Increased Number of Colorectal Interval Cancers in Lynch Syndrome after the SARS-CoV-2 Pandemic: A Survey-Based Study

Michele Russo a  Alberto Barchi a  Alessandro Mannucci a  Marta Puzzono a, b  Raffaella Alessia Zuppardo a  Paolo Biamonte a  Sarah Bencardino a  Gioacchino Leandro c  Renato Cannizzaro d  Fabio Monica e  Rocco Maurizio Zagarì f, g  Luigi Pasquale h  Elisabetta Goni i  Milena Di Leo j  Luigi Ricciardiello k, l  Giulia Martina Cavestro a  on behalf of Italian Society of Gastroenterology (AIGO), Italian Society of Digestive Endoscopy (SIED) and Italian Society of Gastroenterology and Digestive Endoscopy (SIGE)

a Gastroenterology and Gastrointestinal Endoscopy Unit, Vita-Salute San Raffaele University, IRCCS San Raffaele Scientific Institute, Milan, Italy; b Medical Biotechnologies Department, University of Siena, Siena, Italy; c Gastroenterology Unit 1, Gastroenterological Hospital “S. De Bellis” IRCCS, Castellana Grotte, Italy; d Oncological Gastroenterology Unit, CRO, Aviano, Italy; e Gastroenterology and Digestive Endoscopy, Ospedale di Cattinara, Trieste, Italy; f Gastroenterology Unit, IRCCS Azienda Ospedaliero-Universitaria, S. Orsola Hospital, Bologna, Italy; g Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; h Gastroenterology Unit, S.O. Frangipane Hospital, Ariano Irpino, Italy; i Medical Department II, University Hospital, Ludwig Maximilians-University, Munich, Germany; j Digestive Endoscopy Unit, ASST Santi Paolo e Carlo, Milan, Italy; k Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; l IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

Keywords
Hereditary · Colorectal cancer · COVID-19 · Surveillance

Abstract

Background: Hereditary colorectal cancer syndromes require timely endoscopic surveillance. Methods: This study evaluated the approach of Italian gastroenterologists to the management of such patients. It then assessed the impact of SARS-CoV-2. All members affiliated with the leading Italian gastroenterology societies (AIGO, SIED, and SIGE) received an online questionnaire. Results: One hundred and twenty-one clinicians from 96 centers answered, not necessarily experts in the field (mean age 50.26 ± 11.22 years). Many collected family history for genetic risk assessment (74.4%), but only 14.0% used an online predictive software. 65.6% discussed cases in multidisciplinary units. Genetic analysis was available to most centers, but only a few hospitals offered dedicated endoscopy (19.0%), outpatient clinics (33.9%), or surgeries (23.1%). Since the start of the SARS-CoV-2 pandemic, the number of clinicians with a high volume of patients decreased (from 38.8% to 28.1%). Almost half of the responders (45.5%) reported a delay in the surveillance (median: 4–12 months). Ultimately, 30.6% detected one interval colorectal cancer in at least one of their patients. Conclusion: The SARS-CoV-2 pandemic directly affected the surveillance of hereditary colorectal cancer syndromes in Italy. Luigi Ricciardiello and Giulia Martina Cavestro contributed equally to this work.
Introduction

The lifetime risk of colorectal cancer (CRC) increases with germline pathogenic variants in genes associated with CRC. A genetic predisposition exists in 2–8% of all CRCs and one in five CRCs is diagnosed before 50 years of age [1–3]. Lynch syndrome (LS) is the most common hereditary CRC syndrome with an estimated three million people aged between 45 and 70 years in Europe [2, 4]. Patients with LS can reduce their risk of CRC and other cancers (gastric, gynecological, and pancreatic cancers) with surveillance programs [5–10]. Familial adenomatous polyposis is rarer, but it confers a higher lifetime risk of CRC close to 100% [1]. As little as 11–26% of high-risk CRC patients receive genetic risk assessment [11] and, in some cases, the percentage of undiagnosed syndromes could be higher [9, 10, 12].

