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Original Research

Risk factors for Coronavirus Disease 2019 (COVID-19) severity and mortality among solid cancer patients and impact of the disease on anticancer treatment: A French nationwide cohort study (GCO-002 CACovid-19)

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https://doi.org/10.1016/j.ejca.2020.09.035
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KEYWORDS
Cancer; COVID-19; Death; Mortality; Mechanical ventilation; Intensive care unit; Chemotherapy; Radiotherapy; Immunotherapy

Abstract  Background: Cancer patients are thought to have an increased risk of developing severe Coronavirus Disease 2019 (COVID-19) infection and of dying from the disease. In this work, predictive factors for COVID-19 severity and mortality in cancer patients were investigated.

Patients and methods: In this large nationwide retro-prospective cohort study, we collected data on patients with solid tumours and CO VID-19 diagnosed between March 1 and 11th June 2020. The primary end-point was all-cause mortality and COVID-19 severity, defined as admission to an intensive care unit (ICU) and/or mechanical ventilation and/or death, was one of the secondary end-points.

Results: From April 4 to 11th June 2020, 1289 patients were analysed. The most frequent cancers were digestive and thoracic. Altogether, 424 (33%) patients had a severe form of COVID-19 and 370 (29%) patients died. In multivariate analysis, independent factors associated with death were male sex (odds ratio 1.73, 95%CI: 1.18–2.52), The Eastern Cooperative Oncology Group Performance Scale (ECOG PS) ≥ 2 (OR 3.23, 95%CI: 2.27–4.61), updated Charlson comorbidity index (OR 1.08, 95%CI: 1.01–1.16) and admission to ICU (OR 3.62, 95%CI 2.14–6.11). The same factors, age along with corticosteroids before COVID-19 diagnosis, and thoracic primary tumour site were independently associated with COVID-19 severity. None of the anticancer treatments administered within the previous 3 months had any effect on mortality or COVID-19 severity, except for cytotoxic chemotherapy in the subgroup of patients with detectable severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by reverse transcriptase polymerase chain reaction (RT-PCR), which was associated with a slight increase of the risk of death (OR 1.53; 95%CI: 1.00–2.34; p = 0.05). A total of 431 (39%) patients had their systemic anticancer treatment (such as chemotherapy, targeted or immune therapy) interrupted or stopped following diagnosis of COVID-19.

Conclusions: Mortality and COVID-19 severity in cancer patients are high and are associated with general characteristics of patients. We found no deleterious effects of recent anticancer treatments, except for cytotoxic chemotherapy in the RT-PCR-confirmed subgroup of patients. In almost 40% of patients, the systemic anticancer therapy was interrupted or stopped after COVID-19 diagnosis.
1. Introduction

The Coronavirus Disease 2019 (COVID-19) outbreak, caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2), has spread rapidly around the world. Cancer patients were considered particularly vulnerable to this disease due to immunosuppression linked not only to the underlying malignancy and/or the anticancer treatments, but also to the advanced age, comorbidities and poor performance status or malnutrition frequently found in these patients. This vulnerability was suggested by small retrospective studies [1,2], and a meta-analysis reported an overall pooled prevalence of cancer of 2% in patients with COVID-19 [3]. Other studies have suggested that patients with cancer have more severe forms of COVID-19 and higher mortality than do patients without cancer [2,4–6]. However, given the discordant data currently available, the impact of anticancer treatments on COVID-19 severity remains unclear, and there is little in the way of evidence-based data to underpin changes in anticancer treatments made during the peak of the pandemic [1,6–10]. It is therefore necessary to analyse large cohorts of cancer patients to better understand the course of COVID-19 and the factors likely to have an impact on its severity.

On 3rd April 2020 and through the French national network of academic oncology groups in solid cancers such as ANOCEF-IGCNO, ARCAGY-GINECO, FFCD, GERCOR, GORTEC with intergroupe ORL, AND IFCT, we set up a large nationwide cohort of solid-tumour cancer patients diagnosed with COVID-19 since March 1. The aims of this cohort study (named GCO-002 CACOVID-19) were to describe clinical and tumour characteristics as well as outcomes in cancer patients with COVID-19, to identify risk factors associated with severity and mortality, in particular concerning active anticancer treatment, and to determine the consequences of the COVID-19 pandemic on the management of cancer care.

