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Original Study

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Impact of COVID-19 Pandemic on Colorectal Cancer Screening Program

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Abstract

The COVID-19 pandemic has influenced several aspects of daily activity in hospitals. We have confirmed that our colorectal cancer screening program has proved to be worthwhile and safe also during the lockdown period.

Introduction: One of the main clusters of coronavirus disease-2019 (COVID-19) has been identified in Italy. Following European and local guidelines, Italian endoscopy units modulated their activity. We aimed at analyzing the need and safety to continue selective colorectal cancer screening (CRCS) colonoscopies during the COVID-19 pandemic. **Patients and Methods:** We carried out a retrospective controlled cohort study in our "COVID-free" hospital to compare data of the CRCS colonoscopies of the lockdown period (March 9 to May 4, 2020) with those of the same period of 2019 (control group). A pre/post endoscopic sanitary surveillance for COVID-19 infection was organized for patients and sanitary staff. **Results:** In the lockdown group, 60 of 137 invited patients underwent endoscopy, whereas in the control group, 238 CRCS colonoscopies (3.9-fold) were performed. In the lower number of examinations during the lockdown, we found more colorectal cancers (5 cases; 8% vs. 3 cases; 1%; $P = .002$). The "high-risk" adenomas detection rate was also significantly higher in the "lockdown group" than in controls (47% vs. 25%; $P = .001$). A multiple regression analysis selected relevant symptoms (hazard ratio [HR], 3.1), familiarity (HR, 1.99), and lockdown period (HR, 2.2) as independent predictors of high-risk lesions (high-risk adenomas and colorectal cancer). No COVID-19 infections were reported among staff and patients. **Conclusions:** The overall adherence to CRCS decreased during the pandemic, but the continuation of CRCS colonoscopies was efficacious and safe.

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Introduction

An outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), has rapidly spread from China to nearly all the world, with over 800,000 people across 199 countries who have been infected thus far.[1] The World Health Organization declared a public health emergency in late January 2020 and characterized it as a pandemic in March 2020.

Europe was severely affected with an exponential increase in the number of COVID-19 cases and deaths, leading to an overload of the sanitary system and to a high infection rate among health care professionals (almost 10% in Western countries).[1-3]

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One of the main clusters of COVID-19 at the global level was identified in Italy.

The Italian government officially declared the lockdown on March 9, 2020, and the phase 1 started, with a significant impact on the lives of citizens and on daily hospital activities. As of that day, a total of 9172 cases were recorded in Italy; more than one-half (5469) of them were in the northern region of Lombardy, the most affected area (Figure 1).[4]

In our region (Lazio), there were 102 cases as of March 9, 2020. The measures adopted in our hospital setting to prevent the spread of the COVID-19 infection were: (1) suspending of "non-urgent" outpatient consultations, examinations, and surgical interventions (priority class > 10 days); (2) recommending immune-suppressed patients to avoid hospital admissions; and (3) progressively reorganizing hospitals into "COVID-19 dedicated" and "COVID-19—free" centers.

Nowadays, the results of this strategy are emerging, with an initial reduction in the number of infected patients, hospitalizations, intensive care unit accesses, and virus-related mortality.

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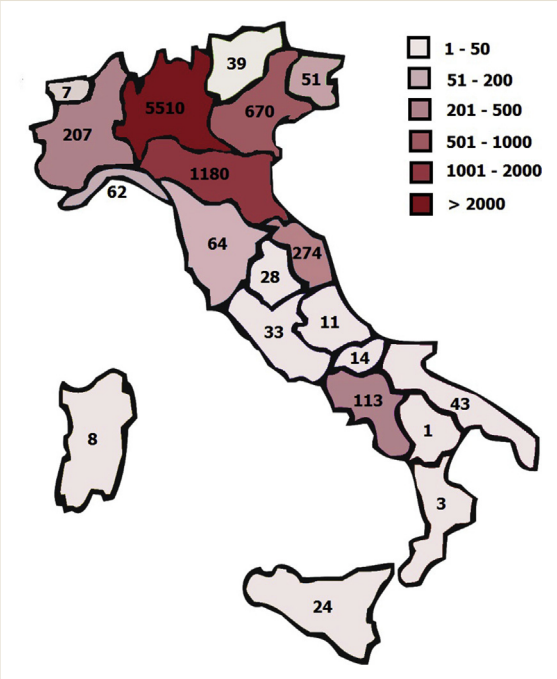
Figure 1 Total Cases of COVID-19 Infections Registered in Italy on March 9, 2020



