Portuguese Results of the ETICC Study: Impact of the Pandemic COVID-19 in the Diagnosis and Management of Colorectal Cancer in 2020 in Portuguese Hospitals

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Abstract

Introduction: The outbreak of coronavirus disease 2019 (COVID-19) had affected clinical practice in several ways, including the restriction of nonessential endoscopic procedures. Therefore, our aim was to evaluate how colorectal cancer (CRC) diagnosis and management was affected during the first year of pandemics in Portugal. *Methods:* This is a Portuguese substudy of the French retrospective multicentric study ETICC (*Etude de l'Impact de la pandémie COVID-19 sur le diagnostic et la prise en charge du Cancer Colorectal*). We compared patients' characteristics, clinical manifestations, CRC staging at diagnosis, delay to first medical appointment, histological diagnosis, surgical and medical treatments between the year previous to the pandemics (control) and the first year of pandemics. *Results:* We included 766 patients: 496 in the control group and 270 in the COVID group. There was no significant difference in CRC staging at diagnosis between both groups, with 21% being diagnosed as metastatic in the control group and 22% in the first year of pandemics ($p = 0.770$). Contrary to what happened in France, there was a significant decrease in CRC diagnosis in asymptomatic patients (25–8.4%; $p < 0.001$) and after a positive fecal immunochemical test (20.8–11.3%; $p = 0.002$) during the pandemics. Although the increase in the overall complication rate at diagnosis was nonsignificant, in Portugal, there was a significant increase in diagnosis of abdominal occlusion (12.1–18.1%; $p = 0.033$). In Portugal, time between the beginning of symptoms and the first medical appointment significantly increased from a median of 50 days to 64 days during COVID ($p < 0.001$). On the contrary, time between histological diagnosis and tumor resection had significantly decreased from a median of 65 to 39 days ($p < 0.001$). Time between histological diagnosis and neoadjuvant treatment was not statistically different (median of

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64–67 days; *p* = 0.590), as was time between histological diagnosis and palliative chemotherapy (median of 50–51 days; *p* = 1.000). Time from CRC resection and adjuvant treatment has significantly decreased from a median of 54 to 43 days (*p* = 0.001). ***Discussion:*** We found a significant impact in CRC diagnosis in the first year of pandemics, more pronounced than what was found in France. These are likely related not only with the closing of endoscopy units but also with the difficulties patients had in finding an appointment with their general practitioners. On the other hand, both in France and Portugal, the first year of pandemics did not worsen CRC staging at diagnosis and did not significantly affect medical and surgical treatments once the diagnosis was made.

Resultados Portugueses do Estudo ETICC: Impacto da pandemia COVID-19 no diagnóstico e tratamento do cancro colorretal em 2020

Palavras Chave

COVID-19 · Cancro colorretal · Pandemia

Resumo

Introdução: A pandemia provocada pelo coronovírus (COVID-19) condicionou a prática clínica de múltiplas formas, incluindo a restrição a exames endoscópicos não urgentes. Por este motivo, decidimos avaliar o impacto do primeiro ano de pandemia no diagnóstico e tratamento do cancro colorretal (CCR) em Portugal. ***Métodos:*** Este é um subestudo do estudo Francês retrospetivo multicêntrico ETICC (*Etude de l'Impact de la pandémie COVID-19 sur le diagnostic et la prise en charge du Cancer Colorectal*). Foram comparadas as características dos doentes, manifestações clínicas, estadiamento do CCR ao diagnóstico, intervalos entre primeiro contacto médico neste contexto, diagnóstico histológico e tratamentos, entre o primeiro ano de pandemia e o ano precedente. ***Resultados:*** Foram incluídos 766 doentes, 496 no grupo controlo e 270 no grupo COVID. Em França e em Portugal não se verificou um agravamento no estadiamento do CCR à data do diagnóstico no primeiro ano de pandemia, com 21% dos casos metastáticos à data de diagnóstico no grupo controlo e 22% no primeiro ano da pandemia (*p* = 0.770). Contudo, apenas em Portugal se constatou uma redução significativa do número de CCR em doentes assintomáticos (25% para 8.4%; *p* < 0.001) ou após uma pesquisa de sangue oculto positiva (20.8% para 11.3%; *p* = 0.002) durante a pandemia. Apesar do aumento na taxa de complicações ao diagnóstico não ser significativa, em Portugal a taxa de diagnósticos em contexto de oclusão intestinal aumentou significativamente (12.1% para 18.1%; *p* = 0.033). Em Portugal, o tempo entre início dos sintomas e a primeira consulta médica aumentou significativamente, de uma mediana de 50 para 64 dias durante o COVID (*p* < 0.001). Por outro lado, o tempo entre diagnóstico histológico e resseção tumoral reduziu significativamente de 65 para 39 dias (*p* < 0.001). O tempo entre diagnóstico histológico e tratamento neoadjuvante (mediana de 64 para 67 dias; *p* = 0.590) ou quimioterapia paliativa (mediana de 50 para 51 dias; *p* = 1.000) não foi estatisticamente significativo, tendo decrescido significativamente o tempo entre resseção e adjuvância (mediana de 54 para 43 dias, *p* = 0.001). ***Discussão:*** Este estudo evidenciou um impacto significativo no diagnóstico de CCR durante o primeiro ano de pandemia, mais pronunciado que em França. Este achado dever-se-á não só à limitação do acesso aos exames endoscópicos, mas também à dificuldade da população portuguesa em aceder aos Cuidados de Saúde Primários. Por outro lado, tanto em França como em Portugal, no primeiro ano de pandemia não se verificou um agravamento no estadiamento ou atraso no tratamento médico e cirúrgico do CCR.

