Association of COVID-19 Lockdown With the Tumor Burden in Patients With Newly Diagnosed Metastatic Colorectal Cancer

Alain R. Thierry, PhD; Brice Pastor, PhD; Ekaterina Pisareva, MD, PhD; Francois Ghiringhelli, MD, PhD; Olivier Bouché, MD, PhD; Christelle De La Fouchardière, MD, PhD; Julie Vanbockstael, MD, PhD; Denis Smith, MD, PhD; Eric François, MD, PhD; Mélanie Dos Santos, MD, PhD; Damien Botsen, MD, PhD; Stephen Ellis, MD; Marianne Fonck, MD, PhD; Thierry André, MD, PhD; Emmanuel Guardiola, MD, PhD; Faiza Khemissa, MD, PhD; Benjamin Linot, MD, PhD; J. Martin-Babau, MD; Yves Rinaldi, MD, PhD; Eric Assenat, MD, PhD; Lea Clavel, MD, PhD; Sophie Dominguez, MD, PhD; Celine Gavoille, MD, PhD; David Sefrioui, MD, PhD; Veronica Pezzella, MS; Caroline Mollevi, PhD; Marc Ychou, MD, PhD; Thibault Mazard, MD, PhD

Abstract

IMPORTANCE The COVID-19 pandemic has been associated with substantial reduction in screening, case identification, and hospital referrals among patients with cancer. However, no study has quantitatively examined the implications of this correlation for cancer patient management.

OBJECTIVE To evaluate the association of the COVID-19 pandemic lockdown with the tumor burden of patients who were diagnosed with metastatic colorectal cancer (mCRC) before vs after lockdown.

DESIGN, SETTING, AND PARTICIPANTS This cohort study analyzed participants in the screening procedure of the PANIRINOX (Phase II Randomized Study Comparing FOLFIRINOX + Panitumumab vs FOLFOX + Panitumumab in Metastatic Colorectal Cancer Patients Stratified by RAS Status from Circulating DNA Analysis) phase 2 randomized clinical trial. These newly diagnosed patients received care at 1 of 18 different clinical centers in France and were recruited before or after the lockdown was enacted in France in the spring of 2020. Patients underwent a blood-sampling screening procedure to identify their RAS and BRAF tumor status.

EXPOSURES mCRC.

MAIN OUTCOMES AND MEASURES Circulating tumor DNA (ctDNA) analysis was used to identify RAS and BRAF status. Tumor burden was evaluated by the total plasma ctDNA concentration. The median ctDNA concentration was compared in patients who underwent screening before (November 11, 2019, to March 9, 2020) vs after (May 14 to September 3, 2020) lockdown and in patients who were included from the start of the PANIRINOX study.

RESULTS A total of 80 patients were included, of whom 40 underwent screening before and 40 others underwent screening after the first COVID-19 lockdown in France. These patients included 48 men (60.0%) and 32 women (40.0%) and had a median (range) age of 62 (37-77) years. The median ctDNA concentration was statistically higher in patients who were newly diagnosed after lockdown compared with those who were diagnosed before lockdown (119.2 ng/mL vs 17.3 ng/mL; P < .001). Patients with mCRC and high ctDNA concentration had lower median survival compared with those with lower concentration (14.7 [95% CI, 8.8-18.0] months vs 20.0 [95% CI, 14.1-32.0] months). This finding points to the potential adverse consequences of the COVID-19 pandemic and related lockdown.

CONCLUSIONS AND RELEVANCE This cohort study found that tumor burden differed between patients who received an mCRC diagnosis before vs after the first COVID-19 lockdown in France. The (continued)
Abstract (continued)

findings of this study suggest that CRC is a major area for intervention to minimize pandemic-associated delays in screening, diagnosis, and treatment.

Introduction

The unprecedented burden placed on health systems worldwide by the COVID-19 crisis has had numerous and substantial implications for cancer care.1,2 People have been more reluctant to come to health care facilities for services because of fear of infection, particularly those with cancer, given that cancer is considered a comorbidity. Reduction or suspension of screening programs and diagnostic services has been a factor in delays in diagnosis in many countries.1,3-5 Access to treatment has been restricted to minimize the risk of SARS-CoV-2 exposure during therapy procedures for patients with cancer.3 The reprioritization of human resources and equipment to COVID-19 pandemic management has also been associated with the provision of suboptimal or delayed care.1,6

These implications have been exacerbated by the COVID-19 containment measures implemented by different countries, which have tended to evolve from recommendations and restrictions to lockdowns at both the local and national levels.1,2 Such measures were initially seen in the first few months of 2020 in Asia and Oceania and had spread to Europe and North and South America by March, depending mainly on the date of the first SARS-CoV-2 infection cases in those areas.2 The sheer number of patients with COVID-19 infection necessitating hospitalization and critical care has continued to strain health services and already limited resources. Individual fears of contracting the virus as well as restrictions on movement imposed by local and national authorities have generated additional physical and psychological barriers for patients who need to access essential care.

We conducted a cohort study to evaluate the association of the COVID-19 pandemic lockdown with the tumor burden of patients who were newly diagnosed with metastatic colorectal cancer (mCRC) before vs after lockdown. To our knowledge, no such clinical evaluation has been performed thus far. Conventional circulating biomarkers, such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9, do not fully satisfy the clinical requirements for monitoring colorectal cancer (CRC) tumor burden in clinical practice because of their moderate levels of sensitivity and specificity.7 Therefore, we used circulating tumor DNA (ctDNA) analysis to assess the patients’ tumor burden.