Effects on Endoscopic Units and Colorectal Cancer Screening Program in Italy

Typical presentations of this infection are fever, cough, myalgia, fatigue, and pneumonia. Several studies also reported the early onset of gastrointestinal symptoms, such as diarrhea or nausea (1%-10%), even in patients without respiratory symptoms.[5-10] It was demonstrated that the SARS-CoV-2 is present in the feces and that it can survive in the gastrointestinal tract where its receptors are expressed, even after respiratory clearance.[11-17] Although both the significance of virus detection in the stool/rectal swabs of asymptomatic subjects and the role of angiotensin-converting enzyme 2 as a direct mediator for SARS-CoV-2 in the gastrointestinal tract are still unclear, these observations emphasize the relevance of an accurate definition of preventive measures, clinical care, and treatment strategies in the gastroenterologic setting.

The need to protect patients, especially those with a high risk of COVID-19 morbidity, led endoscopy units to reschedule an elevated number of procedures, weighing the benefit of endoscopy against the risk of infection on a case-by-case basis.

In endoscopic units, the activities were modulated in compliance with recently published COVID-19 endoscopy unit standard operating procedures,[17-20] according to regional guidelines.

Based on the European Society of Gastrointestinal Endoscopy and Endoscopy Nurse and Associates (ESGE-ESGENA) position statement, colorectal cancer screening (CRCS) colonoscopies were guaranteed in the majority of referral centers and labeled as "high-priority endoscopy procedures."[19]

Although the scheduling of treatments for oncologic patients was not particularly influenced by the emergency, CRCS programs obviously were.

In Italy, the organized CRCS program with fecal immunochemical test (FIT) is performed at the regional level with different adherence rates.[21,22] Barriers to screening normally include lack of proper education on colorectal cancer prevention, low appreciation of the screening benefits, fatalism, or simply fear of the screening tests; all these factors were exasperated by the pandemic.[23,24] The COVID-19 pandemic has resulted in decreased endoscopic testing for colorectal cancer.

The purpose of our study was to establish whether the CRCS program is effective in detecting precancerous lesions and cancer even during the pandemic. We compared the lockdown period data with last year's data in the same time window.

Given the prognostic impact of COVID-19 infection, a secondary objective was to evaluate the safety of selective colonoscopies performed in strict compliance with protective measures.

Patients and Methods

Lockdown Strategy in our Endoscopy Unit

In the context of patients' segregation in "COVID-19—free" and "COVID-19—dedicated" hospitals, the Regional Health Committee selected our Hospital as COVID-19—free.

In line with regional guidance, our endoscopic daily activities continued to encompass the treatment of emergencies, inpatients, and high-priority outpatients.

Adequate protective measures were applied to ensure safety (ie, personal protective equipment was distributed, re-processing of endoscopes was more frequently performed, and premises were increasingly sanitized).

All patients with positive FIT, as well as those waiting for polypectomy surveillance (as foreseen by the CRCS program), were invited over the phone to the pre-test medical interview to plan the second-level screening test if no suspicious symptoms of COVID-19 were reported. All patients were called the day before the scheduled appointment by nurses for screening, and on the day of the procedure, the same questions were asked about fever, new respiratory symptoms, anorexia, diarrhea, vomiting, abdominal pain, and loss of smell or taste.

The option to reschedule the examination after the end of this sanitary emergency was given to all patients, especially to those with comorbidities or older age. On the other hand, the relevance of this exam was underlined to patients waiting for surveillance of resected advanced adenomas.

Study Groups

During the lockdown period (from March 9 to May 4, 2020), data of selective CRCS colonoscopies performed in our endoscopy unit were accurately collected. Included patients were counted in the "lockdown group," whereas invited patients who decided to postpone the exam were recorded.

Collected information included demographic data, indications to examination, presence of relevant or systemic symptoms (paying particular attention to rectal bleeding, weight loss, anemia, changes in bowel habits), medical history, and endoscopic and histopathologic findings.