2. Materials and methods

2.1. Study design

The GCO-002 CACOVID cohort is a French observational nationwide multicentre cohort, set up by the Groupes Coopérateurs en Oncologie (GCO), a French consortium of academic cooperative groups in oncology, including ANOCEF-IGCNO (Association des Neuro-OnCologues d’Expression Francaise/Inter-Groupe Coopérateur de Neuro-Oncologie) for central nervous system (CNS) tumours, ARCAGY-GINECO (Association de Recherche sur les CAncers GYnecologiques-Groupes d’Investigateurs Nationaux pour l’étude des CAncers Ovariens et du Sein) for gynaecological and breast cancers, FFCD (Fédération Francophone de Cancérologie Digestive) for digestive cancers, GERCOR (Groupe Coopérateur Multidisciplinaire en Oncologie), GORTEC (Groupe d’Oncologie Radiothérapie Tête et Cou) with the Intergroupe ORL for head and neck cancers (H&N) and IFCT (Intergroupe Francophone de Cancérologie Thoracique) for thoracic cancers.

The study was approved by the Research Ethics Committee of Caen Normandy University Hospital for all participating centres (Ref: 04/2020/MOR) and obtained the authorisation of the National Commission for Data Protection and Liberties (Ref CNIL: MLD/MFI/AR204586). It was registered on ClinicalTrial.gov (NCT04397575). In accordance with French regulatory laws, all analysed patients were informed and those not agreeing for the use of their clinical data were excluded.

2.2. Patients

The inclusion criteria were patients with a histologically confirmed solid malignant tumour and a diagnosis of COVID-19. Patients undergoing anticancer treatments or treated curatively more than 5 years previously were excluded. The diagnosis of COVID-19 was based on the confirmation of SARS-CoV-2 infection by quantitative RT-PCR on nasopharyngeal swabs, and/or imaging features consistent with COVID-19 pneumonia on CT-scan or based on highly suggestive symptoms combined with positive severe acute respiratory syndrome coronavirus (SARS-CoV-2) serology. Patients with suggestive symptoms of COVID-19 without a RT-PCR, CT-scan or serological confirmation during the study period were excluded from the analysis. Patients were included in the cohort on the basis of clinicians’ reporting of all consecutive cases diagnosed at their center. The cut-off date for our study was 12th June 2020.

2.3. Data collection

The following data were collected by clinicians on an electronic Case Report Form: age, sex, geographical location of patients’ residences, smoking status, body mass index (BMI), comorbidities with the updated Charlson Comorbidity Index (uCCI) [11], usual medication, type and status of cancer, Eastern Cooperative Oncology Group (ECOG) performance status (PS), anticancer therapy in the 4 weeks and in the 3 months before the COVID-19 diagnosis respectively, the course of the COVID-19 infection, complications and treatment, especially admission to hospital and/or intensive care unit (ICU), the need for supplemental oxygen and mechanical ventilation and death.
2.4. Outcomes

The primary end-point was all-cause mortality following the diagnosis of COVID-19. Secondary outcomes were admission to hospital, admission to an ICU, the need for supplemental oxygen and the use of mechanical ventilation during the COVID-19, and the impact of COVID-19 on management of the cancer. The COVID-19 severity outcome was defined as admission to an ICU and/or use of mechanical ventilation and/or death.

2.5. Statistical analysis

Analyses compared patients who died with those still alive on June 11, 2020. Quantitative variables were described using the usual statistics: \( n \), mean, standard deviation, median, interquartile range, minimum and maximum. Qualitative variables were described using numbers and percentages. Missing values were not counted for percentage calculations. For quantitative variables, groups were compared using a Student or Wilcoxon test and for qualitative variables, using a chi-squared test or a Fisher exact test.

Risk factors associated with death and their odds ratios (ORs) were analysed using a univariate logistic regression model. Multivariate regression was used to estimate ORs and 95% confidence intervals (CI) for each factor. Variables for the multivariate analysis were selected according to their significance in the univariate logistic regression (\( P < 0.05 \)). The same analyses were done for COVID-19 severity. We used SAS version 9.4 for the statistical analyses. The tests were all two-sided with a 5% type one error.

3. Results

3.1. Clinical characteristics of patients and impact of COVID-19 on cancer treatment

From April 4 to 11th June 2020, 1354 patients from 153 institutions were registered in the national cohort database. Among these patients, 1289 met the inclusion criteria (Fig. 1): 727 patients diagnosed with COVID-19 between March 1 and April 2 were included retrospectively; the remaining 562 patients were diagnosed after April 2 and included prospectively. The diagnosis of COVID-19 was made on the presence of detectable SARS-CoV-2 by RT-PCR on nasopharyngeal swabs in 952 (73.8%) patients (including 294 patients who also had images consistent with COVID-19 pneumonia on computed tomography (CT)-scan), on only imaging features consistent with COVID-19 pneumonia on CT-scan in 317 (24.6%) patients and on history of highly suggestive symptoms combined with positive SARS-CoV-2 serology in 20 (1.6%) patients.