Circulating tumor DNA is a newly identified source of biological information that has attracted the attention of researchers and clinicians in numerous fields.8 It has substantial clinical potential in oncology, including in molecular profiling, detection of residual disease, control of treatment efficacy, detection of clonal resistance, surveillance of recurrence, and screening.9 It first showed its promise by contributing to companion tests as a liquid biopsy, and then it obtained European Medicines Agency approval for use in the detection of sensitizing and/or resistant somatic alterations in oncogivers, such as those in lung cancer and melanoma, as a tool to guide clinicians in selecting targeted therapies.9,10 Numerous studies have reported that tumors secrete DNA into the bloodstream in quantities that are proportional to their masses,11-13 especially in the case of mCRC, according to several investigations11,14-16 and work that illustrated the association of total ctDNA concentration with increasing hepatic tumor mass as identified by magnetic resonance imaging (eFigure 1 in the Supplement). Thus, ctDNA offers analytical and clinical advantages over conventional antigenic biomarkers, such as CEA, and may be considered as a surrogate marker of disease progression, at least in mCRC.14,15,17-20
Methods

This cohort study included patients from the screening procedure of the ongoing PANIRINOX study (Phase II Randomized Study Comparing FOLFIRINOX + Panitumumab vs FOLFOX + Panitumumab in Metastatic Colorectal Cancer Patients Stratified by RAS Status from Circulating DNA Analysis), who were recruited before and after the first COVID-19 lockdown was enacted in France in the spring of 2020. In the PANIRINOX trial, treatment (FOLFIRINOX [leucovorin, fluorouracil, irinotecan, and oxaliplatin] + panitumumab or mFOLFOX6 [modified fluorouracil, leucovorin, and oxaliplatin] + panitumumab) is allocated according to a randomization procedure. However, the present work was carried out on an ad hoc basis at the time of the screening procedure and before randomization. The PANIRINOX study was reviewed and approved by the human investigations committee Sud Méditerranée IV. All patients provided written informed consent before the screening procedure. This cohort study, along with other trial-related documents, received approval from Unicancer, the sponsor of the PANIRINOX study, which received authorization from the Agence Nationale de Sécurité du Médicament et des Produits de Santé and the Comités de Protection des Personnes, according to French national regulatory requirements. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. 21

The PANIRINOX study is a first-line, phase 2 randomized clinical trial that assesses the activity of a combination chemotherapy with fluorouracil, leucovorin, oxaliplatin, and panitumumab with or without irinotecan (FOLFOX + panitumumab vs FOLFIRINOX + panitumumab) in patients with unresectable mCRC, who were selected by their RAS (GenBank 6237) and BRAF (GenBank 673) tumor status, which was obtained from ctDNA analysis. To our knowledge, it is the first interventional study to use ctDNA as a companion test for selecting patients with mCRC for anti–estimated glomerular filtration rate targeted therapy (eAppendix in the Supplement). It involves 31 hospitals and cancer centers in France. Its primary end point is the complete response rate defined as the complete disappearance of metastatic lesions and CEA level normalization after a maximum of 12 treatment cycles. Among the major patient selection criteria are age 18 to 75 years, Eastern Cooperative Oncology Group Performance Status score of 0 or 1, no previous treatment for metastatic disease, and no previous use of oxaliplatin in an adjuvant setting (eAppendix in the Supplement).

In France, the first mandatory home lockdown of 2020 lasted 55 days, from March 17 to May 11. The PANIRINOX study screening was consequently interrupted for 53 days, starting on March 19 and ending on May 11. We compared the ctDNA concentration in all patients who underwent screening after the lockdown (from May 14, 2020, to September 3, 2020, a 110-day period) with the ctDNA concentration in all patients who underwent screening before the lockdown (from November 11, 2019, to March 9, 2020). These patients were newly diagnosed with mCRC and received care at 1 of 18 different clinical centers in France. We also compared the ctDNA concentration in the prelockdown and postlockdown groups and the fractional cohorts of those who were included from the start of the PANIRINOX study (June-September 2017, September 2017-January 2018, January-April 2018, April-August 2018, August-December 2018, December 2018-March 2019, March-July 2019, and July-November 2019). Preanalytical conditions of the ctDNA analysis followed strict guidelines and methodologies that have been previously validated.22-25

Patients were screened through a blood-sampling procedure to identify their RAS and BRAF tumor status according to plasma analysis of circulating cell-free DNA, using IntPlex technology (DiaDx SAS).22,23 Those whose tumors were considered as RAS and BRAF wild type were subsequently included in the PANIRINOX study if they fulfilled all other inclusion criteria (eAppendix in the Supplement). The present study, therefore, benefited from the accuracy with which ctDNA can evaluate tumor burden and from the trial’s rigorous inclusion procedure and reporting, all of which supported the accuracy of assessment needed to achieve the objective of this study. We examined all patients who underwent screening before and after lockdown (N = 268), regardless of their RAS and BRAF sequence variation status, to preclude any potential bias associated...
with sequence variation status. Given the interventional impact of ctDNA analysis in the PANIRINOX study, the analysis was completed within 5 days of receipt of the blood samples. In addition to ctDNA parameters analysis, we simultaneously collected demographic and clinicobiological parameters that are known to have prognostic value in this setting. 26, 27

Statistical Analysis

Statistical analysis of prelockdown and postlockdown data was performed with the GraphPad Prism, version 6.01 (GraphPad Software Inc) and survival analysis was conducted with Stata, version 16.0 (StataCorp LLC). Where appropriate, data were log transformed before statistical analysis. Continuous variables were compared using the Mann-Whitney test, and categorical variables were compared using the Pearson χ² test. Median follow-up was calculated with the reverse Kaplan-Meier method. Overall survival, defined as the time between the date of first metastatic diagnosis and the date of death from any cause, was estimated with the Kaplan-Meier method and compared using the log-rank test. Correlation analysis was performed using the Spearman test. Hazard ratios (HRs) are given with their 95% CIs. A 2-sided P < .05 was considered to be statistically significant.