The SARS-CoV-2 pandemic had a rapid and dramatic effect on healthcare systems [13]. Many centers had to commit all their human resources to COVID-19 [14, 15]. Endoscopic activity in the UK dropped to 5% of normal at the pandemic peak, with a reduction of 85% in other countries [16, 17]. During the first pandemic wave in Italy (from March 1 to June 30, 2020), 10.7% of gastroenterology divisions were converted to COVID-19 units [18]. Outpatients’ consultations, endoscopic, and ultrasound procedures were limited to urgencies in 85.1%, 96.2%, and 72.2% of units, respectively. 46.7% of Italian gastroenterology units suspended CRC screening. The primary aim of this survey study was to evaluate the burden of the SARS-CoV-2 pandemic on the surveillance of patients with hereditary CRC syndromes. As secondary outcomes, we evaluated (i) the awareness and (ii) the management of hereditary CRC syndromes in Italy.

Materials and Methods

We designed an online, multiple-choice, and open-ended questionnaire with 38 items (10 optional) in 22 sections using Google Forms. The questionnaire core assessed how many patients with hereditary CRC syndromes each gastroenterologist followed before and after March 1, 2020, per year (0, <10, 10–30, 31–50, >50 patients); how many patients they had for first visit and follow-up visits per year; and whether or not follow-up visits and prophylactic surgeries were delayed (if so, estimating by how much). For the secondary aims, we asked: whether patients’ family history was collected; whether a genetic risk assessment tool was used (i.e., PREMM5) [19]; whether mismatch repair (MMR) immunohistochemistry (IHC) was performed on all surgical specimens; their management of MMR-deficient CRCs; whether there was a genetics laboratory, a multidisciplinary group, dedicated outpatient clinics, endoscopy units, and/or surgery. If not, participants were asked where the nearest dedicated facilities were.

We performed descriptive analyses using percentages for categorical variables. The distributions of answers were analyzed by plots (boxplots and bar charts), whereas summary statistics, across all centers, were reported as the minimum, maximum, average, standard deviation, and the total number of cases aggregated by type. Statistical analyses were performed using SPSS software.

Results

A total of 121 gastroenterologists and endoscopists (males 60.3%; mean age 50.26 ± 11.22 years; mean years of clinical activity: 20.13 ± 11.69) from 96 Italian gastroenterology or endoscopy units completed the questionnaire (16.5% gastroenterologists, 31.4% endoscopists, 52.1% both) (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000524393). The survey included 18 regions and 64 cities (online suppl. Tables 2–3): 53 (55.2%) were in the North, 25 (26.0%) in the center, 19 (19.8%) in the South, and 2 (2.1%) in Sardinia (online suppl. Fig. 1).

Before the pandemic, 23.1% and 38.8% of participants had a high volume of patients (>10/year) at first or follow-up visits, respectively, while 52.1% and 38.0% had fewer than 10 patients per year at first examination or follow-up visit, respectively. After the pandemic, there was a decrease in the number of clinicians with a high volume of patients at first visit (from 23.1% to 18.2%) and at follow-up (from 38.8% to 28.1%). Similarly, there was an increase in the number of clinicians with no patients at first
visit (from 24.8% to 25.6%) and at follow-up visits (from 23.1% to 25.6%). Clinicians confirmed the procrastination of control visits (45% of participants), with a delay of 4–12 months in 65.3% of cases (Fig. 1).

30.6% of clinicians diagnosed one or more interval cancers (CRC diagnosed in the time between two scheduled/delayed surveillance examinations) in at least one of their patients. Most diagnosed 1–3 interval cancers, but 8.1% reported up to five interval cancers. This result was likely not the consequence of endoscopy units shutting down because most units resumed endoscopy services shortly after the first wave [20]. Endoscopic emergencies were still performed (73.3% of cases). Prophylactic surgical procedures were discontinued in 27.3% of cases (mostly procrastinated by 4–6 months), even though 43.0% of participants could not answer this question. Therapeutic surgical procedures were performed in other centers (44.6% of cases), and in those centers, the presence of a dedicated surgery was confirmed in 27.8%.

Most gastroenterologists and endoscopists (85.1%) referred to updated guidelines and scientific papers, while 6.6% received updates through congresses or symposia, 5.8% through the internet, and 2.5% admitted not being up-to-date. 74.4% collected family history, but only 14.0% used the PREMM5 genetic risk assessment tool. 61.2% of clinicians used MMR-IHC on surgical specimens. When positive, 8.1% ordered genetic testing, 54.1% discussed the case in a multidisciplinary group, 32.4% referred to genetic counseling, and 5.4% did not perform further analysis or admitted not knowing what to do. When MLH1 was not expressed, 24.4% evaluated MLH1 promoter hyper-methylation or BRAF V600E; 9.5% tested for MSI; and 20.3% requested germline tests, but the majority (45.9%) performed no further testing.

