

Outcomes of the 2019 novel coronavirus in patients with or without a history of cancer: a multi-centre North London experience

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Abstract

Background: This study aims to compare the outcomes of COVID-19-positive disease in patients with a history of cancer to those without.

Methods: We retrospectively collected clinical data and outcomes of COVID-19 positive cancer patients treated consecutively in five North London hospitals (cohort A). Outcomes recorded included time interval between most recent anti-cancer treatment and admission, severe outcome [a composite endpoint of intensive care unit (ITU) admission, ventilation and/or death] and mortality. Outcomes were compared with consecutively admitted COVID-19 positive patients, without a history of cancer (cohort B), treated at the primary centre during the same time period (1 March–30 April 2020). Patients were matched for age, gender and comorbidity.

Results: The median age in both cohorts was 74 years, with 67% male, and comprised of 30 patients with cancer, and 90 without (1:3 ratio). For cohort B, 579 patients without a history of cancer and consecutively admitted were screened from the primary London hospital, 105 were COVID-19 positive and 90 were matched and included. Excluding cancer, both cohorts had a median of two comorbidities. The odds ratio (OR) for mortality, comparing patients with cancer to those without, was 1.05 [95% confidence interval (CI) 0.4–2.5], and severe outcome (OR 0.89, 95% CI 0.4–2.0) suggesting no increased risk of death or a severe outcome in patients with cancer. Cancer patients who received systemic treatment within 28 days had an OR for mortality of 4.05 (95% CI 0.68–23.95), $p=0.12$. On presentation anaemia, hypokalaemia, hypoalbuminaemia and hypoproteinaemia were identified predominantly in cohort A. Median duration of admission was 8 days for cancer patients and 7 days for non-cancer.

Conclusion: A diagnosis of cancer does not appear to increase the risk of death or a severe outcome in COVID-19 patients with cancer compared with those without cancer. If a second spike of virus strikes, rational decision making is required to ensure optimal cancer care.

Keywords: cancer pathways, cancer patients, chemotherapy, COVID-19, pandemic

Received: 8 June 2020; revised manuscript accepted: 13 August 2020.

Introduction

The 2019 novel coronavirus disease (COVID-19) was first detected as a case of pneumonia of unknown cause in late 2019 in Wuhan, China.¹ On 11 March 2020, the World Health Organisation (WHO) declared COVID-19 a pandemic due to the global spread of this new disease and the

significant risk of further transmission.² As of 29 May 2020, there were 269,127 confirmed cases in the United Kingdom (UK), with 37,837 deaths.³

The pathogen causing COVID-19, the severe acute respiratory syndrome coronavirus (SARS-CoV-2), is an enveloped RNA virus belonging to

Ther Adv Med Oncol

2020, Vol. 12: 1–9

DOI: 10.1177/
1758835920956803

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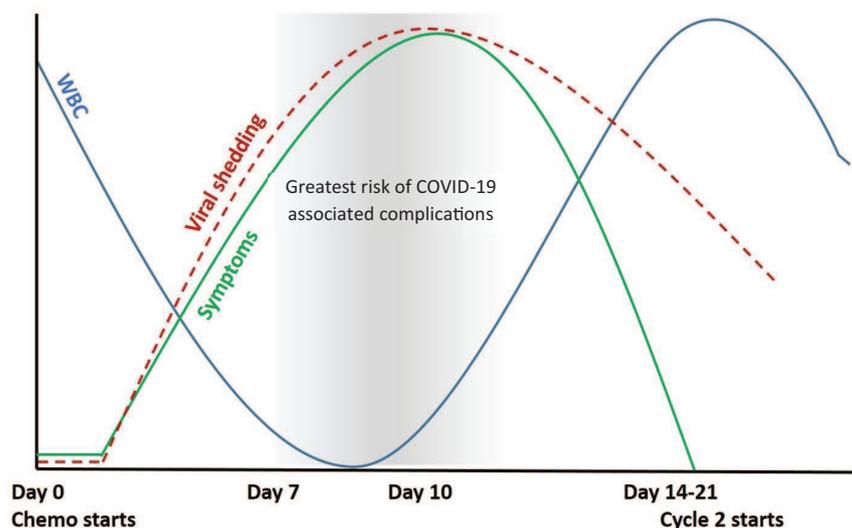