Results

We analyzed the ctDNA concentration in 80 patients who underwent screening before (n = 40) or after (n = 40) the first COVID-19 lockdown in France in 2020. These patients included 48 men (60.0%) and 32 women (40.0%) and had a median (range) age of 62 (37-77) years.

As shown in Figure 1, the median (interquartile range [IQR]) ctDNA concentration was 17.3 (9.57-43.78) ng/mL before lockdown and 119.2 (43.38-315.8) ng/mL after lockdown (eTable 1 in the Supplement). This postlockdown ctDNA concentration represented a 6.9-fold increase. A statistically significant difference between the 2 cohorts was observed (17.3 [95% CI, 13.58-33.52] vs 119.2 [95% CI, 53.13-278.1]; P < .001) (Figure 1 and Figure 2). The values obtained from patients included before lockdown (n = 40) were similar to those obtained from all patients in the fractional cohorts (n = 188), who were included in the PANIRINOX study starting 30 months before lockdown, showing a median (IQR) ctDNA concentration in plasma of 13.0 (6.43-46.13) ng/mL (Figure 2). In addition, the median (IQR) ctDNA concentration in the fractional cohorts showed no statistical difference from the levels in the prelockdown cohort (June-September 2017: 29.94 [5.27-149.2] ng/mL, P > .99; September

![Figure 1. Comparison of Circulating Tumor DNA (ctDNA) Concentration in Patients With Newly Diagnosed Metastatic Colorectal Cancer in the Prelockdown and Postlockdown Periods](https://jamanetwork.com/)

The long horizontal bars indicate the median; shorter bars, the 95% CIs; and each dot, the ctDNA concentration in a single patient. The Mann-Whitney test was performed to compare the patient distributions and revealed a significant difference between the prelockdown and postlockdown periods.
2017-January 2018: 9.13 [6.37-13.61] ng/mL, \( P = .07 \); January-April 2018: 18.36 [3-220.2] ng/mL, \( P = .71 \); April-August 2018: 18.51 [6.99-55.06] ng/mL, \( P = .99 \); August-December 2018: 13.38 [9.17-55.85] ng/mL, \( P = .89 \); December 2018-March 2019: 9.19 [4.72-40.91] ng/mL, \( P = .27 \); March-July 2019: 18.38 [5.11-49.25] ng/mL, \( P = .54 \); July-November 2019: 12.91 [7.05-49] ng/mL, \( P = .40 \), whereas they were statistically different from the levels in the postlockdown cohort (Figure 2).

Regarding patient characteristics, no difference was observed in the groups who received a diagnosis before vs after lockdown (Table; eFigures 2 and 3 in the Supplement). The delay of blood sample delivery was also similar, as was the alteration in ctDNA concentration and the alteration in allele frequency (eFigures 4 to 6; eTable 1 in the Supplement). For example, the median (IQR) alteration in allele frequency was 10.45% (0.88%-19.22%) in the prelockdown cohort and 6.18% (0.45%-21.96%) in the postlockdown cohort (eTable 1). The median white blood cell count, lactate dehydrogenase (LDH) level, and CEA level were slightly higher in the postlockdown vs prelockdown setting, but the differences were not statistically significant (Table; eFigures 7 to 9 in the Supplement). The ctDNA concentration was significantly associated with an increase in LDH level (\( r = 0.72; P < .001 \)) and white blood cell count (\( r = 0.73; P < .001 \)) in patients who underwent screening after lockdown. The CEA level was associated with an increase of ctDNA concentration in patients in the prelockdown (\( r = 0.38; P = .04 \)) and postlockdown (\( r = 0.22; P = .24 \)) groups (eFigures 10 to 14 in the Supplement). When dichotomizing this cohort by the median (IQR) ctDNA concentration (24.4 [2.3-1406] ng/mL), we found that patients who had higher ctDNA plasma concentration showed a statistically lower median survival (14.7 [95% CI, 8.8-18.0] months vs 20.0 [95% CI, 14.1-32.0] months; HR, 1.74 [95% CI, 1.2-2.6]; \( P = .005 \)) (Figure 3B; eTable 2 in the Supplement).