The participating institutions were spread over the entire country (Fig. 2) and were general hospitals, university hospitals, private centres and comprehensive cancer centres, accounting for 31%, 28%, 25% and 16% of cases, respectively. The median follow-up from COVID-19 diagnosis was 34 days (95% CI: 32–36).

Patient demographics are shown in Table 1. The median age was 67 years and 795 (62%) patients were male. Digestive cancers were the most common type of cancer (36%), followed by thoracic (24%) and breast (13%) cancers and 59% of patients had a metastatic
disease. During the 3 months before the COVID-19 diagnosis, 755 (59%) patients had received a systemic anticancer treatment.

Eighty-two percent of patients experienced typical symptoms during the course of COVID-19. The most common symptoms were fever (52%), cough (37%) and fatigue (26%). Gastrointestinal symptoms were identified in 12%, anosmia or ageusia were present in only 4% and 3%, respectively. In total, 734 (65%) patients were admitted to hospital, of whom 110 (10%) were admitted to an ICU; 412 (42%) patients required oxygen and 49 (5%) mechanical ventilation.

In the overall cohort, only 107 (11%) patients had their anticancer treatment modified (drug withdrawal or change, modification of the time interval between drug administrations) preventively before the COVID-19 infection because of the pandemic context. However, the systemic anticancer treatment was interrupted or stopped following the diagnosis of COVID-19 in 431 (39%) patients (Table 2).

3.2. Patient outcome and risk factors for death and COVID-19 severity

With a median follow-up of 34 days, 370 (29%) patients had died. The death was attributable to COVID-19 in most patients (N = 322, 87%) and occurred after a median of 10 days (IQR: 5–24). As shown in Table 1, compared with survivors, patients who died were older, more likely to be male and to be current or former smokers, had more frequently comorbidities, long-term or recent corticosteroids (for another reason than COVID-19), angiotensin II antagonists (AIIA) or angiotensin converting enzyme inhibitor (CEI) and anticoagulant therapy as their usual medication. They also had a poorer ECOG PS and a higher proportion of metastatic disease and were more likely to have undergone cytotoxic chemotherapy in the 4 weeks or 3 months before the COVID-19 diagnosis. The impact of immune checkpoint inhibitors or other anticancer treatment on the course of COVID-19 could not be analysed because...
Table 1
Clinical features of the 1289 cancer patients with COVID-19.