Figure 1. Proposed association between chemotherapy nadir and COVID-19 symptoms/viral shedding.⁸ COVID-19, 2019 novel coronavirus disease; WBC, white blood cells.

the family of Coronaviridae and is one of seven species of coronavirus known to infect humans. Four strains typically cause common cold symptoms and two, Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) and Middle East Respiratory Syndrome coronavirus (MERS-CoV), can cause fatal respiratory diseases.⁴

The clinical spectrum of COVID-19 ranges from asymptomatic infection to severe respiratory failure and death.⁵ A retrospective study of 191 adult inpatients in Wuhan found an increased odds of death with older age [odds ratio (OR) 1.10, 95% confidence interval (CI) 1.03–1.17], and in those with coronary heart disease and diabetes.⁵ Individuals with serious chronic medical conditions, including cardiovascular disease, diabetes, and lung disease, are deemed vulnerable and considered to be at higher risk of critical illness,⁶ particularly acute respiratory distress syndrome (ARDS).⁷ In a prospective nationwide analysis of 1590 patients with COVID-19 in China, 18 (1%) had a history of cancer, which is higher than the prevalence of cancer in the general Chinese population. These patients were more likely to have a severe event [39% versus 8% in patients without cancer, hazard ratio (HR) 5.34, 95% CI 1.8–16.18, $p=0.0003$], defined as the requirement of invasive ventilation or death.^{8,9} Of the cancer patients with previous history available, the majority were undergoing routine follow up after primary resection (12 out of 16), with the rest having received chemotherapy or surgery within

the past month (4 out of 16).⁸ However, this study had a small sample size of cancer patients, with significant heterogeneity between diseases.¹⁰ The majority of patients were cancer survivors; thus, it is unclear whether these outcomes can be generalised to the oncology population, and outcome is likely to be confounded by a higher median age than those without cancer.¹¹ A similar retrospective study of 28 patients with a history of cancer from three Wuhan hospitals found that lung cancer was the most prevalent tumour amongst COVID-positive patients (25%). Patients who had received their last systemic anti-cancer treatment (SACT) within 14 days had an increased risk of developing severe events (HR = 4.079, 95% CI 1.086–15.322, $p=0.037$),¹² highlighting the importance of carefully reviewing the necessity and priority of SACT in these potentially high-risk patients during the pandemic. A larger multi-centre study of 105 cancer patients compared with age matched non-cancer patients in Wuhan, China also demonstrated an increased risk of death, intensive care unit (ITU) admission and requirement for ventilation; however, cohorts were not fully matched.¹³

One of the bigger challenges with COVID-19 is its long incubation period (Figure 1) and potential spread through asymptomatic patients. In cancer patients, there is likely to be considerable difficulty in assessing patients suitability for chemotherapy, as oncologists often rely only on symptoms and haematological/biochemical parameters, as well

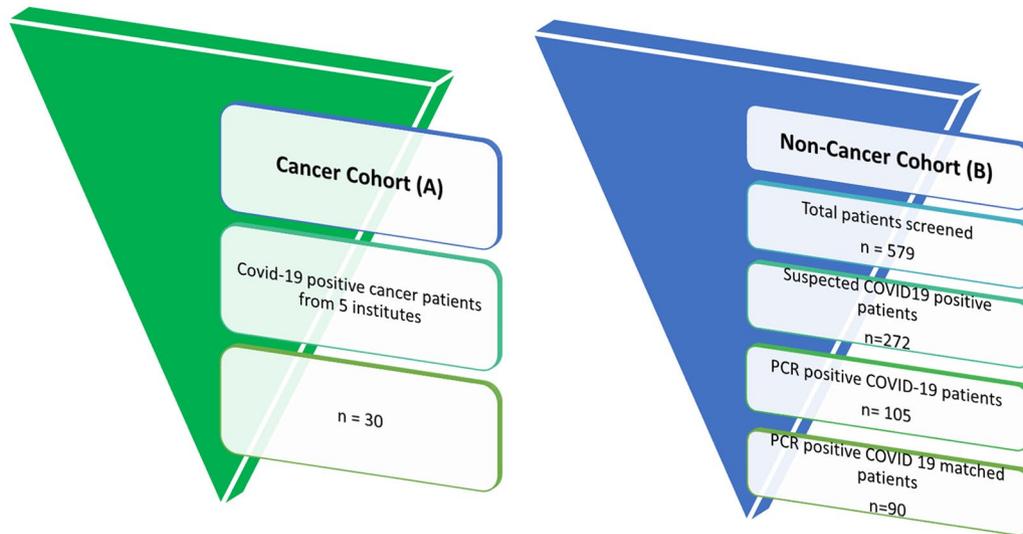


Figure 2. Study schematic.
COVID-19, 2019 novel coronavirus disease; PCR, polymerase chain reaction.

as performance status. Patients may be in the asymptomatic phase when initially assessed in clinic, and the onset of symptoms may coincide with the myelosuppressive nadir of chemotherapy (Figure 1).