The boxplot represents circulating tumor DNA (ctDNA) concentration in patients in the 110-day fractional cohorts vs patients in the prelockdown (n = 40) and postlockdown (n = 40) periods. The Mann-Whitney test was performed to compare patient distributions. The horizontal bars inside the boxes indicate the median; error bars, the 10th to 90th percentile; squares, the median between the 25th percentile and the 75th percentile; whiskers, the 10th to 90th percentile; and each dot, the ctDNA concentration of a single patient outside the 10th to 90th percentile.
Discussion

The differences in tumor burden between patients who were diagnosed before vs after lockdown and the resulting risk of reduced survival point to the association between the pandemic-related lockdown and unfavorable consequences for patients with newly diagnosed mCRC, who may have delayed their first visit to an oncologist. The lower number of mCRC diagnoses during the beginning of the COVID-19 pandemic\(^1\)\(^3\) may be associated with patients’ reluctance to visit a physician or health care facility. A possible reason for this reluctance was fear of COVID-19 infection or burdening the health system, as described by a quote from a patient with cancer\(^2\)\(^8\) (eAppendix in the Supplement).

In addition to patients’ subjective anxieties and reticence, numerous reports observed the

| Table. Patient Characteristics |
|--------------------------------|
| Characteristic                | No. (%) | Prelockdown group | Postlockdown group | P value |
| No. of patients               | 80 (100) | 40 (50)           | 40 (50)            | 9.86    |
| Age, y                        |         | 62 (37-77)        | 61 (39-77)         | .65     |
| Missing data                  | 1        | 0                 | 1                 | .56     |
| Sex                           | 48 (60.0) | 25 (62.5)     | 23 (57.5)          | .62     |
| Location of primary tumor     | 19 (24.0) | 9 (23.1)       | 10 (25.0)          | .84     |
| Left colon                    | 60 (76.0) | 30 (76.9)     | 30 (75.0)          | .84     |
| Location of primary tumor     | 1        | 1                 | 0                 | .81     |
| Liver involvement             | 55 (84.6) | 27 (84.4)      | 28 (84.9)          | .96     |
| Limited liver disease         | 10 (15.4) | 5 (15.6)       | 5 (15.1)           | .81     |
| LDH level, U/L                | 345 (137-2690) | 263 (148-2690) | 410 (137-1256)    | .46     |
| WBC count, G/L                | 9.1 (4.4-27.3) | 8.5 (4.8-22.4) | 9.4 (4.4-27.3)    | .31     |
| CEA level, ng/mL              | 39.8 (0.7-13590) | 34.0 (0.7-9902) | 40.8 (1.4-13590) | .49     |

Abbreviations: CEA, carcinoembryonic antigen; LDH, lactate dehydrogenase; WBC, white blood cell.

SI conversion factors: To convert CEA level to micrograms per liter, multiply by 1.0; LDH level to microkatal per liter, multiply by 0.0167; WBC count to ×10⁹/L, multiply by 0.001.
considerable delays in sending out millions of solicitations for bowel cancer screening and a backlog (in England alone) of thousands of individuals awaiting further investigation after receiving a positive screening result.² ³

Although the COVID-19 lockdown was a necessity, it led to unintended consequences in the diagnosis of various cancers. The pandemic has affected all aspects of the cancer care pathway, especially the areas of screening, diagnosis, and surgical treatment.⁴ ²⁹ ³⁰ For instance, De Vincentiis et al.⁴ reported that the number of cancer diagnoses in Italy decreased by 39% in the first 6 months of 2020 compared with the mean number recorded in 2018 and 2019. The highest decreases in diagnosis rates were observed in prostate cancer (75%), bladder cancer (66%), and CRC (62%), when the number of new or first metastatic malignant diagnoses during lockdown (weeks 11-20 of 2020) was compared with the number in the same period in the previous 2 years.⁴ Given that colonoscopy numbers are closely associated with initial CRC diagnoses, a 55% decrease in colon examinations was found between March and April 2020, as reported by Cancer Australia.³¹

In addition to the abrupt reduction (86%) in preventive CRC screenings in the US after the declaration of the COVID-19 national emergency (March 1, 2020), a 64% decrease (ie, 95 000) in the number of colonoscopies performed between March 15 and June 16, 2020, compared with previous years has been reported.³¹ Furthermore, after June 16, 2020, weekly volumes remained 36% lower than the pre–COVID-19 levels.³¹ Particularly relevant to the present study is the finding of an

Figure 3. Overall Survival Analysis of Patients With Newly Diagnosed Metastatic Colorectal Cancer (mCRC)

A Kaplan-Meier survival curve of the full cohort (N = 135)

B Kaplan-Meier survival curve and log-rank test by ctDNA concentrations dichotomized by the median (24.4 ng/mL)

C Kaplan-Meier survival curve and log-rank test by ctDNA concentrations dichotomized by the median (100 ng/mL)

ctDNA indicates circulating tumor DNA.
observational Taiwanese cancer registry study based on 39,000 newly identified CRC cases that increases in the risk of death were significantly associated with the delay between diagnosis and treatment; the results for an interval of 31 to 150 days were an HR of 1.51 (95% CI, 1.43-1.59) and an HR of 1.64 (95% CI, 1.54-1.76) for 151 days or more. The French ONCOCARE-COV study (Oncology Care Pathway's Modifications Impact During COVID-19 Pandemic) confirmed a reduction in CRC fecal immunochemical test screenings (−86%), CRC biomolecular somatic analyses (−59%), and the number of new patient files being discussed in multidisciplinary tumor board meetings (−39%) during the 3-month lockdown period in 2020 compared with the same trimester in 2019. On a broader level, the ONCOCARE-COV study revealed the decreases in screening (−86% to −100%), diagnosis (−39%), and surgical treatment (−30%).