| Patients' characteristics | All patients (N = 1289) | Patients who died (N = 370) | Patients who survived (N = 919) | P value |
|---------------------------|--------------------------|-----------------------------|--------------------------------|---------|
| **Age, years**            |                          |                             |                                |         |
| Median (range)            | 67 (19–100)              | 70 (22–98)                  | 66 (58–74)                     | <0.001  |
| <65                       | 534 (42%)                | 121 (33%)                   | 413 (45%)                      | <0.001  |
| 65–74                     | 430 (33%)                | 137 (37%)                   | 293 (32%)                      |         |
| ≥75                       | 325 (25%)                | 112 (30%)                   | 213 (23%)                      |         |
| **Sex**                   |                          |                             |                                |         |
| Female                    | 494 (38%)                | 113 (30%)                   | 381 (41%)                      | <0.001  |
| Male                      | 795 (62%)                | 257 (70%)                   | 538 (59%)                      |         |
| **Region of patient's residence** |                          |                             |                                |         |
| Northeast                 | 995 (79%)                | 286 (78%)                   | 709 (79%)                      | 0.13    |
| Southeast                 | 100 (8%)                 | 28 (8%)                     | 72 (8%)                        |         |
| Northwest                 | 69 (5%)                  | 26 (7%)                     | 43 (5%)                        |         |
| Southwest                 | 75 (6%)                  | 24 (6%)                     | 51 (6%)                        |         |
| Centre                    | 22 (2%)                  | 2 (1%)                      | 20 (2%)                        |         |
| **BMI (kg/m²)**           | N = 1110                 | N = 347                     | N = 774                        |         |
| Median (range)            | 24.3 (12.1–52.7)         | 23.9 (13.0–43.6)            | 24.6 (12.1–52.7)               | 0.20    |
| <18.5                     | 101 (9.1%)               | 38 (11%)                    | 63 (8%)                        | 0.24    |
| 18.5 ≤ BMI < 25           | 515 (46%)                | 167 (48%)                   | 348 (45%)                      |         |
| 25 ≤ BMI < 30             | 311 (28%)                | 82 (23%)                    | 229 (30%)                      |         |
| 30 ≤ BMI < 35             | 137 (12%)                | 41 (12%)                    | 96 (12%)                       |         |
| 35 ≤ BMI < 40             | 32 (3%)                  | 10 (3%)                     | 22 (3%)                        |         |
| ≥40                       | 14 (1%)                  | 6 (2%)                      | 8 (1%)                         |         |
| **Obesity (BMI ≥ 30)**    | 183 (16%)                | 57 (17%)                    | 126 (16%)                      | 0.96    |
| **Tobacco smoking status**|                          |                             |                                |         |
| Never smoked              | 515 (48%)                | 126 (38%)                   | 389 (52%)                      | <0.001  |
| Former smoker             | 393 (36%)                | 149 (44%)                   | 244 (33%)                      |         |
| Current smoker            | 171 (16%)                | 59 (18%)                    | 112 (15%)                      |         |
| **Comorbidities, N/total**|                          |                             |                                |         |
| Congestive heart failure  | 95/1151 (8%)             | 45/349 (13%)                | 50/802 (6%)                    | <0.001  |
| Coronary insufficiency    | 99/1019 (9%)             | 45/328 (14%)                | 54/691 (8%)                    | 0.0029  |
| Chronic obstructive pulmonary disease | 124/1020 (12%) | 55/328 (17%) | 69/692 (10%) | 0.0019 |
| Diabetes                  | 241/1151 (21%)           | 84/349 (24%)                | 157/796 (20%)                  | 0.08    |
| Hypertension              | 529/1151 (46%)           | 189/349 (54%)               | 340/802 (42%)                  | 0.0002  |
| **Number of comorbidities**| N = 1289                | N = 370                     | N = 919                        |         |
| 0                         | 175 (14%)                | 21 (6%)                     | 154 (17%)                      |         |
| 1                         | 280 (22%)                | 48 (13%)                    | 232 (25%)                      | <0.001  |
| 2                         | 294 (23%)                | 87 (23%)                    | 207 (22%)                      |         |
| 3                         | 216 (17%)                | 79 (21%)                    | 137 (15%)                      |         |
| ≥4                        | 324 (25%)                | 135 (36%)                   | 189 (21%)                      |         |
| **Updated Charlson comorbidity index** | N = 932              | N = 299                     | N = 633                        |         |
| 0–3                       | 284 (30%)                | 56 (19%)                    | 228 (36%)                      | <0.001  |
| ≥4                        | 648 (70%)                | 243 (81%)                   | 405 (64%)                      |         |
| **Usual medication, N/total** |                          |                             |                                |         |
| Long-term corticosteroids | 131/1141 (11%)           | 51/344 (15%)                | 80/797 (10%)                   | 0.02    |
| Transient corticosteroids (ongoing or ≤ 4 weeks) | 46/1011 (4%) | 24/323 (7%) | 22/688 (3%) | 0.003 |
| NSAIDs                    | 40/1142 (3%)             | 17/345 (4.9%)               | 23/797 (2.9%)                  | 0.08    |
| Immunosuppressive therapy | 35/1012 (3%)             | 11/324 (3%)                 | 24/688 (3%)                    | 0.94    |
| CEI or AIA                | 222/1143 (19%)           | 81/346 (23%)                | 141/797 (18%)                  | 0.02    |
| Anticoagulant therapy     | 358/1140 (31%)           | 141/344 (41%)               | 217 (796 (27%))                | <0.001  |
| **History of Cancer**     |                          |                             |                                |         |
| Cancer type               | N = 1287                 | N = 370                     | N = 919                        |         |
| Digestive                 | 470 (36%)                | 146 (39%)                   | 324 (35%)                      | <0.001  |
| Thoracic                  | 311 (24%)                | 113 (30%)                   | 198 (22%)                      |         |
| Gynaecological            | 252 (20%)                | 44 (12%)                    | 208 (22%)                      |         |
| Breast Cancer             | 173 (68.7%)              | 26 (59.1%)                  | 147 (70.7%)                    |         |
| Other gynaecological      | 79 (31.3%)               | 18 (40.9%)                  | 61 (29.3%)                     |         |
| Head and neck             | 104 (8%)                 | 22 (6%)                     | 82 (9%)                        |         |
| Central nervous system    | 65 (5%)                  | 19 (5%)                     | 46 (5%)                        |         |
| Genitourinary             | 65 (5%)                  | 21 (6%)                     | 44 (5%)                        |         |
| Dermatological            | 14 (1%)                  | 3 (1%)                      | 11 (1%)                        |         |
| Others                    | 6 (<1%)                  | 2 (<1%)                     | 4 (<1%)                        |         |

(continued on next page)
of the relatively low percentage of patients given such treatments.