Introduction

The outbreak of coronavirus disease 2019 (COVID-19), caused by coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly around the world, constituting an unprecedented pandemic that has influenced various aspects of daily activity in hospitals. The Portuguese government officially declared the lockdown on March 18, 2020, which lasted until May 2020 [1].

COVID-19 has affected clinical practice in several ways and disrupted health care delivery systems worldwide. Measures were taken to prevent the transmission of SARS-CoV-2, including the restriction of nonessential endoscopic procedures [2]. However, despite the benefits in terms of pandemic control, the prolonged suspension of everyday gastrointestinal practice has already resulted in a compromised colorectal cancer (CRC) screening and management [3–8]. Additionally, the fear of getting infected with SARS-CoV-2 has led to a delay in hospital admission in some patients, with harmful consequences

concerning cancer management [9]. During the lockdown period, CRC detection rates decreased 72% in the UK [3] and 37% in Hong Kong [4]. Despite the recovery by the second semester of 2020, the rates of CRC diagnosis have not exceeded those previous to the pandemic [7]. Therefore, the pandemic has led to an overall delay in CRC diagnosis. In Portugal, CRC is the most prevalent cancer, accounting for 17.4% of new cancer cases in 2020, and is the second cause of cancer-related death [10]. Since mortality rate is highly dependent on the TNM staging [11] at diagnosis, an increase in the morbidity and mortality rate from CRC is expected with the pandemics. In England, it has been calculated that over 3,500 fewer people were diagnosed and treated for CRC between April and October 2020 [7].

In Portugal, during the lockdown period, about half of the hospitals only performed emergency endoscopies. Of the 15 public hospitals involved in CRC screening, which is recommended for asymptomatic patients between 50 and 74 years old [12], only 1 did not suspend this screening. Although by May 2020, most Portuguese gastroenterology departments and endoscopy clinics had started resuming their usual activity, by September 2020, most departments had not recovered to levels similar to those pre-pandemic [1].

The authors considered it important to evaluate how the pandemic has affected the CRC diagnosis and management during the first year of COVID-19 pandemic. Therefore, this study aimed to compare the context in which the CCR diagnosis was made, the CCR staging at diagnosis, and all the timings between the beginning of symptoms and CCR medical/surgical management.

Materials and Methods

This is a Portuguese substudy of the French retrospective matched case-control multicentric study ETICC (*Etude de l'Impact de la pandémie COVID-19 sur le diagnostic et la prise en charge du Cancer Colorectal*) coordinated by the *Association Nationale des Gastroentérologues des Hôpitaux Généraux*. The French study included 11 centers, with a total of 961 patients – 470 in the COVID group (CRC diagnosed between the 1st of March 2020 and the 28th of February 2021) and 491 in the control group (CRC diagnosed in 2019), with preliminary results already presented in France [13]. In Portugal, 4 centers were included. Patients included in the control group had a diagnosis of CRC made between 1 January 2019 and 29 February 2020 and patients included in the COVID group had a diagnosis performed between 1 March 2020 and 28 February 2021.

Data were collected regarding patients' characteristics (sex, age at diagnosis, comorbidities) and tumors' characteristics (clinical manifestations, staging according to the 8th TNM classification from the Union for International Cancer Control [10], complications at diagnosis). Dates of the first medical consultation concerning CRC, histological diagnosis, surgical resection, neoadjuvant treatment, adjuvant, or palliative chemotherapy were also collected. It was registered if there was a perception of a delay in the diagnosis or treatment of the CRC.

To compare the "control" and "COVID" groups, nonparametric tests were used to compare quantitative variables, and χ^2 and the conditional independence Mantel-Haenszel test were used to compare qualitative variables. A p value <0.05 was considered statistically significant.