Several studies have generated model-based estimates of the clinical consequences of delaying the first visit of patients who have been newly diagnosed with cancer. In the UK, Sud et al found that even a modest delay of 3 to 6 months in surgery for cancer may mitigate 19% to 43% of the life-years gained by hospitalization. Lai et al estimated that approximately 18,000 excess cancer deaths over the next 12 months may be attributed to the COVID-19 crisis. In the US, in addition to the 1 million deaths from breast cancer that are expected to occur in the next decade, approximately 10,000 deaths have been estimated as the outcome of pandemic-related delays of less than 6 months in screening and cancer care.

The health outcomes of COVID-19–associated lockdowns are particularly notable in oncology, and repeated or extended lockdowns may lead to decreased surveillance and advance care planning. To address this threat, regulatory institutions, such as the American Society of Clinical Oncology and the European Society for Medical Oncology, established recommendations and guidance for delivering care to patients with cancer during the pandemic and lockdowns. To minimize risks to patients with gastrointestinal malignant neoplasms, for instance, the American College of Surgeons, Society of Surgical Oncology, French digestive oncology intergroup guideline (Thésaurus National de Cancérologie Digestive), and the European Society for Medical Oncology set new priorities, such as prioritizing surgery for colon cancer involving imminent obstruction or for locally advanced rectal cancer. Similarly, new priorities concerning CRC management were set by the Colorectal Cancer Alliance, Thésaurus National de Cancérologie Digestive, National Comprehensive Cancer Network, European Society for Medical Oncology, and the City of Hope National Medical Center. Such recommendations were used to reclassify and reprioritize ongoing CRC care and management during the lockdown.

When CRC is diagnosed early, the treatment outcome is more favorable. In a large meta-analysis, Hanna et al reported that even a 4-week delay in treatment was associated with increased mortality for 7 cancers, particularly CRC (HR, 1.04; 95% CI, 0.95-1.13). This quantitative observation, although focused on a small sample of a specific type of patient with cancer, showed that delays in diagnosis would unnecessarily cost lives and life-years. This increase in ctDNA concentration after lockdown is striking and points to the levels of tumor burden at diagnosis, which have been associated with patient survival.

To estimate the association between tumor burden and survival, we retrospectively analyzed data from 2 previous clinical studies that examined ctDNA concentration in the same way. Each of these studies used an identical, rigorous method to assess ctDNA before patients began first-line chemotherapy. All patients with newly diagnosed mCRC were identified from their data. In the present study, patients who were diagnosed with higher ctDNA plasma concentration had a statistically lower median survival compared with those with lower ctDNA concentration. Such comparisons illustrate and anticipate the lockdown’s unfavorable implications for patient survival. The full lockdown-related consequences for patient survival will be examined in a future 3-year survival study.

In response to the proliferation of the virus and its variants, many countries will likely implement further lockdowns. Thus, we believe that corrective action should be taken to minimize the clinical implications of delayed cancer diagnosis, including (1) reinforcing mass screening using the fecal
occult blood test, (2) improving the communication strategy to avoid late patient diagnosis, and (3) providing adequate resources and creating robust plans to deal with backlogs in diagnosis and treatment. Patient triage could be performed by a quick assessment of tumor burden and testing of biomarkers with predictive and prognostic value (such as immunohistochemistry for mismatch repair proteins; sequence variation analysis for KRAS [GenBank 3845], NRAS [GenBank 4893], and BRAF). For this purpose, we believe that ctDNA analysis that reveals qualitative (tumor molecular profiling) or quantitative information can be an ideal tool, as previously reported. The diagnostic power of ctDNA would be largely improved by using a multianalyte approach. Such a strategy would include both qualitative (such as genetic or epigenetic alterations) and quantitative (such as tissue or cell of origin or structural characteristics) markers. Artificial intelligence may also help achieve this goal as highlighted in a recent report.

Despite the growing number of reports about the magnitude of the burden that the pandemic has placed on health systems worldwide, no study has yet evaluated the increased tumor burden of patients who received a postlockdown cancer diagnosis. To our knowledge, this study was the first to assess the association between COVID-19 restrictions and delayed treatment and diagnostic services for a specific cancer. The findings suggest that CRC can benefit from interventions to minimize the adverse clinical outcomes of pandemic-associated delays.

Limitations
This study has some limitations. Although LDH level, white blood cell count, and to a lesser extent, CEA level were associated with an increase of ctDNA concentration, we could not provide tumor volume assessment by imaging in this study. Nonetheless, ctDNA concentration offers strong additional power to the routinely assessed serum markers. Although numerous studies found that lockdown was associated with delays in care and care seeking, we could not draw a direct association between our observation on tumor burden and the distinct delays in care for the newly diagnosed patients enrolled in the PANIRINOX study. It would be premature to evaluate the outcomes of the delays in screening, diagnosis, and treatment. This exploratory study instead offers a snapshot of a situation that continues to evolve.

Conclusions
This cohort study pointed out the differences in tumor burden for patients who were diagnosed before vs after COVID-19 lockdown, including risk of reduced survival for those with postlockdown diagnoses. The findings of this study suggest that CRC is a major area for intervention to minimize the clinical implications of a pandemic-associated diagnostic delay.
Author Contributions: Drs Thierry and Mazard had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Thierry, Botsen, Ellis, Fonck, Ychou, Mazard.