The association between prognostic parameters and all-cause mortality are shown in Supplementary Table 1 and Fig. 3. In univariate analysis, age, sex, the ECOG PS, the updated Charlson comorbidity index, smoking status, thoracic primary tumour location, metastatic tumour stage, lung metastases, cytotoxic chemotherapy during the 3 months before the COVID-19 diagnosis, corticosteroids before the COVID-19 diagnosis, anticoagulant therapy, converting enzyme inhibitor (CEI) or angiotensin II antagonist (AIIA), and admission to an ICU were significantly associated with an increased risk of death. In the multivariate analysis sex, the ECOG PS, the uCCI and admission to an ICU remained statistically significant risk factors for death. Age, smoking status and corticosteroids before the COVID-19 diagnosis also showed a statistically non-significant increased risk of death. Importantly, the administration of cytotoxic chemotherapy in the 3 months before COVID-19 diagnosis was not associated with an increased risk of death.

Overall, 424 (33%) patients had a severe form of COVID-19 defined by admission to an ICU and/or mechanical ventilation and/or death but only 129 (9%) patients were admitted to ICU and/or had mechanical ventilation...
ventilation without death, that a majority of patients died without a previous admission to ICU or a mechanical ventilation. The association between prognostic parameters and COVID-19 severity are shown in Supplementary Table 2 and Fig. 4. In univariate analysis, age, sex, the ECOG PS, the updated Charlson Comorbidity Index (uCCI), corticosteroids before the COVID-19 diagnosis and thoracic primary tumour location remained independent predictors of COVID-19 severity. Age was associated with a statistically non-significant increase in the risk of death either. Again, the administration of cytotoxic chemotherapy in the 3 months before COVID-19 diagnosis was not associated with COVID-19 severity.

When the multivariate analysis was restricted only to patients with RT-PCR-documented SARS-CoV-2 (n = 952), ECOG PS, uCCI and ICU admission remained statistically significant risk factors for death, as were age, smoking status and cytotoxic chemotherapy administered within 3 months before the COVID-19 diagnosis (Supplementary Table 3). The ECOG PS and the uCCI were the only independent predictors of COVID-19 severity (Supplementary Table 4).

4. Discussion

After starting in December 2019 in Wuhan, China, the COVID-19 epidemic quickly spread to Europe in March 2020 and then to the rest of the world with a speed that shook saturated healthcare systems unprepared for such a pandemic. In the wake of a small Chinese study

| Anticancer treatment | Type of modification | Number (%) |
|----------------------|----------------------|------------|
| Systemic therapy     |                      |            |
|                      | Modification of the regimen | 53 (5%)    |
|                      | Temporary interruption  | 321 (29%)  |
|                      | Definitive interruption | 110 (10%)  |
| Radiotherapy         |                      |            |
|                      | Cancellation          | 1 (<1%)    |
|                      | Modification of the radiation scheme | 5 (<1%) |
|                      | Postponement          | 43 (4%)    |
|                      | Definitive interruption | 13 (1%)    |
| Surgery              |                      |            |
|                      | Modification of the extent of surgery | 1 (<1%) |
|                      | Cancellation          | 16 (2%)    |
|                      | Postponement          | 24 (2%)    |
| Interventional radiology | Cancellation | 2 (<1%) |
|                      | Postponement          | 3 (<1%)    |

4.2.1. Modification or interruption of anticancer treatments due to COVID-19 diagnosis.

Table 2
Modification or interruption of anticancer treatments because of COVID-19 diagnosis.

| Anticancer treatment | Type of modification | Number (%) |
|----------------------|----------------------|------------|
| Systemic therapy     |                      |            |
|                      | Modification of the regimen | 53 (5%)    |
|                      | Temporary interruption  | 321 (29%)  |
|                      | Definitive interruption | 110 (10%)  |
| Radiotherapy         |                      |            |
|                      | Cancellation          | 1 (<1%)    |
|                      | Modification of the radiation scheme | 5 (<1%) |
|                      | Postponement          | 43 (4%)    |
|                      | Definitive interruption | 13 (1%)    |
| Surgery              |                      |            |
|                      | Modification of the extent of surgery | 1 (<1%) |
|                      | Cancellation          | 16 (2%)    |
|                      | Postponement          | 24 (2%)    |
| Interventional radiology | Cancellation | 2 (<1%) |
|                      | Postponement          | 3 (<1%)    |

Fig. 3. Forest plot of the multivariate analysis of factors associated with all-cause mortality in the overall cohort of 1289 cancer patients with COVID-19.