57.9% of clinicians reported having a genetic laboratory, while 2.5% did not know whether their center had one. Concerning participants without a genetic laboratory (39.7%), the nearest was in the same province (54.1%), same region (43.8%), or another region (2.1%). 33.1% of participants had access to somatic tests. However, 33.9% were not able to answer this question. Concerning those who declared not having this facility in their center (33.1%), the nearest dedicated laboratory was in their province (45.0%), their region (50.0%), or outside their region (2.5%), while 2.5% did not know. An endoscopic room, outpatient clinics, and surgical room for hereditary syndromes were not present in 81.0%, 66.1%, and 76.9% of participant centers, respectively. A multidisciplinary group was available in 63 out of 96 centers (65.6%) (Fig. 2).

**Discussion**

This survey analyzed the Italian experience with hereditary CRC syndromes during the COVID-19 pandemic, covering 18 of 20 regions. 45.5% of the participants reported a delay in the surveillance endoscopic exams (median: 4–12 months). 30.6% of clinicians reported a diagnosis of interval CRC since the beginning of the pandemic. Participants were not exclusively specialists in hereditary CRC syndromes. They had, on average, over 20 years of clinical activity, and 52.1% of them practiced gastroenterology and endoscopy both.
Surveillance can reduce CRC risk in LS by up to 60%, but patient-specific risk factors and compliance can limit its effectiveness [21]. The benefit decreases with the procrastination of surveillance [20], much like what happened during the SARS-CoV-2 pandemic, as shown in this survey. Reduced surveillance, on one hand, and delays in colonoscopies, on the other, can contribute to later-stage CRC diagnoses [22]. 30.6% of clinicians from this survey witnessed at least one interval CRC during the pandemic (the prospective per-patient rate of interval cancer is estimated at 1.8% by Engel et al. [23]). SARS-CoV-2 caused immediate challenges to surveillance and screening services since March 2020 [24]. During the first pandemic wave in Italy, only 12.4% of endoscopy units were shut down. Of these, 66.7% were shut down only briefly, from March 1, 2020, to June 30, 2020. Although procedures continued, patients might not have attended endoscopic surveillance or visits. This discrepancy could be explained by the poor compliance of patients to follow-ups, maybe due to fear of SARS-CoV-2 infection. This survey did not investigate compliance directly, but 74.4% of responders reported a slight decrease in the number of patients followed per year after the pandemic. 45.5% of clinicians confirmed procrastination of follow-ups, with an average delay time of 4–12 months, which supports this explanation. The impact of SARS-CoV-2 on the delays in cancer diagnosis and cancer death is concerning.

In the majority of Italian centers, there was neither an endoscopic room nor a dedicated surgery for hereditary CRC syndromes. 85.1% of clinicians relied on guidelines, and 74.4% collected family history [8]. Although clinical models (i.e., PREMM5) allow adequate genetic assessment for LS and other hereditary CRC syndromes [19, 25], only 14.0% used it. MSI and IHC were used in 9.5% and 61.2%, respectively, but the management of results seemed more challenging. 45.9% of participants did not know of MLH1 promoter hypermethylation or BRAF V600E analysis. Genetic facilities are widely available (57.9% of centers), but only a few clinicians (32.4%) referred patients to genetic counseling, and even fewer (8.1%) requested genetic tests. This could be explained by the absence of a geneticist in the team (39.7% did not have a genetic counselor). This data highlights the need to use multidisciplinary team discussions [26–28] to improve diagnostic accuracy and adherence to guidelines, especially for complex patients [29].

One limitation of this study was the presence of discrepancies between clinicians from the same center. We
Interval Colon Cancers and COVID-19

contacted all 11 centers to solve major inconsistencies. This pragmatic choice may have limited precision. Concerning the reported rate of interval cancers, another limitation of this study is that the survey assessed the number of clinicians diagnosing interval cancers, not the number of interval cancers [22, 23]. Besides limitations, the mean number of patients with interval cancers was reportedly high (up to three per hospital), and several centers reported a postponement of prophylactic surgical procedures.