Acquisition, analysis, or interpretation of data: Thierry, Pastor, Pisareva, Ghiringhelli, Bouché, De La Fouchardièr, Vanbockstael, Smith, François, Dos Santos, André, Guardiola, Khemissa, Linot, Martin-Babau, Rinaldi, Assenat, Clavel, Dominguez, Gavoille, Sefrioui, Pezzella, Mollevi, Mazard.

Drafting of the manuscript: Thierry, Pastor, Ellis, Khemissa, Mollevi, Ychou, Mazard.

Critical revision of the manuscript for important intellectual content: Thierry, Pisareva, Ghiringhelli, Bouché, De La Fouchardièr, Vanbockstael, Smith, François, Dos Santos, Botsen, Fonck, André, Guardiola, Linot, Martin-Babau, Rinaldi, Assenat, Clavel, Dominguez, Gavoille, Sefrioui, Pezzella, Mazard.

Statistical analysis: Thierry, Pastor, Pisareva, Assenat, Mollevi.

Obtained funding: Thierry, Smith, Fonck, Mazard.

Administrative, technical, or material support: Thierry, Pastor, Martin-Babau, Assenat, Clavel, Sefrioui, Pezzella, Ychou.

Supervision: Thierry, Rinaldi, Mazard.

Conflict of Interest Disclosures: Dr Bouché reported receiving personal fees from Amgen, Roche, Merck, and Servier outside the submitted work. Dr De La Fouchardièr reported receiving personal fees from Servier, Amgen, Bayer, Eisa, Ipsen, Lilly, Merck, MSD, Pierre Fabre, and Roche as well as nonfinancial support (travel for American Society of Clinical Oncology and European Society for Medical Oncology meetings) from Amgen, Roche, Sanofi-Aventis, and Servier. Dr Botsen reported receiving personal fees from Amgen, Chugai Pharmaceutical Co Ltd, Pierre Fabre, Sanofi, and Fresenius Kabi outside the submitted work. Dr André reported receiving personal fees from Amgen, Astra Zeneca, Astellas Pharma Inc, Bristol Myers Squibb, MSD, Gritstone Oncology, GlaxoSmithKline, Servier, Pierre Fabre, Roche, Ventana, Hallix, and Kaleido Biosciences outside the submitted work. Dr Khemissa reported receiving other (Congress fees) from Roche, Servier, Ipsen, and Fresenius Kabi as well as personal fees from Sanofi and Bayer outside the submitted work. Dr Sefrioui reported receiving personal fees from Ipsen, Roche, Servier, and Bayer outside the submitted work. Dr Thierry reported being a shareholder of DiaDx SAS. Dr Mazard reported receiving grants from Amgen SAS; nonfinancial support from Servier and MSD; and personal fees from Merck Serono, Bristol Myers Squibb, Sanofi Genzyme, AAA, Sandoz, and Bayer outside the submitted work. No other disclosures were reported.

Funding/Support: The PANIRINOX study was funded by Amgen and sponsored by Unicancer Research and Development (R&D). Dr Pastor was supported in part by grant INCa_Inserm_DGOS_12553 from SIRIC Montpellier Cancer. Dr Thierry was supported by INSERM.

Role of the Funder/Sponsor: The funder, Amgen, had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript, but had a role in the decision to submit the manuscript for publication. The sponsor, Unicancer R&D, had a role in the collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank the patients and their families for their trust; all of the participating physicians and supporting staff; Unicancer Datacenter members (Institut Régional du Cancer de Montpellier); all clinician research associates and clinical co-investigators; and Marie Bergeaud, MsBS, Unicancer R&D. We thank Cynthia Sanchez, MS, and Andrei Kudriavtsev, MD, Institut Régional du Cancer de Montpellier, for providing excellent technical assistance. These individuals received no additional compensation, outside of their usual salary, for their contributions. We also thank Cormac McCarthy, MsLitt, McCarthy Consultant, for editing the English-language manuscript; Mr McCarthy received compensation for his services.

REFERENCES

1. Richards M, Anderson M, Carter P, Ebert BL, Mossialos E. The impact of the COVID-19 pandemic on cancer care. *Nat Cancer*. 2020;1(6):1-3. doi:10.1038/s43018-020-0074-y
2. Uzzo RG, Kutinov A, Geynisman DM. COVID-19: cancer screening, diagnosis, post-treatment surveillance in uninfected patients during the pandemic and issues related to COVID-19 vaccination in cancer patients. Accessed October 9, 2020. https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-cancer-screening-diagnosis-treatment-and-posttreatment-surveillance-in-uninfected-patients-during-the-pandemic

3. Greenwood E, Swanton C. Consequences of COVID-19 for cancer care—a CRUK perspective. Nat Rev Clin Oncol. 2021;18(1):3-4. doi:10.1038/s41571-020-00446-0

4. De Vincentis L, Carr RA, Mariani MP, Ferrara G. Cancer diagnostic rates during the 2020 ‘lockdown’, due to COVID-19 pandemic, compared with the 2018-2019: an audit study from cellular pathology. J Clin Pathol. 2021;74(3):187-189. doi:10.1136/jclinpath-2020-206833

5. Kaufman HW, Chen Z, Niles J, Fesko Y. Changes in the number of US patients with newly identified cancer before and during the coronavirus disease 2019 (COVID-19) pandemic. JAMA Netw Open. 2020;3(8):e2017267. doi:10.1001/jamanetworkopen.2020.17267