Results

We included 766 patients: 496 in the control group and 270 in the COVID group, with similar median ages (70 years old, IQR 58–82) and sex distribution (60% men) between groups. Although there were more patients with comorbidities in the COVID group (10.4%) than in the control group (7.7%), this was not statistically different ($p = 0.202$).

Concerning the staging of the CRC at the time of diagnosis, no statistical difference was found between groups ($p = 0.770$). About one-fourth of patients had a metastatic cancer (TNM 4) at diagnosis (21% in the control group and 22% in the COVID group). Early stages (TNM 0 and 1) represented 19% of those in the control group and 15% in the COVID group (Fig. 1). Similar results were found in France, with 28% of metastatic CRC at diagnosis in both control and COVID groups and without significant differences in TNM staging before and during the pandemics.

In the control group, 25% of patients were asymptomatic at the time of diagnosis, whereas in the COVID group, this proportion significantly decreased to 8.4% ($p < 0.001$). There was also a significant decrease in diagnosis after a positive fecal immunochemical test (FIT): 20.8% in the control group and 11.3% in the COVID group ($p = 0.002$). In France, no significant decrease in CRC diagnosis in asymptomatic patients was found and the proportion of patients with a CRC diagnosis after a positive FIT has significantly increased (Table 1). 31.7% and 41.1% of patients initiated their follow-up at the hospital after going to the emergency room in the control and COVID groups, respectively, and 53.6% and 48.5% after consulting their general practitioner ($p = 0.020$).

The rate of complications at the time of diagnosis has increased, but without statistical significance, from 17.8% in the control group to 23.7% in the COVID group ($p = 0.050$). Abdominal occlusion was the principal complication and has significantly increased during COVID,
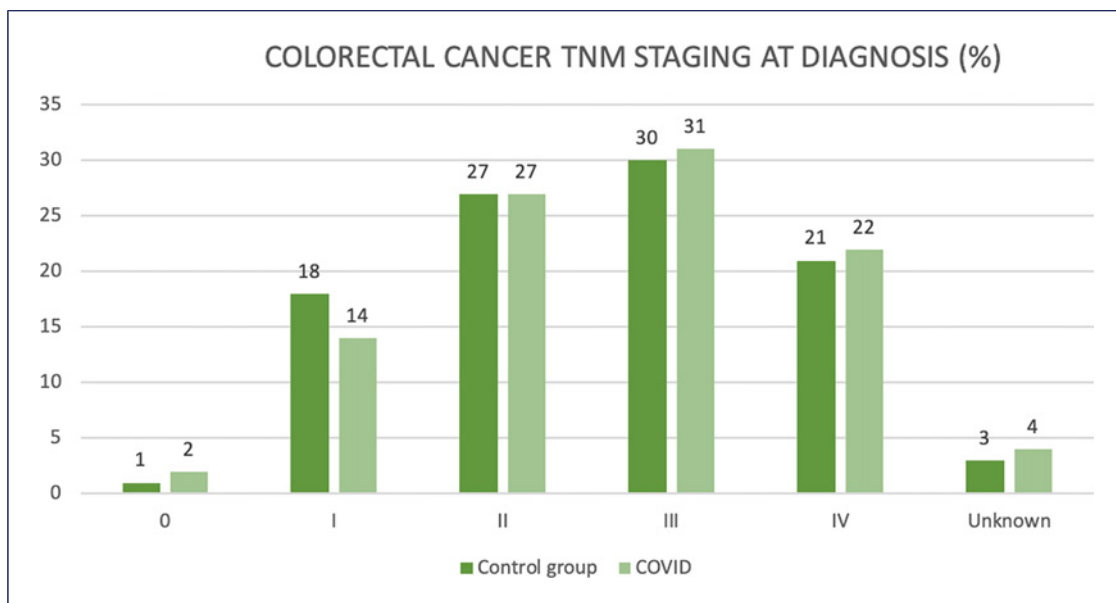
Fig. 1. CRC TNM staging at diagnosis in the control and COVID groups.

Table 1. Comparison of clinical presentation at CRC diagnosis between control and COVID groups

	Control group	COVID group	*p* value
Asymptomatic patients, %			
Portugal	25.0	8.4	**<0.001**
France	20.8	25.5	0.081
Diagnosis after a positive FIT, %			
Portugal	20.8	11.3	**0.002**
France	19.0	10.0	**<0.001**
Presence of a complication at diagnosis, %			
Portugal	17.8	23.7	0.05
France	20.6	18.5	0.377
Type of complication, %			
Occlusion	72.6	82.3	0.145
Perforation	6.0	9.7	
Abscess	11.9	3.2	
Hemorrhage	9.5	4.8	

CRC, colorectal cancer; FIT, fecal immunochemical test.

from 12.1 to 18.1% ($p = 0.033$). In France, there was no significant difference in the rate of all complications or abdominal occlusion at the time of diagnosis.

