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Impact of the COVID-19 pandemic in the early-onset colorectal cancer

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A B S T R A C T

The COVID19 pandemic has affected the spectrum of cancer care worldwide. Early onset colorectal cancer (EOCRC) is defined as diagnosis below the age of 50. Patients with EOCRC faced multiple challenges during the COVID19 pandemic and in some institutions it jeopardized cancer diagnosis and care delivery. Our study aims to identify the clinicopathological features and outcomes of patients with EOCRC in our Centre during the first wave of the pandemic in comparison with the same period in 2019 and 2021.

Patients with EOCRC visited for the first time at Vall d'Hebron University Hospital in Spain from the 1st March to 31st August of 2019, 2020 and 2021 were included in the analysis. 177 patients with EOCRC were visited for the first time between 2019 and 2021, of which 90 patients met the inclusion criteria (2019: 30 patients, 2020: 29 patients, 2021: 31 patients). Neither differences in frequency nor in stage at diagnosis or at first visit during the given periods were observed. Of note, indication of systemic therapy in the adjuvant or metastatic setting was not altered. Days to treatment initiation and enrollment in clinical trials in this subpopulation was not affected due to the COVID-19 outbreak.

Introduction

Colorectal cancer (CCR) ranks as the third most common cancer type and the second leading cause of cancer-related death [1]. Colorectal cancer incidence and mortality rates vary worldwide and are tightly linked to human development index level, with low and middle-income countries historically presenting the lowest rates [2]. Over the past decades, there is a trend to stabilization or decreasing in high-income countries mainly due to the acquisition of a healthier lifestyle and the implementation of colorectal cancer screening programs that lead to the removal of precursor lesions interrupting the adenoma-carcinoma sequence [3], while increasing rates are being registered in low and middle-income countries.

As cancer is an ageing-associated disease, the rates of CRC incidence and death grow steeply after the age of 50, with an estimated 90% of worldwide cases and deaths occurring after this age. The median age of onset of colon cancer is 68 in men and 72 years in women, while for rectal cancer is 63 years in both genders [4]. However, cancer registries are reporting accumulating evidence of increasing global rates of early-onset CRC (EOCRC), generally defined as CRC diagnosed in individuals <50 years of age. In recent years, an increase in the incidence of CRC in young patients has been observed worldwide, especially in high-income countries [5]. In Europe, from 2004 to 2016 the incidence of CRC increased annually by 7.9% in subjects aged 20–29 years; by 4.9% in subjects aged 30–39 years; and by 1.6% in age group 40–49 years [6]. This trend is expected to continue in the coming years, with a predicted increase in the incidence of colon and rectal cancer in patients between 20 and 34 years of age of 90% and 124%, respectively, by 2030 [7].

The reasons for this increase in incidence are not entirely clear. Only 10–30% of patients with EOCRC patients have cancer predisposition syndromes and, of these, 34–71% have a diagnosis of Lynch syndrome

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[8,9]. Plausible hypotheses to explain this increased incidence are related to the exposome and include increased exposure to possible risk factors, such as a Western-style diet enriched in ultra-processed foods, lack of physical exercise, obesity or the use of antibiotics [10–12].

Early-onset CRC presents clinical and pathological characteristics in comparison with CRC in older patients. Thus, the diagnosis of the disease in advanced stages of the disease (stage III-IV) is more frequent (62% vs 46%) and has been associated with a higher prevalence of synchronous and metachronous CRC than in older patients. This may be due to the lack of screening programs in this subpopulation and the delay in the diagnosis. In terms of pathological features, a higher frequency of aggressive and less differentiated tumors has been observed, and a higher prevalence of signet ring cell histology [13]. However, at the molecular level, the frequency of molecular alterations is similar to that described in older patients.

This progressive elevation in the incidence of EOCRC collided in 2020 with the COVID-19 pandemic. In response to the spread of the SARS-CoV-2, countries and territories all over the world enforced lockdowns of varying stringency. In Spain, a national lockdown was implemented on 15 March 2020. Strict precautions and restrictions lasted for 2 months, requiring home confinement and strict lockdown, and authorities steadily lifted restrictions until the ending of the state of alarm on 21 June 2020. Accordingly, in the first half of the year 2020, the spectrum of cancer care was profoundly challenged worldwide by the unfolding of the SARS-CoV-2 pandemic. Most healthcare systems were affected by limitation of hospital attendance and a substantial decrease in cancer screenings, medical visits, therapy initiation or continuation, and curative surgeries, with variation by cancer type and site of service has been reported [14,15]. In the United States, at the highest peak of the pandemic in April 2020, screenings for colon, breast, prostate, and lung cancers were lower by 75%, 85%, 74%, and 56%, respectively [14].

