies ($P < 0.001$) ⁸ [10].

In a national survey, CRC diagnoses decreased by 11.9% from 2019 to 2020. A comparison between 2019 and 2020 ¹⁴ showed fewer CRC diagnoses in the North (-13.7%), ⁷ Center (-16.5%) and South (-4.1%) ⁷ [6]. The authors performed an audit to evaluate the

impact of COVID-19 pandemic-related delays in the diagnosis of major cancers at a Pathology Unit of a Secondary Care Hospital Network in Italy ^[7]. Cancer diagnoses fell in 2020 by 39% compared with the average number recorded in 2018 and 2019, and CRC was the tumour type with the greatest decrease.

A multicentric study evaluated the impact of the 2019 outbreak on 41 Italian endoscopic units. ¹ In 27 (65.9%) units, endoscopists were relocated to other hospital departments. ¹ In 31 (75.6%) units, nurses were relocated to other hospital departments. ¹ Most endoscopy units limited their activity to urgent cases, also including patients at high risk of cancer. ¹ After the COVID-19 outbreak, 39 endoscopy units (95.1%) continued to perform urgent procedures, 39 (95.1%) continued inpatient procedures ³ and 28 (68.3%) continued screening colonoscopies for CRC. ³ In quantitative terms, this corresponded to a 75%–99% reduction in activity in 28% of endoscopic units and to a 50%–75% reduction in 9% of units, with only a single unit maintaining its workload unchanged. Finally, most EUs limited their activity to urgent cases, including patients at high risk of cancer ^[13]. Examining Gastroenterology Divisions in Italy, a national survey that analysed data between March and April 2020 underscored that 46.7% of gastroenterology divisions ¹⁷ had suspended their endoscopic screening programmes for colorectal cancer during the COVID-19 pandemic, ¹¹ 10.7% of Gastroenterology Divisions had been converted to COVID units, and endoscopic procedures had been limited to urgencies and oncology cases in 96.2% of units ^[12].

Similar data were reported from countries outside Italy. In South Australia, the total number of colonoscopies decreased by 51.1% from 2019 to 2020 ^[31]. In the UK, ¹ endoscopic cancer detection was reduced by 58% overall and by 72% for colorectal cancer in particular during the period impacted by COVID (March–May 2020) ^[32]. In France, roughly 250,000 fewer colonoscopy preparations were dispensed during the first 6 mo of the COVID-19 pandemic ^[33]. In Hong-Kong, the mean number of lower endoscopies performed per week decreased by 51.0% after the beginning of the pandemic ^[34]. ¹⁵ The number of obstructive colorectal cancers in Japan has increased

during the COVID-19 pandemic, as a possible consequence of CRC screening discontinuation [35].

Consequences of reduced CRC screening activity

This review demonstrates the remarkable impact of the pandemic on endoscopic services in Italy. Interruption and discontinuation of CRC screening inevitably translated into a substantial and concerning reduction in CRC detection. It is commonly believed that screening delays beyond 4–6 mo would significantly increase advanced CRC cases and, if lasting beyond 12 mo, mortality as well [15]. In patients with CRC, 3–10-year survival is lower if treatment is started >90 days from diagnosis, and similar data are reported for other cancers [36]. The ideal timing of resection of colon cancer specifically has been estimated to be between 3 and 6 wk from diagnosis, which is unlikely to be achieved during the COVID-19 outbreak [37]. In a study where patients who underwent surgery for colorectal cancer in the pre-COVID era (October 2019–February 2020) were compared to those who did so after the end of the second wave (January 2021–May 2021), an increase in T4 tumours with higher preoperative levels of CEA and CA 19-9 was observed. These tumours required more extensive lymph node dissection. The authors speculated that this finding could be attributed to the reduced number of colonoscopies performed during the lockdown, as well as to patients' fears of potential infections in the hospital setting [37].

A survey by the Italian Federation of the Digestive Diseases Societies found that in gastroenterology units, 11.9% fewer CRC cases were diagnosed between 1 January and 31 October 2020, compared with the same period in 2019 [6].

Surgical oncology services around the world suffered a remarkable reduction in activity, resulting in a doubling of waiting lists as a result of delays in the screening and diagnosis of colorectal cancer due to the restrictions imposed by the pandemic.