A delay in the diagnosis and management was inferred in 16.6% of patients in the control group and in 33.6% in the COVID group ($p < 0.001$). Time between the beginning of symptoms and the first medical appointment significantly increased from a median of 50 days in the control group to 64 days in the COVID group ($p < 0.001$). On the contrary, time between histological diagnosis and tumor resection has decreased from a median of 65 days in the control group to 39 days in the COVID group ($p < 0.001$). Time between histological diagnosis and neoadjuvant treatment was not statistically different (median of 64–67 days; $p = 0.590$), as was time between histological diagnosis and palliative chemotherapy (median of 50–51 days; $p = 1.000$). Time from CRC resection and adjuvant treatment has significantly decreased from 54 days in the control group to 43 days in the COVID group ($p = 0.001$). In France, the only statistically significant interval difference was between CRC histological diagnosis and resection, which, similarly to what happened in Portugal, decreased from 29.5 in the control group to 23 days in the COVID group ($p = 0.013$).

Discussion

This study only included 4 district hospitals: 3 from the Lisbon region and 1 from southern Portugal. Therefore, and since our study has a relatively small sample size, these results might not represent the real impact of the first year of COVID-19 pandemic on CRC diagnosis and treatment in Portugal. Moreover, the data were collected retrospectively, leading to some missing and misleading data regarding timings, reducing the reliability of the analysis concerning the delays between symptoms, diagnosis, and treatment. Although it was not the end point of our study and since we cannot directly compare the number of CRC diagnosis

between the control group (which included not only the year 2019 but also the first 2 months of 2020) and the COVID group (which included 12 months), we can still admit that fewer CRCs were diagnosed and treated during the first year of pandemics (average of 35.4 CRC diagnosis per month in the control group against 22.5 in the COVID group).

Nonetheless, our study revealed that in Portugal, unlike what happened in France, it took more time for patients to find medical care after the appearance of symptoms, with less CRC diagnosis in asymptomatic patients or after a positive FIT. We also identified a significant increase in the proportion of patients presenting with bowel obstruction. These findings might be biased by the smaller sample size in the Portuguese cohort, but we also believe that they are likely related not only with the closing of endoscopy outpatient clinics during the lockdown but also to the difficulties that Portuguese patients encountered in making an appointment with their general practitioner since general practitioners were overwhelmed with the follow-up of patients infected with COVID.

On the other hand, both in France and Portugal, the first year of pandemics did not worsen the TNM stage at diagnosis and did not significantly affect most medical and surgical treatments once the diagnosis was made. In fact, time between histological diagnosis and surgical resection has decreased in both countries, probably because most elective non-oncological surgeries were postponed during the pandemics. However, the significant increase in abdominal occlusion can mislead these results since histological diagnosis and surgical resection are usually simultaneous in these situations. What is still unknown is whether we were able to resume consultations and colonoscopies in time and number to recover without further damage or whether a significant increase in advanced CRC at diagnosis will occur after the first year of pandemics.

Our results are in line with the previously published data concerning the impact of COVID-19 in digestive cancers in Portugal, with more patients presenting at the emergency department and referred after urgent surgery and fewer patients referred from the outpatient clinic. Similarly, tumor staging in CCR was not significantly different before and during the first months of pandemics [13]. The significant decrease we found in CCR diagnosis in asymptomatic patients or after a positive FIT is probably related to the already published data concerning the decrease in the number of colonoscopies performed during the first months of pandemics in Portugal [1].

In conclusion, although we might already assume the pandemics negatively affected CRC diagnosis and management, this study has a short follow-up to deduce the real impact of COVID-19 in overall CRC burden. Further research including the subsequent years of pandemics must be pursued to infer its real consequences regarding CRC morbimortality.

Statement of Ethics

The study protocol was reviewed and approved by the ethics committees of the hospitals involved. Written informed consent was not obtained. Exemption was granted due to the retrospective and anonymous design of the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Maria Ana Rafael: data collection and manuscript writing. Cristiana Sequeira, Sónia Isabel da Silva Barros, and Bárbara Silva Abreu: data collection. Cristina Teixeira: Portuguese coordinator of the ETICC study and manuscript revision. Pierre Lahmek: statistical analysis. Marine Besnard and Bruno Lesgourgues: coordinators of the ETICC study.

Data Availability Statement

Data collected are available to editors, reviewers, and readers in a total anonymity excel file.

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