The data of CRCS colonoscopies performed in our endoscopy unit during the same period in 2019 (from March 9 to May 4,

2019) were collected separately to analyze the efficacy of our scheduled CRCS program. These patients were named the "control group."

The study protocol is in line with the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from all participants.

The only exclusion criterion was patients' refusal to participate.

All data on demography, colonoscopy, and histopathology were recorded by the screening center in a regional database and in our endoscopy unit general database.

Endoscopic Management

CRCS colonoscopies were performed in a dedicated session, using high-resolution instruments (Olympus 190, EVIS EXERA III, Olympus Corporation), CO2 insufflation, and water pump jet.

All patients underwent conscious sedation, and deep sedation was occasionally offered to selected fragile patients.

The Boston Bowel Preparation Scale was used to assess bowel toilette. If poor or inadequate in any colonic tract (total score < 6 or score < 2 in a single segment), the colonoscopy was rescheduled.[25]

Superficial neoplastic lesions detected during the examinations were accurately studied also through optical and virtual chromoendoscopy (vital colorants and narrow-band imaging).

Endoscopically resectable superficial neoplastic lesions were removed during colonoscopy through polypectomy or endoscopic mucosal resection (en bloc or piecemeal according to morphology and sizing).

Based on morphologic characteristics (mucosal and vascular pattern), colorectal superficial neoplastic lesions suspicious for deep submucosal infiltration were sent to referral centers for endoscopic submucosal dissection (ESD). Patients with evident advanced neoplastic lesions underwent biopsy, endoscopic tattooing to mark the lesions, and multidisciplinary evaluation (gastroenterologist, surgeon, radiologist, pathologist, and oncologist) as provided by the CRCS program.

All histopathologic data (including surgical and endoscopic data coming from other centers) were collected.

Patients were considered as negative in case of no polyps or inflammatory or hyperplastic lesions.

Patients with adenomas were considered as high-risk according to ESGE criteria in case of more than 3 lesions, size $\geq$ 10 mm, serrated, detection of high grade dysplasia, or villous component.[26]

Colorectal cancers were stratified according to TNM classification.

The same management was adopted in both cohorts.

COVID-19 Infection Surveillance

All staff were submitted to an infectious surveillance program. In case of slight respiratory, systemic, or gastrointestinal symptoms or high-risk COVID-19 contacts (relatives or patients), an oropharyngeal swab was performed. At the end of the lockdown period, an oropharyngeal swab and a serologic test were done on all nurses and medical staff.

Patients who were visited during the lockdown period were called over the phone 14 days after the endoscopic procedure to determine whether they or their relatives were symptomatic or not.

Statistical Analysis

Our analysis aimed to compare demographic, clinical, and histopathologic data of the 2 cohorts of patients. Numerical variables are expressed in as the means $\pm$ standard deviations and were compared using the Student t test for unpaired data. Categorical variables are expressed as numbers and proportions and were compared using χ^2 tests.

P values less than .05 were considered significant.

Moreover, to identify possible predictors of high-risk lesions, a multiple regression analysis, considering 5 variables (age, gender, relevant symptoms, reported colorectal cancer familiarity, and study period) was performed. Not significant variables were removed, and the analysis was repeated to confirm the statistical significance of remaining factors.

NCSS (Number Cruncher Statistical System) software 2007 was used for statistical analysis.

Results

Patients

The majority of the baseline patient characteristics of the 2 cohorts were comparable (gender, smoking habits, previous colorectal surgery). The main reasons behind the invitations to CRCS were

Table 1 Baseline Demographic and Clinical Characteristics of the 2 Cohorts of Patients

	Lockdown Group (n = 60), n (%)	Control Group (n = 238), n (%)	P
Gender (M/F), n (% of male)	26/34 (43)	131/107 (55)	NS (.1)
Age, y	59 ± 8.2	65 ± 7	NS (.2)
Invitation indication			
FIT	51 (85)	213 (89)	
Polypectomy surveillance	4 (7)	12 (5)	NS (.3)
Familiar surveillance	5 (9)	14 (6)	
Reported familiarity	22 (36)	49 (20)	.008
Relevant symptoms	11 (18)	19 (8)	.02

Abbreviations: F = female; FIT = fecal immunochemical test; M = male; NS = not significant.

also homogenous, all patients of both cohorts were called for FIT positivity, and polypectomy surveillance was provided for in the organized CRCS program (Table 1).