6. Vecchione L, Stintzing S, Pentheroudakis G, Douillard J-Y, Lordick F. ESMO management and treatment adapted recommendations in the COVID-19 era: colorectal cancer. ESMO Open. 2020;5(suppl 3):e000826. doi: 10.1136/esmoopen-2020-000826

7. Ludwig JA, Weinstein JN. Biomarkers in cancer staging, prognosis and treatment selection. Nat Rev Cancer. 2005;5(11):845-856. doi:10.1038/nrc1739

8. Thierry AR, El Messaoudi S, Gahan PB, Anker P, Stroun M. Origins, structures, and functions of circulating DNA in oncology. Cancer Metastasis Rev. 2016;35(3):347-376. doi:10.1007/s10555-016-9629-x

9. Wan JC, Massie C, García-Corbacho J, et al. Liquid biopsies come of age: towards implementation of circulating tumour DNA. Nat Rev Cancer. 2017;17(4):223-238. doi:10.1038/nrc.2017

10. Diaz LA Jr, Bardelli A. Liquid biopsies: genotyping circulating tumor DNA. J Clin Oncol. 2014;32(6):579-586. doi:10.1200/JCO.2012.45

11. Wei T, Zhang Q, Li X, et al. Monitoring tumor burden in response to FOLFIRINOX chemotherapy via profiling circulating cell-free DNA in pancreatic cancer. Mol Cancer Ther. 2019;18(1):196-203. doi:10.1158/1535-7163.MCT-17-1298

12. Fiala C, Diamandis EP. Utility of circulating tumor DNA in cancer diagnostics with emphasis on early detection. BMC Med. 2018;16(1):166. doi:10.1186/s12916-018-1157-9

13. Kananen L, Hurme M, Jylhä M, et al. Circulating cell-free DNA level predicts all-cause mortality independent of other predictors in the Health 2000 survey. Sci Rep. 2020;10(1):13809. doi:10.1038/s41598-020-70526-9

14. Thierry AR, Pastor B, Jiang Z-Q, et al. Circulating DNA demonstrates convergent evolution and common resistance mechanisms during treatment of colorectal cancer. Clin Cancer Res. 2017;23(16):4578-4591. doi:10.1158/1078-0432.CCR-17-0232

15. Saluja H, Karapetis CS, Pedersen SK, Young GP, Symonds EL. The use of circulating tumor DNA for prognosis of gastrointestinal cancers. Front Oncol. 2018;8:275. doi:10.3389/fonc.2018.00275

16. Xu X, Yu Y, Shen M, et al. Role of circulating free DNA in evaluating clinical tumor burden and predicting survival in Chinese metastatic colorectal cancer patients. BMC Cancer. 2020;20(1):1006. doi:10.1186/s12885-020-07516-7

17. El Messaoudi S, Mouliere F, Du Manoir S, et al. Circulating DNA as a strong multimarker prognostic tool for metastatic colorectal cancer patient management care. Clin Cancer Res. 2016;22(12):3067-3077. doi:10.1158/1078-0432.CCR-15-0297

18. Barault L, Amatu A, Siravegna G, et al. Discovery of methylated circulating DNA biomarkers for comprehensive non-invasive monitoring of treatment response in metastatic colorectal cancer. Gut. 2018;67(11):1995-2005. doi:10.1136/gutjnl-2016-313372

19. Spindler KG. Methodological, biological and clinical aspects of circulating free DNA in metastatic colorectal cancer. Acta Oncol. 2017;56(1):7-16. doi:10.1080/0284186X.2016.1253861

20. Hamfjord J, Guren TK, Dajani O, et al. Total circulating cell-free DNA as a prognostic biomarker in metastatic colorectal cancer before first-line oxaliplatin-based chemotherapy. Ann Oncol. 2019;30(7):1088-1095. doi:10.1093/annonc/mdz139

21. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg. 2014;12(12):1495-1499. doi:10.1016/j.ijsu.2014.07.013

22. Thierry AR, Mouliere F, El Messaoudi S, et al. Clinical validation of the detection of KRAS and BRAF mutations from circulating tumor DNA. Nat Med. 2014;20(4):430-435. doi:10.1038/nm.3511
23. Thierry AR, El Messaoudi S, Mollevi C, et al. Clinical utility of circulating DNA analysis for rapid detection of actionable mutations to select metastatic colorectal patients for anti-EGFR treatment. Ann Oncol. 2017;28(9):2149-2159. doi:10.1093/annonc/mdx330

24. Meddeb R, Pisareva E, Thierry AR. Guidelines for the preanalytical conditions for analyzing circulating cell-free DNA. Clin Chem. 2019;65(5):623-633. doi:10.1373/clinchem.2018.298323

25. Mouliere F, El Messaoudi S, Pang D, Dritschilo A, Thierry AR. Multi-marker analysis of circulating cell-free DNA toward personalized medicine for colorectal cancer. Mol Oncol. 2014;8(5):927-941. doi:10.1016/j.molonc.2014.02.005

26. Chibaudel B, Bonnetain F, Tournigand C, et al. Simplified prognostic model in patients with oxaliplatin-based or irinotecan-based first-line chemotherapy for metastatic colorectal cancer: a GERCOR study. Oncologist. 2011;16(9):1228-1238. doi:10.1634/theoncologist.2011-0039