Another significant challenge for these patients is the consideration of re-starting chemotherapy, or commencing any other oncological intervention such as immunotherapy or oral targeted therapy in COVID-19 positive patients. It has been suggested in a case report that recurrence in patients with previously positive COVID-19 may occur, or that patients may remain persistently positive despite resolution of symptoms.¹⁴ In the case report, following inpatient treatment for symptomatic COVID-19-positive disease and two subsequent negative results, the patient had a recurrent positive swab result despite remaining asymptomatic. It is not yet fully understood if patients develop immunity following exposure to COVID-19, much like other coronaviruses, or if the virus can remain latent, potentially putting immunocompromised patients at a greater risk of recurrence.

Over the last 6–8 weeks, cancer services all over the world have been compromised. In the UK, categories have been made for prioritisation of chemotherapy, based on the level of immunosuppression associated with treatments and cancer types, capacity and resource issues, and balancing the benefits of allowing patients to have the best opportunity for cure or disease control of cancer

with the potential risks of serious illness from COVID-19.¹⁵ Although studies in individuals with cancer suggest worse outcomes in these patients, to our knowledge comparisons with matched cohorts have yet to be carried out outside of China.

Here, we present a study of 30 patients with cancer matched to 90 patients without a history of cancer (at a ratio of 1:3), admitted with COVID-19 in five North London Hospitals (Figure 2), to expand on the data in this setting and to determine if a diagnosis of cancer significantly worsens COVID-19 related outcomes.

Method

Patient population

The study data includes patients admitted and diagnosed with COVID-19 between 1 March and 30 April 2020 at five London hospitals. We defined a confirmed diagnosis of COVID-19 based on reverse-transcription polymerase chain reaction (RT-PCR) from respiratory tract swabs. Cohort A comprised 30 patients with a history of cancer (both solid organ and haematological). Clinically relevant outcomes were then compared with 90 SARS-CoV-2 RT-PCR positive patients without a history of cancer, matched by age, gender and number of comorbidities, consecutively admitted at the primary centre during the same time period (cohort B).

Data collection

Patient records were reviewed using the hospital electronic medical records (EMR) for clinical and radiological characteristics, including age, gender, comorbidities, presenting haematological and radiological characteristics and the COVID-19 management of these patients. Data specific for cohort A included site of primary tumour, intent of treatment, treatment modality and time interval between last treatment and admission with COVID-19. Investigators from the different hospitals provided data of consecutively admitted COVID-19 positive patients for cohort B at their sites and were blinded to the data from other hospitals. Severe outcome was defined as a composite of ITU admission, invasive ventilation or death. Approval of the study was obtained from the Institutional Research and Governance team at North Middlesex University Hospital.

Sample size and statistics

Patient demographics and clinical characteristics were explored descriptively using STATA v15.1 (StataCorp, College Station, TX, USA). The estimated mortality rate in all hospitalised patients is ~5%^{16,17}; however, as the control group are matched to cancer patients on age and comorbidities, it is expected that their mortality rate will be notably worse. Under the assumption that the true rate of mortality in the non-cancer patients is 10%, with 30 patients in cohort A and 90 in cohort B, we would have 80% power to detect an OR of 5.1 or higher at the 5% significance level. Logistic regression was used to determine the OR for mortality and severe outcomes in those with a diagnosis of cancer *versus* those without. Baseline factors were compared between cancer and non-cancer patients using chi-squared tests and their prognostic value was assessed using logistic regression; *p* values < 0.05 were considered significant.