Nevertheless the mean age and the proportion of male patients was slightly but not significantly lower in the lockdown group (59 ± 8.2 vs. 65 ± 7 years; $P = .2$ and 43% vs. 55%; P = ns, respectively).

During the pre-endoscopic medical interview, relevant symptoms or familiarity ranked far higher in the lockdown group ($P = .0149$) (Table 1).

During the pandemic lockdown, 137 patients resulted positive for FIT and were invited to a pre-endoscopic medical interview. Only 74 patients accepted the pre-endoscopic visit, and 60 patients (lockdown group) agreed to undergo colonoscopy after medical interview adhesion.

All patients gave their consent to participate to the study. For 2 (3%) patients, the colonoscopy was interrupted and repeated after a few days owing to inadequate bowel preparation.

In the control period, 238 patients accepted to undergo colonoscopy after medical interview adhesion (control group) (3.9-fold). In this group, 3% of colonoscopies were interrupted and repeated shortly after because of inadequate bowel preparation.

Endoscopic and Histopathologic Findings

Colorectal lesions were detected during 61% of colonoscopies in the lockdown group and 53% in the control group, with a similar adenoma detection rate ($P = .2$).

All lesions were endoscopically resected during the diagnostic colonoscopy, with the exception of 3 advanced neoplastic lesions per group (Kudo Vi, JNET 3) sent to surgery and 2 superficial neoplastic lesions per group (laterally spreading tumors "granular mixed nodular" or "flat pseudodepressed" ranging in size from 35-50 mm) sent to referral centers for ESD.

Given the histopathologic results, we excluded 5% hyperplastic and 2% inflammatory lesions from the colorectal lesions analysis (Table 2 and Figure 2).

The adenoma detection rate (ADR) was slightly higher in the lockdown group than in the control group (57% vs. 47.5%), but it failed to reach statistical significance ($P = .2$).

The high-risk ADR was, instead, significantly higher in the lockdown group (47% vs. 25%; $P = .001$). Based on a sub-analysis, 4 of 5 high-risk variables, (adenoma > 10 mm, villous component, high grade dysplasia, and serrated) were observed far more frequently in the lockdown group. Accordingly, the overall and high-risk adenomas mean sizes were significantly higher in this group ($P < .001$) (Table 2).

After post-surgical examination and radiologic staging, the previously described advanced neoplastic lesions were confirmed as stage I or IIA adenocarcinoma (pT2 or 3, N0, M0). In the lockdown group, 2 adenocarcinomas limited to the submucosa (pT1), were found in 2 resected lesions with advanced pattern, whereas none were found in the control group. No high-risk findings for nodal metastasis (grade > 2, no vascular or lymphatic infiltration, high budding, submucosal infiltration > 1 mm) were documented in these 2 patients. In those cases, the choice was to manage them by endoscopic and radiologic follow-up, in line with the patients' decisions.

All superficial neoplastic lesions sent to ESD turned out to be high-risk adenomas.

A multiple regression analysis has identified selected symptoms (hazard ratio [HR], 3.1), familiarity (HR, 1.99), and lockdown period (HR, 2.2) as independent predictors of high-risk lesions (high-risk adenomas and colorectal cancer) (Table 3).

No adverse events related either to diagnostic or operative CRCS colonoscopies were recorded in the 2 groups.

Safety

During the lockdown period, no members of the sanitary staff had any symptoms or high-risk COVID-19 contact. Oropharyngeal swabs and serologic tests collected at the end of the lockdown period from all staff members were negative.

During the post-endoscopic follow-up, no nosocomial COVID-19 infections of patients and of families were referred.