Our investigation sought to study the impact of the first wave of the COVID-19 pandemic on the number of patients with EOCRC visited for the first time in our Centre during that period and the care delivery.

Material and methods

This retrospective analysis assessed whether variation in health service for EOCRC was significantly impacted by the stay-at-home policies during the first wave of the COVID-19 pandemic. To accomplish this task, we collected data from all patients with a diagnosis of colorectal cancer below the age of 50 years visited for the first time in the Department of Oncology at Vall d'Hebron University Hospital in Spain between 1 March and 31 August in 2019, 2020 and 2021, to have a matched period of time over the years. The study was approved by the Institutional Review Board (independent ethics committee) at our center and was conducted in accordance with the requirements of the regulatory authorities.

Data about clinicopathological features, including age, sex, stage at diagnosis and at visit in our Centre and molecular status (RAS/BRAF and microsatellite status), and treatment were extracted from digital medical records. We compared data from the year of the first wave of the pandemic with the previous year and the following year. Indication of systemic therapy in the adjuvant or metastatic setting and delay in treatment initiation was reviewed by two different medical oncologists. In case of disagreement, a third medical oncologist would be involved.

Data were summarized using descriptive statistics. Quantitative and categorical variables were compared using Wilcoxon rank-sum test and Fisher's exact test, assuming a P value (α) of 0.05.

Results

A total of 176 patients with EOCRC were visited for the first time between 2019 and 2021 (Fig. 1). Of them, 30, 29 and 31 patients were visited from the 1st March to 31st August in 2019, 2020 and 2021 respectively, adding up a total of 90 patients for the given periods, who were captured for the analysis. Comparison of the number of patients visited for the first time in our Department during those periods (area in blue in Fig. 1) did not show statistical differences ($p = 0.70$).

Concerning clinicopathological features, data about age at onset, sex and primary tumour location are summarized in Table 1. Stage at visit in our Centre did not differ in time, nor was influenced by the Sars-CoV-2 pandemic, since no statistical differences were found when comparing stage at first visit in 2019, 2020 and 2021 between March and August ($p = 0.7$, Fig. 2). Stage at diagnosis was also consistent during those periods (Table 1).

Last, the first wave of the pandemic did not impact on disease management. Indication of systemic therapy in the adjuvant or metastatic setting was reviewed by two different medical oncologists. No disagreement on treatment decision occurred and it was determined that disease management had not been altered by the pandemic in any case. Nine, 11 and 12 patients started a new line of treatment between the 1st March to 31st August in 2019, 2020 and 2021 and no statistical differences were found when comparing frequency of patients starting treatment ($p = 0.6$). Delay in treatment initiation for patients with EOCRC was not observed, as median days and range to treatment initiation since first visit was 18.5 (17–23), 20 (7–76) and 23 (2–69), respectively, with