27. Goey KKH, Mahmoud R, Serbye H, et al. Reporting of patient characteristics and stratification factors in phase 3 trials investigating first-line systemic treatment of metastatic colorectal cancer: a systematic review. Eur J Cancer. 2018;96:115-124. doi:10.1016/j.ejca.2018.03.026

28. Daly N. Cancer tests and operations dropped up to 50 percent during April lockdown, data shows. Accessed September 14, 2020. https://www.abc.net.au/news/2020-09-14/cancer-tests-operations-drop-up-to-50-per-cent-april-coronavirus/12622396

29. Brugel M, Carlier C, Essner C, et al. Dramatic changes in oncology care pathways during the COVID-19 pandemic: the French ONCOCARE-COV Study. Oncologist. 2021;26(2):e338-e341. doi:10.1002/onco.13578

30. Dimmohamed AG, Visser O, Verhoeven RHA, et al. Fewer cancer diagnoses during the COVID-19 epidemic in the Netherlands. Lancet Oncol. 2020;21(6):750-751. doi:10.1016/S1470-2045(20)30265-5

31. Desai A, Warner J, Kuderer N, et al. Crowdsourcing a crisis response for COVID-19 in oncology. Nat Cancer. 2020;1(5):1-4. doi:10.1038/s43018-020-0065-z

32. Lee SY, Lei B, Mallick B. Estimation of COVID-19 spread curves integrating global data and borrowing information. PLoS One. 2020;15(7):e0236860. doi:10.1371/journal.pone.0236860

33. Hanna TP, King WD, Thibodeau S, et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. BMJ. 2020;371:m4087. doi:10.1136/bmj.m4087

34. Sud A, Torb B, Jones ME, et al. Effect of delays in the 2-week-wait cancer referral pathway during the COVID-19 pandemic on cancer survival in the UK: a modelling study. Lancet Oncol. 2020;21(8):1035-1044. doi:10.1016/S1470-2045(20)30392-2

35. Desai A, Warner J, Kuderer N, et al. Crowdsourcing a crisis response for COVID-19 in oncology. Nat Cancer. 2020;1(5):1-4. doi:10.1038/s43018-020-0065-z

36. Maringe C, Spicer J, Morris M, et al. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. Lancet Oncol. 2020;21(10):1023-1034. doi:10.1016/S1470-2045(20)30388-0

37. Bronkhorst AJ, Ungerer V, Holdenrieder S. Early detection of cancer using circulating tumor DNA: biological, physiological and analytical considerations. Crit Rev Clin Lab Sci. 2019;58(1):174-1758. doi:10.1080/10408363.2019.1700902

38. Tanos R, Tosato G, Otandault A, et al. Machine learning-assisted evaluation of circulating DNA quantitative analysis for cancer screening. Adv Sci (Weinh). 2020;7(18):2000486. doi:10.1002/advs.202000486

SUPPLEMENT.

eAppendix. Materials and Methods

eFigure 1. Illustration of the Correlation Between the Tumor Burden and Total cirDNA Level in Three Metachronous mCRC Patients (One Site) With Increasing Hepatic Tumor Mass as Determined by MRI
eFigure 2. Comparison of the Age of the Newly Diagnosed mCRC Patients From the Pre- and Post-Lockdown Study Cohorts (N=80)

eFigure 3. Comparison of the Gender of the Newly Diagnosed mCRC Patients From the Pre- and Post-Lockdown Study Cohorts (N=80)

eFigure 4. Comparison of the Delivery Delay of Blood Samples From the Newly Diagnosed mCRC Patients From the Pre- and Post-Lockdown Study Cohorts

eFigure 5. Comparison of the Mutant cirDNA Concentration in the Newly Diagnosed Mutant mCRC Patients From the Pre- and Post-Lockdown Study Cohorts (N=48)

eFigure 6. Comparison of the Mutant Allele Frequency in the Newly Diagnosed Mutant mCRC Patients From the Pre- and Post-Lockdown Study Cohorts (N=48)

eFigure 7. Comparison of the Lactate Dehydrogenase (LDH) of the Newly Diagnosed mCRC Patients From the Pre- and Post-Lockdown Study Cohorts (N=56)

eFigure 8. Comparison of the White Blood Cell Count in the Newly Diagnosed mCRC Patients From the Pre- and Post-Lockdown Study Cohorts (N=61)

eFigure 9. Comparison of the Carcinoembryonic Antigen (CEA) in the Newly Diagnosed mCRC Patients From the Pre- and Post-Lockdown Study Cohorts (N=61)

eFigure 10. Pearson r Correlation Analysis of the cirDNA, LDH, White Blood Cell Count, and CEA Levels in the Newly Diagnosed mCRC Patients From the Pre- and Post-Lockdown Study Cohorts

eFigure 11. Scatter Plots Showing the Correlation Between LDH and cirDNA Concentrations in the Pre- and Post-Lockdown Cohorts

eFigure 12. Scatter Plots Showing the Correlation Between White Blood Cell Count and cirDNA Concentrations in the Pre- and Post-Lockdown Cohorts

eFigure 13. Scatter Plots Showing the Correlation Between CEA and cirDNA Concentrations in the Pre- and Post-Lockdown Cohorts

eFigure 14. Scatter Plots Showing the Correlation Between White Blood Cell Count and LDH Concentration in the Pre- and Post-Lockdown Cohorts

eTable 1. CirDNA Analysis for Pre-Lockdown and Post-Lockdown Cohorts

eTable 2. Cox Models Data on Median Survival of mCRC Patients