Discussion

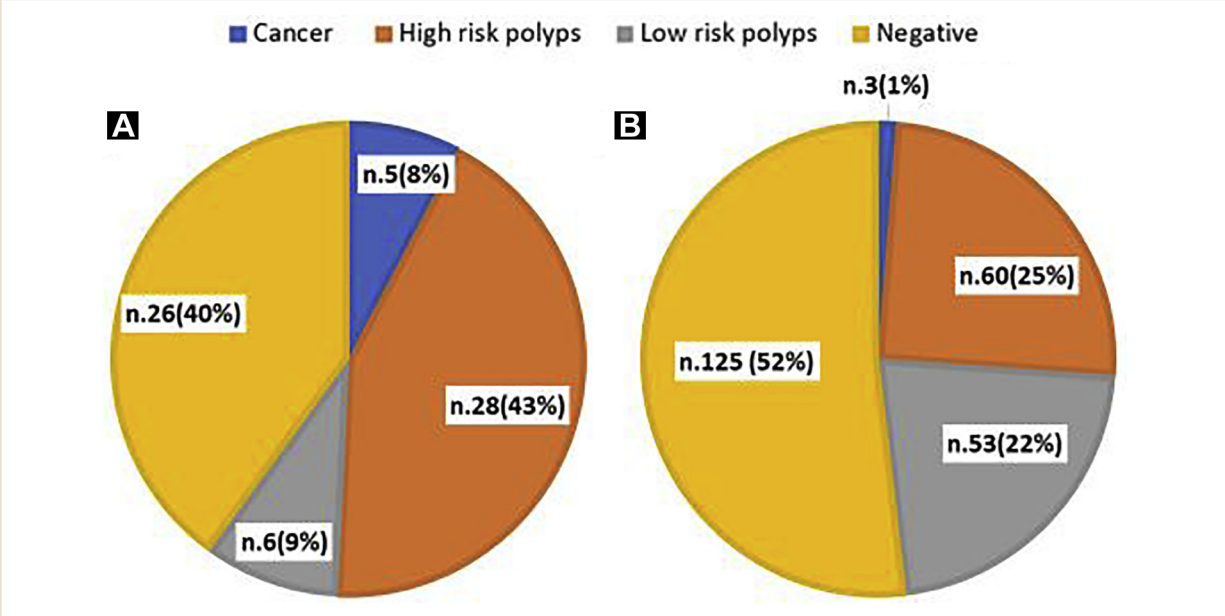
This epidemic is having an enormous impact on our lives and health care systems. Although COVID-19 is related to a direct relevant mortality, the fear of the infection may cause numerous other deaths owing to diagnostic delays of life-threatening diseases. In the Italian cardiologic setting, a worrying increase in out-of-hospital cardiac arrests and related morbidity and mortality has already been described.[27] Given their relevance, CRCS programs are going on, albeit with some limitations. The recently published ESGE position statement clearly suggested that CRCS colonoscopies should be guaranteed as "high-priority endoscopy procedures," but no data are available yet to confirm that this indication was followed in practice.

Table 2 Histopathologic Findings of the 2 Cohorts of Patients

	Lockdown Group (n = 60), n (%)	Control Group (n = 238), n (%)	*P*
Colorectal cancer			
Any stage	5 (8)	3 (1)	.002
Stage > 1	3 (5)	3 (1)	.06
Adenoma detection rate	34 (57)	113 (47.5)	NS (.2)
High-risk adenoma detection rate	28 (47)	60 (25)	.001
High-risk variables			
Adenoma > 10 mm	24 (40)	31 (13)	<.0001
>3 adenomas	10 (17)	24 (10)	.15
High-grade dysplasia	15 (25)	15 (6)	<.0001
Villous component	13 (22)	27 (11)	.03
Serrated	4 (7)	2 (1)	.004
Mean adenoma size, mm	12.8 ± 2.2	8.5 ± 6.9	<.001
Mean high risk adenoma size, mm	21 ± 12.5	11.6 ± 8.4	<.001

Abbreviation: NS = not significant.

Figure 2 Comparison of Detected Lesions in Lockdown Group (March 9 to May 4, 2020, COVID-19 Period) (A) and Control Group (Same Period 2019) (B). Total CRCS Colonoscopies in Lockdown Group Versus Control Group (n = 60 vs. n = 238). High-Risk and Low-Risk Superficial Neoplastic Lesions Were Classified according to European Society of Gastrointestinal Endoscopy Guidelines



Abbreviation: CRCS = colorectal cancer screening.

Based on these assumptions, we conducted a study to verify the effectiveness and safety in performing selective CRCS program in a COVID-free hospital. By comparing the same time window in 2019, we observed that, although the number of selective CRCS colonoscopies decreased sharply during the lockdown period, the ADR, the rate of detected cancer as well as high-risk adenomas increased.