A study was designed to evaluate the effects of COVID-19-related delays in colorectal cancer screening in 20 hospitals of Northern Italy by comparing 1755 patients who underwent colorectal cancer surgery in 2019 vs 1481 in 2020. The results showed that

colorectal cancers in 2020 (compared to 2019) were more likely to be symptomatic (OR 1.36 [95%CI 1.09 to 1.69]), to be clinical stage T4 (OR 1.38 [95%CI 1.03 to 1.85]) and to have multiple liver metastases (OR 2.21 [95%CI 1.24 to 3.94]), although they were not more likely to be associated with surgical complications (OR 0.79 [95%CI 0.68 to 0.93]) [38]. In particular, locally advanced disease, as well as the presence of CRC metastases to the liver, are definite prognostic factors in patients affected by CRC.

Another study evaluated the impact of the COVID-19 emergency on elective oncological surgical activity in 54 surgical units in Italy, including 11 colorectal units. Among the latter, 9 (82%) experienced a reduction of their surgical activity by 60%, with an expected prolongation of 5 wk between multidisciplinary meetings and surgery [39].

In the absence of proper catch-up campaigns aiming to recuperate those who missed their scheduled screening, the prognosis of patients with colorectal cancer could worsen. In fact, the long-term effects of the delay in colorectal cancer diagnosis due to interruption of screening activity could result in a rise in late-stage CRC cases and eventually in an undesirable loss of life years due to the lack of appropriate treatments for these patients [40].

Based on a procedural model using real-world data, in Italy a significant increase in deaths (12%) can be estimated at 5 years after a delay of longer than 12 mo in access to colonoscopy. In particular, in a study comparing baseline (0–3 mo), moderate (7–12 mo) and long (>12 mo) delays, a significant increase in advanced CRC (from 26% to 29% and 33%, respectively), was seen. Thus, the authors have estimated a significant increase in the total number of deaths (12.0%) when moving from a 0–3-month to a >12-month delay ($P < 0.005$) and a significant change in the mortality distribution by stage from baseline to >12 mo ($P < 0.001$) [41].

CONCLUSION

The results of our review confirm that the COVID-19 emergency has caused detrimental effects on CRC screening programmes in Italy, similarly to what occurred in other

counties on all continents. In most hospitals and territorial healthcare services, a time-limited suspension of CRC screening services was observed. At the time of writing, the situation is different from that observed at the beginning of the COVID-19 crisis. Indeed, advances in the treatment of patients affected by COVID-19, as well as prevention with massive vaccine campaigns, has significantly decreased the growth in the total number cases and rates of hospitalization. As a consequence, screening activity has now resumed in many Italian regions. Nonetheless, sporadic COVID-19 outbreaks due to the diffusion of new variants of the virus continue to modify the activities of healthcare services, and the duration of the effects of the COVID-19 pandemic on social life and healthcare in general is difficult to predict. The delayed diagnoses of CRC cases attributable to screening discontinuation is expected to result in an increase in advanced cancer cases—and possibly deaths—in the coming years. It is of the utmost importance that healthcare services of countries around the world develop reliable policies to maintain standard CRC screening activity in the presence of new pandemic outbreaks or similar extraordinary events.

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Internet | 79 words — 2% |
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Internet | 42 words — 1% |

8	B. Germana', S. Bellio, C. Barbiellini Amidei, G. Capodaglio et al. "PC.01.11 IMPACT OF COVID-19 PANDEMIC ON COLONOSCOPY AND SURGICAL INTERVENTIONS FOR COLORECTAL CANCER IN VENETO REGION", Digestive and Liver Disease, 2021 Crossref	31 words — 1%
9	Matteo Rottoli, Gianluca Pellino, Antonino Spinelli, Maria E. Flacco et al. "Impact of COVID-19 on the oncological outcomes of colorectal cancer surgery in northern Italy in 2019 and 2020: multicentre comparative cohort study", BJS Open, 2022 Crossref	31 words — 1%
10	www.science.gov Internet	22 words — 1%
11	" Week 2020 Poster Presentations ", United European Gastroenterology Journal, 2020 Crossref	18 words — < 1%
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19 MA Javed, A Kohler, J Tiernan, A Quyn, P Sagar. 14 words — < 1%
"Evaluating potential delays and outcomes of patients undergoing surgical resection for locally advanced and recurrent colorectal cancer during a pandemic", The Annals of The Royal College of Surgeons of England, 2022
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