Fig. 3. Forest plot of the multivariate analysis of factors associated with all-cause mortality in the overall cohort of 1289 cancer patients with COVID-19.
suggesting that patients with cancer had a high risk of severe respiratory complications related to SARS-CoV-2 infection and that patients with the highest risk were those who had received chemotherapy or surgery in the month preceding the infection [1], the medical community began to modify various practices in the treatment of cancer during the COVID-19 pandemic. The main objectives of these changes were to avoid very high-risk situations such as surgery or intensive cytotoxic chemotherapy and to minimise patients’ exposure to SARS-CoV-2.

For these reasons, in France, the French health authority published on March 11, 2020 guidelines to protect patients with cancer against SARS-CoV-2 infection [12]. Then, another study in Wuhan reported that cancer patients who had received their last anticancer treatment during the 14 days before the diagnosis of COVID-19 had an increased risk of experiencing severe events [13]. In this context, international and national panels recommended delaying or suspending anticancer treatments, when feasible, thereby raising the issue of potential cancer progression [14–22]. We created a national multicentre cohort in order to better understand the risk factors for mortality and severity of COVID-19, particularly the impact of various anticancer treatments, in order to determine the best practices and to help clinicians in their decision-making, and to assess the impact of COVID-19 on anticancer treatments.

First, our results show that the mortality rate in cancer patients with COVID-19 is far higher (29%) than that in COVID-19 patients overall [23,24]. To date, all studies that have included a significant number of cancer patients with COVID-19 have reported a mortality rate >10%. However, this rate is very variable between studies [4–9,25–28], ranging from 11% to 12% [5,25,28] to 28% in two studies, including the United Kingdom (UK) Coronavirus Cancer Monitoring Project (UKCCMP) cohort that included 800 patients [4,8]. Of note, the highest mortality rate published to date (33%) comes from the international cohort of patients with thoracic cancers and COVID-19 (TERAVOLT) [26]. In our cohort, the 311 patients with thoracic cancer had a mortality rate of 36%, which was the highest mortality rate of all tumour locations. The variations in mortality rates observed between studies could be explained, in part, by disparities in the proportions of patients with significant comorbidities or poor PS and in the proportions of the different types of tumours, as well as differences in the use of intensive care resources. It may also depend on hospital admission criteria to secondary care. In some countries, like in the US, a lower threshold is likely to exist and mild or asymptomatic patients might be admitted. A plausible explanation for the high mortality rate observed in our cohort is both its larger size, and the 'selection bias', leading to a greater likelihood of registering patients with adverse COVID-19 outcomes, while cancer patients with less severe...
infections may not have been included in our cohort since not consulting during this period of time. Thus, the patients included in the French cohort were mainly hospitalized patients with most often symptomatic COVID-19 and thus probably more severe. Similarly, it is possible that at the time of the analysis some information may have been missing, especially in cases of ambulatory care for diseases with a benign course. The relatively low rate of ICU transfer (10%) in our cancer patients compared to others studies [7,9,13,27,28] could be explained by a general ICU policy, since all ICU departments in areas of high COVID-19 incidence in France were overwhelmed at that period, with a lack of available ICU beds. Patients without severe comorbidities were thus prioritized for ICU admission, and cancer patients with their underlying comorbidities could have been excluded from intensive care. However similar rates of ICU transfer (7% and 10% respectively) have been reported in the UKCCMP and TERAVolt studies [8,26], probably for the same reasons. Retrospectively, the relevance of such triage strategy raises an ethical question and one can legitimately wonder whether these policies should continue in the event of a second wave, during which a better organization of intensive care access is to be hoped for.

We confirm the risk factors for death that have already been reported in previous studies, such as male sex, the ECOG PS or the presence of comorbidities, including cardiovascular disease, hypertension or chronic obstructive pulmonary disease (COPD) [4,6–9]. One point that remains unclear is the impact of cancer treatments on the severity of COVID-19 and its mortality. According to our analysis, the recent administration of cytotoxic chemotherapy was not a significant risk factor for death in the overall cohort but slightly increased the risk of death in the sub-population of RT-PCR positive patients, at the limit of significance (OR = 1.53 95%CI: 1.00–2.34; p = 0.05). The results in the literature are very discordant in this regard. Two Chinese studies showed that recent cytotoxic chemotherapy was associated with increased mortality [6,9]. However, more recent results from the two large cohorts of cancer patients in the UK and the United States of America (USA) [7,8] and from the TERAVolt cohort of patients with thoracic cancers [26] concluded that chemotherapy had no effect on COVID-19-related mortality. Added to these last data, our results suggest that chemotherapy should be continued in confirmed SARS-CoV-2-negative patients during the pandemic, without significantly endangering the patient, but this would need to be confirmed on larger series, encouraging us to promote collaborative projects pooling data from different cohorts.