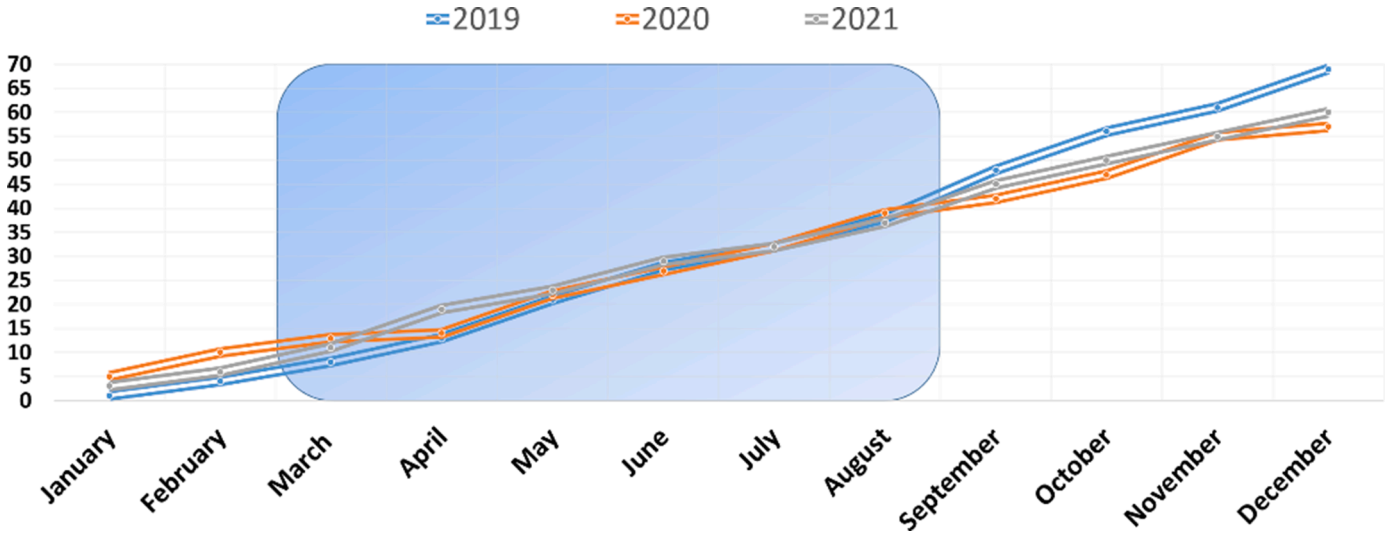

Fig. 1. Accumulative number of patients with EOCRC visited in our Centre for the first time in 2019, 2020 and 2021.

Table 1
Clinicopathological features of patients with EOCRC visited for the first time between March 1st and August 31st of 2019, 2020 and 2021.

	2019 $N = 30$	2020 $N = 29$	2021 $N = 31$
Age, median (range)	41 (27–49)	43 (29–49)	44.5 (30–49)
Sex, n			
Female	15 (50%)	14 (48%)	15 (48%)
Male			
	15 (50%)	15 (52%)	16 (52%)
Site of primary tumour, n (%)			
Right	8 (28%)	4 (14%)	12 (39%)
Left	13 (44%)	20 (69%)	12 (39%)
Rectum	9 (30%)	5 (17%)	7 (22%)
Stage at diagnosis, n (%)			
Localized	7 (23%)	3 (11%)	5 (16%)
Metastatic	23 (77%)	26 (89%)	26 (84%)
Stage at visit in our Centre, n (%)			
Localized	11 (37%)	8 (28%)	13 (42%)
Metastatic	19 (63%)	21 (72%)	18 (58%)
Molecular status, n (%)			
KRAS mutated	19 (64%)	13 (45%)	14 (45%)
NRAS	2 (7%)	0 (0%)	1 (3%)
BRAF	2 (7%)	1 (4%)	1 (3%)
Unknown	2 (7%)	4 (14%)	8 (26%)
Microsatellite status, n (%)			
MSI	1 (3%)	2 (7%)	1 (3%)
MSS			
	29 (97%)	27 (93%)	30 (93%)

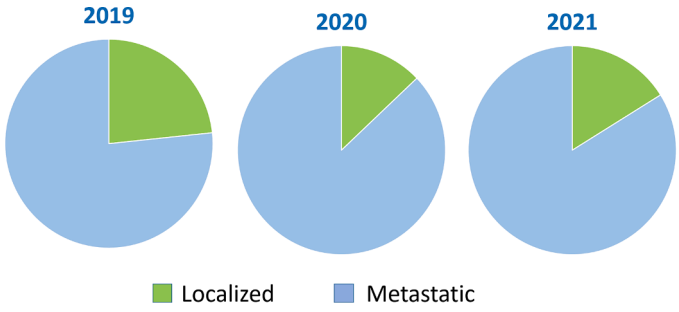

Fig. 2. Stage disease at first visit in our Centre for patients with EOCRC visited for the first time between March 1st and August 31st of 2019, 2020 and 2021.

no statistical differences ($p = 0.40$). Although many clinical trials in Oncology restricted patient inclusion during the first wave, enrollment of patients with EOCRC was not affected in our Centre, given that a similar number of them were included in clinical trials, in comparison with the previous and the following year (9, 7 and 7 patients with EOCRC were included in clinical trials, $p = 0.7$).