Even though the increase in ADR was not significant (57% vs. 47.5%; $P = .2$), it was remarkably high in both periods. In our center, the main colonoscopy quality indicators for both periods were adequate for the requested standard of CRCS programs, being above the Italian average values reported by Zorzi et al.[21] Not only does this suggest that the standard endoscopic skill of medical staff was not significantly influenced by the events, but also emphasizes that the results of our monocentric study could be replicated in other CRCS centers (high-volume of CRCS colonoscopies > 1000/year, dedicated session, endoscopists with adequate expertise).

Table 3 Logistic Regression Analysis of Independent Predictive Factors of High-risk Colorectal Lesions (High-risk Adenomas and Colorectal Cancers)

	P	Hazard Ratio	Confidence Interval
Reported colorectal cancer familiarity	.02	1.99	1.1-3.6
Relevant symptoms	.006	3.1	1.4-6.8
Lockdown period	.01	2.2	1.2-4

The increase in high-risk adenomas and cancer detection rates (47% vs. 25%; $P = .001$ and 8% vs. 1%; $P = .002$, respectively) during the lockdown period were significantly higher, whereas on the other hand, the low-risk adenoma detection rate decreased sharply (9% vs. 22%). More than one-half of the colonoscopies performed during the lockdown period allowed the detection of high-risk pre-neoplastic or neoplastic lesions. As a result, we can postulate that, given the reduction of patients in the lockdown period, we might have missed only those without significant endoscopic findings. Rescheduling these colonoscopies is a less relevant issue, as it merely relates to the organization of our daily activities in the endoscopy unit.

Interestingly, we observed significantly more frequent more high-risk factors (FIT positive, familiarity, or relevant symptoms such as rectal bleeding, recent modification of bowel habits) in patients in the lockdown group. It was probably in relation to a higher commitment in emphasizing to these patients the importance of this exam during the pre-endoscopic interview and to a self-selection by the patient through balancing both fear of COVID-19 and finding a cancer. Only a few patients without risk factors asked for the chance to delay colonoscopy after the pre-endoscopic interview because of their fear of being infected.

Our multivariate analysis clearly indicates that patients with one or more high-risk factors (FIT-positive, familiarity, or alarm symptoms), independently of gender and age, should still receive endoscopy as soon as possible, even in the lockdown period.[28-31] The lockdown period was proven to be an independent factor probably as a result of either the above mentioned patient self-selection and the related fear of COVID-19 infection.

During the lockdown period and the post-endoscopic follow-up, not a single patient, relative, or medical staff member tested positive for COVID-19 infection, nor did any of them reveal any symptoms.

Conclusion

We think that our results are novel, as current real data dealing with cancer screening or, specifically, for colorectal cancer, during the pandemic were not available. The only clinical data concerning cancer care demonstrating a reduction of urgent any kind of cancer referrals in the COVID-19 pandemic versus the pre-pandemic period concern the United Kingdom and Northern Ireland.[32,33] A potential utility of an enhanced DNA-based tool testing for CRCS during crises has been instead only hypothesized in the United States.[34]

Our results might be also very relevant for the practical health care pandemic and post-pandemic management.[35] The choice to split hospitals into COVID-dedicated and COVID-free was very relevant to reduce the infectious risk and infectious fear in non-COVID patients. Moreover, in these hospitals, less personal protective equipment to perform exams was needed, and these hospitals did not experience a shortage of personnel (necessary in any case to guarantee non-deferrable emergencies) available to carry on not urgent high-risk procedures.

In conclusion, we proved that our CRCS program is: (1) effective and worthwhile: the significantly higher proportion of high-risk lesions by selecting patients fully justified the inclusion of selective CRCS colonoscopies in high-risk procedures; (2) safe: whenever it is performed in endoscopy units of COVID-19−free hospitals and by strictly following rules in terms of COVID-19 prevention; and (3) cost-saving in terms of personal protective equipment and personnel shortages if performed in COVID-19−free hospitals.

Clinical Practice Points

- Our take home message is that, following the prevention rules in terms of COVID-19, a more selective CRCS program must go on during the current pandemic and even in case of any fallout.
- To ensure safety both for patients and staff, the CRCS program has to be carried on selectively in endoscopy units of COVID-19−free hospitals (following the measures adopted as in Italy).

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Disclosure

The authors have stated that they have no conflicts of interest.

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