In conclusion, the pandemic of SARS-CoV-2 had an impact on people with a hereditary risk of CRC in Italy. The worst repercussion was the reported increase in interval cancers during the pandemic. This probably resulted from poor compliance to surveillance, due to the fear of SARS-CoV-2. Therefore, CRC surveillance should resume and avoid the possible long-term consequences of its interruption, especially for hereditary CRC syndromes. In the meantime, all gastroenterology and endoscopic centers should carefully reorganize their activities to face the burden of delayed endoscopies. This represents a major challenge for the next year.

Statement of Ethics

The paper is exempt from ethical committee approval because an ethics statement was not required for this study type where no human or animal subjects or materials were used.

Conflict of Interest Statement

Luigi Ricciardiello is a managing editor of the journal; Rocco Maurizio Zagari is an editorial board member of the journal; other authors have no conflicts of interest to declare.

Funding Sources

This research received no external funding.

Author Contributions

G.M.C.: conception and design; M.D.L. and G.L.: analysis and interpretation of the data; M.R., A.B., and G.M.C.: drafting of the article; G.M.C., A.M., M.P., R.A.Z., P.B., S.B., M.D.L., R.M.Z., E.G., L.P., R.C., F.M., and L.R.: critical revision of the article for important intellectual content and final approval of the article. All the authors have read and agreed to the published version of the manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author (G.M.C.) upon reasonable request.