Discussion

The rapidly disseminating SARS-CoV-2 during the first wave of the pandemic in 2020 and the limited health care system capacity imposed an unprecedented emergency to prioritize the appropriate allocation of health care resources. One of the major fears of individuals and health caregivers during the first wave was the heavy impact that the pandemic could be having on the health care delivery system, with special emphasis for oncological patients. An analogy for contemporary warfare has been used for oncological patients and oncological medical providers during the COVID-19 outbreak, since it was essential to achieve a balance between Sars-CoV-2 exposures and delay in cancer diagnosis and risks due to significant treatment disruptions [16].

But a third front should be considered for patients under 50 with a diagnosis of CRC. In fact, a delayed path to diagnosis has been previously reported for subjects with EOCRC [17]. In 2018, prior to the beginning of the pandemic, a comprehensive survey launched by The Colorectal Cancer Alliance aiming to capture self-reported experiences of EOCRC patients and survivors completed by more than 1000 subjects reported that 62% of the respondents had been waiting more than 3 months after first symptom noticed to visit a doctor. After first consultation, many patients suffered misdiagnosis and had to visit different practitioners (75% of surveyees were seen but at least two physicians before diagnosis) leading to a higher frequency of disseminated disease as a consequence of delay in diagnosis.

In this analysis, we aimed to investigate whether the first wave of the Sars-CoV-2 outbreak had an impact on a population that is currently being deeply ravaged by the continuous challenge they have to face. The first wave in Spain is considered to have lasted from March to June 2020, coinciding with the state of alarm [18]. Data collected in the analysis was conscientiously extended to the end of August to capture as well those subjects under 50 whose cancer-related symptoms started at the very beginning of the COVID-19 pandemic but who did not visit a doctor until much later due to restrictions policies, to mitigate the bias due to the inherent delay in this subpopulation in visiting a doctor. Fortunately, we did not observe differences in terms of frequency, stage or management during the given period, in comparison with the previous and the following years. The lack of impact of the COVID-19 pandemic on the EOCRC that we report could be related to the fact that, upon diagnosis, patients with EOCRC often receive more aggressive treatment due to their robust performance and young age [19–22], which could have led to practitioners to maintain and prioritize management without variation despite the limitation of health care resources. Nevertheless, our study is limited by its retrospective nature and the small sample size due to the rareness of this population and the time frame of the first wave of the COVID-19 pandemic in Spain.

Although enrollment in clinical trials was worldwide altered during the first wave due to safety concerns and although there were national restrictions on displacements, referral of patients that had been previously treated in other hospitals to our Centre was not affected and patients were not deprived from treatment opportunities, as the number of patients included in clinical trials reflects. Finally, the wide range in time to treatment initiation is explained by inclusion in clinical trials, requiring molecular tumour board, prescreening, slot assignation and screening and by turnaround time in molecular testing in patients with recent diagnosis.

CRediT authorship contribution statement

Iosune Baraibar: Conceptualization, Visualization, Project administration, Methodology, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Ariadna García:** Project administration, Methodology, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Francesc Salvà:** Methodology, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Javier Ros:** Methodology, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Nadia Saoudi:** Methodology, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Raquel Comas:** Project administration, Methodology, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Gloria Castillo:** Project administration, Methodology, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Mireia Sanchis:** Project administration, Methodology, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Alejandro García-Álvarez:** Methodology, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Jorge Hernando:** Methodology, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Jaume Capdevila:** Methodology, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Marta R Castells:** Methodology, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Marc Martí:** Methodology, Resources,

Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Stefania Landolfi:** Methodology, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Eloy Espín:** Methodology, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Begoña Navalpotro:** Methodology, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Jorge Guevara:** Methodology, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Cristina Dopazo:** Methodology, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Paolo Nuciforo:** Project administration, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Ana Vivancos:** Project administration, Methodology, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Josep Tabernero:** Conceptualization, Visualization, Project administration, Methodology, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Elena Élez:** Conceptualization, Visualization, Project administration, Methodology, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Conflicts of interest

Iosune Baraibar has received accommodation and travel expenses from Amgen, Merck, Sanofi and Servier.

Ariadna García does not report any conflict of interest.

Francesc Salvà reports personal financial interests, honoraria for advisory role, travel grants, research grants (past 5 years): Hoffman La-Roche, Sanofi Aventis, Amgen, Merck Serono, Servier, Bristol-Myers Squibb.