As recently reported in the two cohorts in the UK and US [7,8], we found no association between mortality and the recent administration of non-cytotoxic systemic anticancer treatments, whether immunotherapy, targeted therapy or hormone therapy. Immunotherapy did not worsen outcomes for patients with COVID-19 in other studies, including two studies dedicated to patients with thoracic cancer [26–28]. However, the role of immunotherapy as a risk factor or not for COVID-19 severity or mortality remains to be clarified given the contradictory data from two previous Chinese studies reporting an increased risk of death or of severe disease with recent immunotherapy [6,25]. Recent case reports have suggested that it is safe to maintain targeted therapy with ALK/ROS1 tyrosine kinase inhibitors in non-small cell lung cancer (NSCLC) patients with asymptomatic SARS-CoV-2 interstitial pneumonia. This is important as there is a high risk of a cancer flare-up following discontinuation of such a treatment, with a rapidly progressive adverse cancer course leading to death [29].

One of the objectives of our cohort was to analyse the impact of a COVID-19 diagnosis on cancer treatment. We found that COVID-19 was responsible for a temporary or definitive interruption of cytotoxic chemotherapy in 39% of patients and a change in the chemotherapy regimen in 5% of cases. We do not have sufficient hindsight to measure the consequences of these therapeutic modifications, but in the future, it will be essential to determine whether COVID-19-related changes in treatment were responsible for faster cancer progression and shorter survival.

The GCO-002 CACovid cohort has some limitations. First, the diagnosis of COVID-19 was mainly made by RT-PCR and/or CT-scan. Due to their limited availability in France during the early phase of the pandemic, RT-PCR were reserved for patients with suggestive symptoms and therefore not carried out systematically throughout the country, even in vulnerable populations. This, added to the estimated 20–30% of false-negatives, probably contributed not only to an underestimation of the number of patients with COVID-19, as it was recently demonstrated [30], but also to an overestimation of the proportion of severe forms of COVID-19 since included patients were necessarily symptomatic and/or hospitalized. As the first part of the cohort was retrospective, some data were missing, but the database completion rate was ≥85% for the majority of the parameters. Finally, the study does not provide an estimate of COVID-19 prevalence in cancer patients since we do not yet have the total number of cancer patients followed during the study period.

Despite these weaknesses, the cohort has strengths. To our knowledge, it is the largest cohort of cancer patients with COVID-19 to date. It covers the entire national territory and perfectly reflects the epidemiology of SARS-CoV-2 infection in France since the geographic distribution of cancer patients with COVID-19 is similar to that of all infected patients in the country, the most affected regions being Greater Paris, and the Northeast and Southeast of France.
In conclusion, this nationwide cohort indicates that mortality in cancer patients with COVID-19 is high and is associated with general characteristics of patients. Age Patients receiving corticosteroids before COVID-19 diagnosis and patients with thoracic cancers had also more severe COVID-19. We found no deleterious effects of recent cytotoxic chemotherapy, except in the subgroup of patients with PCR-detected SARS-CoV-2 RNA. This suggests that cytotoxic treatments should be continued in SARS-CoV-2-negative patients during the pandemic, without significantly endangering the patient although such recommendation deserves to be confirmed on larger series. In almost 40% of patients, the systemic anticancer therapy was interrupted or stopped after COVID-19 diagnosis. The impact of these interruptions on cancer evolution will be evaluated in the future, as well as the impact of social inequalities on the severity and management of COVID-19 infections.

Author contributions section

AL, AT, IRC, KLM, JT, OB, ACHB, DD, GZ and TA conceived and designed the study. AL and KLM designed the statistical analysis plan, analysed the data and developed the figures and tables. All authors, except for KLM and XP, coordinated data contributions at their respective sites and provided patients’ data. All authors contributed intellectual content during the drafting and revision of the work and approved the final version.