References

1 Valle L, Vilar E, Tavtigian SV, Stoffel EM. Genetic predisposition to colorectal cancer: syndromes, genes, classification of genetic variants and implications for precision medicine. J Pathol. 2019;247:574.
2 Yurgelun MB, Kulke MH, Fuchs CS, Allen BA, Uno H, Hornick JL, et al. Cancer susceptibility gene mutations in individuals with colorectal cancer. J Clin Oncol. 2017;35:1086–95.
3 Uson PLS, Riegert-Johnson D, Boardman L, Kisiel J, Mountjoy L, Patel N, et al. Germline cancer susceptibility gene testing in unscreened patients with colorectal adenocarcinoma: a multicenter prospective study. Clin Gastroenterol Hepatol. 2022 Mar;20(3):e508–28.
4 Valle L, Gruber SB, Capellá G. Hereditary colorectal cancer: genetic basis and clinical implications. Hered Color Cancer Genet Basis Clin Implic. 2018:1–505.
5 Mannucci A, Zappardo RA, Crippa S, Carrera P, Patricelli MG, Russo Raucci A, et al. MSH6 gene pathogenic variant identified in familial pancreatic cancer in the absence of colon cancer. Eur J Gastroenterol Hepatol. 2020;32:345–9.
6 Domínguez-Valentín M, Crosbie EJ, Engel C, Aretz S, MacRae F, Winship I, et al. Risk-reducing hysterectomy and bilateral salpingooophorectomy in female heterozygotes of pathogenic mismatch repair variants: a Prospective Lynch Syndrome Database report. Genet Med. 2021;23:705–12.
7 Seppälä TT, Domínguez-Valentín M, Crosbie EJ, Engel C, Aretz S, Macrae F, et al. Uptake of hysterectomy and bilateral salpingo-oophorectomy in carriers of pathogenic mismatch repair variants: a Prospective Lynch Syndrome Database report. Eur J Cancer. 2021;148:124–33.
8 Domínguez-Valentín M, Seppälä T, Engel C, Aretz S, Macrae F, et al. Risk-reducing gynecological surgery in Lynch Syndrome: results of an international survey from the Prospective Lynch Syndrome Database. J Clin Med. 2020;9:2290.
9 Monahan KJ, Brashaw N, Dolwani S, Desouza B, Dunlop MG, East JE, et al. Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG). Gut. 2020;69:411.
10 Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110:223–63.
11 Seppälä TT, Latchford A, Negoí I, Sampaio Soares A, Jimenez-Rodríguez R, Sánchez-Guillén L, et al. European guidelines from the EHTG and ESCP for Lynch syndrome: an updated third edition of the Mallorca guidelines based on gene and gender. Br J Surg. 2021 May 27;108(5):484–98.
12 Wagner A, Aretz S, Auranen A, Bruno MJ, Cavestro GM, Crosbie E, et al. The management of Peutz-Jeghers Syndrome: European Hereditary Tumour Group (EHTG) guideline. J Clin Med. 2021;10:473.
13 Scaldaferrí F, Pugliese D, Privitera G, Onali S, Lopetuso LR, Rizzatti G, et al. Impact of COVID-19 pandemic on the daily management of biotechnological therapy in inflammatory bowel disease patients: reorganisational response in a high-volume Italian inflammatory bowel disease centre. United European Gastroenterol J. 2020;8:775–81.
14 Magro F, Abreu C, Rahier JF. The daily impact of COVID-19 in gastroenterology. United European Gastroenterol J. 2020;8:520–7.
15 Chai N, Mei Z, Zhang W, Du C, Wang X, Li L, et al. Endoscopy works during the pandemic of coronavirus COVID-19: recommendations by the Chinese Society of Digestive Endoscopy. United European Gastroenterol J. 2020;8:798–803.
16 Hunt RH, East JE, Lanas A, Malferttheiner P, Satsangi J, Scarpignato C, et al. COVID-19 and gastrointestinal disease: implications for the gastroenterologist. Dig Dis. 2021;39:119–39.
17 Francisco CP, Cua IH, Aguila EJ, Cabral-Prodigalidad PA, Sy-Janairo ML, Dumagpi JE, et al. Moving forward: gradual return of gastroenterology practice during the COVID-19 pandemic. Dig Dis. 2021;39:140–9.
18 Maida M, Sferrazza S, Savarino E, Ricciardello L, Repici A, Morisco F, et al. Impact of the COVID-19 pandemic on Gastroenterology Divisions in Italy: a national survey. Dig Liver Dis. 2020;52:808–15.
19 Kastrinos F, Uno H, Ukaegbu C, Alvero C, McFarland A, Yurgelun MB, et al. Development & validation of the PREMM5 model for comprehensive risk assessment of Lynch syndrome. J Clin Oncol. 2017;35:2165–72.
20 Lindberg IJ, Rasmussen M, Andersen KK, Nilbert M, Therkildsen C. Benefit from extended surveillance interval on colorectal cancer risk in Lynch syndrome. Colorectal Dis. 2020;22:529–36.
21 Newton K, Green K, Laloo F, Evans DG, Hill J. Colonoscopy screening compliance and outcomes in patients with Lynch syndrome. Colorectal Dis. 2015;17:38–46.
22 Argillander TE, Koornstra JJ, van Kouwen M, Langers AM, Nagengast FM, Vecht J, et al. Features of incident colorectal cancer in Lynch syndrome. United European Gastroenterol J. 2018;6:1215–22.
23 Engel C, Rahmer N, Schulmann K, Holinski-Feder E, Goecke T, Schackert HK, et al. Efficacy of annual colonoscopic surveillance in individuals with hereditary nonpolyposis colorectal cancer. Clin Gastroenterol Hepatol. 2010;8:174–82.
24 Perin DMP, Elfström KM, Bulliard J-L, Burón A, Campbell C, Flugelman AA, et al. Early assessment of the first wave of the COVID-19 pandemic on cancer screening services: The International Cancer Screening Network COVID-19 survey. Prev Med. 2021;151:106642.
25 Mannucci A, Sloane Furniss C, Ukaegbu CI, Horiguchi M, Fehlmann T, Uno H, et al. Comparison of colorectal and endometrial microsatellite instability tumor analysis and premm 5 risk assessment for predicting pathogenic germline variants on multigene panel testing. J Clin Oncol. 2020;38:4086–94.
26 Borras J, Albreht T, Audisio R, Briers E, Casalli P, Esperou H, et al. Policy statement on multidisciplinary cancer care. Eur J Cancer. 2014;50:475–80.
27 Pullen LC. Evidence supports the use of multidisciplinary team meetings. CA Cancer J Clin. 2017;67:351–2.
28 Basta YL, Baur OL, van Dieren S, Klinkenbijl JHG, Fockens P, Tytgat KMAJ. Is there a benefit of multidisciplinary cancer team meetings for patients with gastrointestinal malignancies? Ann Surg Oncol. 2016;23:2430.
29 Kanth P, Grimmett J, Champine M, Burt R, Samadder NJ. Hereditary colorectal polyposis and cancer syndromes: a primer on diagnosis and management. Am J Gastroenterol. 2017;112:1509–25.