Javier Ros has received personal speaker honoraria from Sanofi and Amgen, and accommodation expenses from Pierre-Fabre, Servier, Amgen, and Merck.

Nadia Saoudi has received accommodation and travel expenses from Amgen and Merck.

Raquel Comas does not report any conflict of interest.

Gloria Castillo does not report any conflict of interest.

Mireia Sanchis does not report any conflict of interest.

Alejandro García-Álvarez has received personal speaker honoraria from Angelini and has received accommodation and travel expenses from Pfizer, Ipsen, EISAI, Advanz and AAA.

Jorge Hernando has received personal speaker honoraria from Novartis, Eisai, Ipsen, Angelini, Adacap and Terumo.

Jaume Capdevila reports personal financial interest in form of scientific consultancy role (speaker and advisory roles) from Novartis, Pfizer, Ipsen, Exelixis, Bayer, Eisai, Advanced Accelerator Applications, Amgen, Sanofi, Lilly, Hudchmed, ITM, Merck Serono, Roche, Esteve, Advanz and research support in form of research grants from Novartis, Pfizer, Astrazeneca, Advanced Accelerator Applications, Eisai, Amgen and Bayer.

Marta R Castells has received personal speaker honoraria from ROVI and accommodation expenses from BMS, Amgen and Merck.

Marc Martí does not report any conflict of interest.

Stefania Landolfi does not report any conflict of interest.

Eloy Espín having served as Proctor for Intuitive Surgical.

Begoña Navalpotro does not report any conflict of interest.

Jorge Guevara does not report any conflict of interest.

Cristina Dopazo does not report any conflict of interest.

Paolo Nuciforo reports personal financial interest in form of scientific consultancy role for Targos Molecular Pathology. His-institution has received research funding from Daiichi-Sankyo.

Ana Vivancos reports personal financial interest for advisory board from Bayer, Bristol Meyers Squibb, Guardant Health, Incyte and Roche; personal financial interest in form of stocks/shares from Reveal Genomics and research support in form of research grants from Incyte and Roche.

Josep Tabernero reports personal financial interest in form of scientific consultancy role for Array Biopharma, AstraZeneca, Bayer, Boehringer Ingelheim, Chugai, Daiichi Sankyo, F. Hoffmann-La Roche Ltd, Genentech Inc, HalioDX SAS, Hutchison MediPharma International, Ikena Oncology, Inspirna Inc, IQVIA, Lilly, Menarini, Merck Serono, Merus, MSD, Mirati, Neophore, Novartis, Ona Therapeutics, Orion Biotechnology, Peptomyc, Pfizer, Pierre Fabre, Samsung Bioepis, Sanofi, Scandion Oncology, Scorpion Therapeutics, Seattle Genetics, Servier, Sotio Biotech, Taiho, Tessa Therapeutics, TheraMyc and Tolremo Therapeutics. Stocks: Oniria Therapeutics and also educational collaboration with Imedex/HMP, Medscape Education, MJH Life Sciences, PeerView Institute for Medical Education and Physicians Education Resource (PER).

Elena Élez has received personal speaker honoraria from Organon and Novartis; and personal advisory board honoraria from Amgen, Bayer, Hoffman-La Roche, Merck Serono, Sanofi, Pierre Fabre, MSD, and Servier. Her institution has received research funding from Amgen Inc, Array Biopharma Inc, AstraZeneca Pharmaceuticals LP, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Debiopharm International SA, F. Hoffmann-La Roche Ltd, Genentech Inc, HalioDX SAS, Hutchison MediPharma International, Janssen-Cilag SA, MedImmune, Menarini, Merck Health KGAA, Merck Sharp & Dohme, Merus NV, Mirati, Novartis Farmacéutica SA, Pfizer, Pharma Mar, Sanofi Aventis Recherche & Développement, Servier, Taiho Pharma USA Inc. She held/holds non-remunerated roles as Coordinator of the SEOM +MIR Section of Residents and Young Assistants of the Sociedad Española de Oncología Médica (SEOM), Speaker of the ESMO Academy of the European Society for Medical Oncology (ESMO), and Volunteer member of the ASCO Annual Meeting Scientific Program Committee: Developmental Therapeutics – Immunotherapy of the American Society of Clinical Oncology (ASCO).

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