Funding support

The study was funded and coordinated by the FFCD, ANOCEF-IGCNO, ARCAGY-GINECO, FFCD, GERCOR, GORTEC/intergroupe ORL, and IFCT were responsible for the study design, data collection, data interpretation, and writing the report. The FFCD was responsible for database management and the statistical analysis. The corresponding authors had full access to the data and had final responsibility for the decision to submit for publication.

Role of the funding sources

The funding sources had no role in the preparation and finalisation of the manuscript.

Conflict of interest statement

Pr Lièvre reports grants from Bayer Lilly, Merck and Novartis, personal fees from AAA, Amgen, Bayer, BMS, Celgene, HalioDx, Incyte, Ipsen, Lilly, Merck, Novartis, Pierre Fabre, Roche, Sandoz, Sanofi, Servier and non-financial support from AAA, Amgen, bayer, Incite, Ipsen, Merck, Novartis, Pierre Fabre, Pfizer, Roche, Sandoz, Servier and Integragen outside of the submitted work.

Dr. Turpin reports personal fees from MYLAN, personal fees from MERCK SERONO, personal fees from AMGEN, non-financial support from MERCK-SERONO, non-financial support from SANOFI, non-financial support from PFIZER outside the submitted work.

Dr. Ahle reports grants from Biogen, grants from Novartis, grants from Roche, grants from Sanofi, grants from Abbvie, outside the submitted work. Dr Bouché reports personal fees from Merck KGaA, Roche Genentech, Bayer, Astra-Zeneca, Grunenthal, MSD, Amgen, Servier, and Pierre Fabre outside the submitted work.

Dr. Neuzillet reports personal fees from SERVIER, other from OSE Immunotherapeutic, grants from ROCHE, personal fees and other from AstraZeneca, personal fees and other from Bristol-Myers Squibb, personal fees from Amgen, personal fees from Merck, personal fees from MSD, personal fees from Novartis, personal fees from Incyte, personal fees from Mylan, personal fees from Baxter, personal fees from Nutricia, personal fees from Fresenius-Kabi, outside the submitted work.

Pr Michel reports personal fees from Bayer, Servier, Amgen, Shire and Lilly and non-personal fees from Bayer, Merck, Amgen, Shire, Roche and Lilly outside the submitted work.

Dr. Canellas reports personal fees from BMS, personal fees from AstraZeneca, non-financial support from Boehringer Ingelheim, non-financial support from Roche, outside the submitted work.

Dr. Wislez reports personal fees from Boehringer Ingelheim, personal fees and non-financial support from ROCHE, personal fees and non-financial support from MSD, personal fees from BMS, personal fees from AstraZeneca, personal fees from Amgen, outside the submitted work.

Dr. Mansi reports personal fees from Roche, personal fees from Eisai, personal fees from Exact Science, personal fees from Novartis, outside the submitted work.

Dr Colomba received personal fees from IPSEN, BMS, Pfizer, Sanofi, GSK outside the submitted work.

Pr. Idbaih reports grants and other from Carthera (September 2019), grants from Transgene, grants from Sanofi, grants from Air Liquide, other from Leo Pharma, grants from Nutritheragene, outside the submitted work.

Pr. Aparicio reports personal fees and non-financial support from Roche, personal fees from Ipsen, personal fees from Amgen, personal fees from Servier, personal fees from Sanofi, outside the submitted work.

All other authors declare no competing interests.
Acknowledgements

We would first like to thank the patients and their families. We thank the directors of the GCO: Maryline Vo (ANOCEF-IGCNO), Bénédicte Votan (ARCAGY-GINECO), Cécile Girault (FFCD), Christine Delpeut (GERCOR), Franck Morin (IFCT) and the Operational team of the GCO-002 CACOVID-19 cohort: Charlène Barraux, Olayiđe Boussari, Caroline Choine, Claire Dubois, Quentin Gautherot, Fadil Masskouri, Marie Moreau. Thanks also to Philip Bastable for proof-reading the documents. Finally, we thank the other members of the GCO network: Alexandra Guerrier (ARCAGY-GINECO), Arthur Arraitz (ARCAGY-GINECO), Anna Koziol (ARCAGY-GINECO), Marie-Line Garcia-Larnicol (GERCOR), Camille Duranton (GERCOR), Natacha Colin-Bataillou (GORTEC), Marie-Hélène Girard—Calais (GORTEC), Camille Vidaud (GORTEC/Intergroupe ORL), Nathalie Archirel (IFCT), Pascale Missy (IFCT), Mathieu Boone (ANOCEF-IGCNO), Khé Hoàng-Xuan (ANOCEF-IGCNO) and Maud Pouwels (StARCC).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.09.035.

Appendix

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