Results

Patient characteristics

Baseline characteristics of the study population. A total of 120 patients were included in this study, 30 and 90 in cohorts A and B, respectively. Data was collected on the 30 cancer patients from five London Hospitals. For cohort B, 579 patients without a history of cancer and admitted consecutively were screened from the primary London hospital; 105 were COVID-19 positive and 90

were matched and included. The median age of both cohorts was 74. Patients were predominantly male in both cohorts (67%). Excluding malignancy, the median number of comorbidities was two in each group (Table 1).

Cancer-specific characteristics (cohort A). Cohort A included patients with a variety of tumour types. Prostate cancer was the most frequent in seven patients (23%), with colorectal and lung cancers the next most frequent (five patients of each tumour type). Most patients (80%; 24/30) had received anti-cancer therapy, 47% (14/30) chemotherapy, 23% (7/30) targeted treatment, 7% (2/30) immunotherapy and 3% (1/30) patient had received radiotherapy. The majority of these patients (79%; 19/24) had received anti-cancer therapy within 28 days of admission. One patient had undergone radical surgery alone. Treatment intent was palliative in 67% (20/30) of patients, all of whom had advanced stage of disease. The remaining 10 patients had early stage cancers and were being treated radically (Table 2). The median time from most recent anti-cancer treatment to presentation was 8 days.

Pathological and radiological features

The clinical, laboratory and radiographic features of all 120 patients are summarised in Table 3. Of the cancer patients, eight (27%) were neutropenic on admission, all of whom had received recent SACT within 28 days; two (2.2%) non-cancer patient had a presenting neutropenia. Of the patients in both cohorts, 73% (22/30) (A) and 78% (70/90) (B) were lymphopenic, and 70% (21/30) (A) and 32% (29/90) (B) were anaemic at presentation. Most patients in both cohorts had abnormal C-reactive protein (CRP), with a median value of 100 mg/l (A) and 122 mg/l (B) (7% and 3% of cohorts A and B, respectively, had a normal CRP). As per previous reports of cancer patients with COVID-19, hypokalaemia, hypoalbuminaemia and hypoproteinaemia were frequently features on admission; these were normal at presentation in 21% (6/29) in cohort A and 8% (7/89) of cohort B. Computed tomography (CT) chests were less frequent, performed in 33% (10/30) of cancer patients and 2% (2/90) of those without cancer, with only one normal in each cohort.

Outcomes of the study population

Compared with non-cancer COVID-19-positive patients, patients with cancer had no increased

risk of mortality (OR 1.05; 95% CI 0.4–2.5, $p=0.9$), or increased risk of a severe outcome (OR 0.87; 95% CI 0.4–2.0, $p=0.7$).

One (3%) cancer patient was admitted to ITU for invasive ventilation, and all others received ward-based supportive care only. Supportive treatment generally consisted of intravenous fluids, antibiotics and supplemental oxygen; 10% (3/30) in cohort A received non-invasive ventilatory support [continuous positive airway pressure (CPAP)], all of whom subsequently died. In total, 37% (11/30) patients in cohort A died, with no other cases meeting the predefined markers of severity. Within the non-cancer patients, 40% (36/90) met the predefined marker of severity (ventilation, ITU admission or death) and 36% (32/90) of patients died. (Table 1).

The median age in those who died was 82 years in cohort A, and 80 years in cohort B. Of those who died, 72% (31/43) were male.

The median hospital stay for patients admitted with COVID-19 in cohort A was 8 days, and 7 days in cohort B.

On admission, patients with cancer were more likely to have anaemia (70% (A) *versus* 32% (B); $p<0.001$), neutropenia (27% (A) *versus* 2.2% (B); $p<0.001$), hypoproteinaemia (57% (A) *versus* 9.4% (B); $p<0.001$ and hypoalbuminaemia [40% (A) *versus* 23% (B); $p=0.07$] than non-cancer patients (Table 3). Univariate analysis of blood parameters (listed in Table 3) found that the presence of anaemia, lymphopenia, hypoproteinaemia, hypokalaemia or hypoalbuminaemia on admission were not associated with increased risk of death in both cohorts pooled.

Cancer-specific outcomes

Although not significant, cancer patients who received systemic treatment within 28 days appeared to have an increased risk of death [OR 4.05 (95% CI 0.68–23.95), $p=0.12$]. There were too few deaths for a multivariable regression to be considered reliable; however, it should be noted that adjustment for treatment intent (palliative *versus* radical) did not dilute the effect of treatment within 28 days [adjusted OR 4.63 (95% CI 0.69–31.14), $p=0.12$].

Of those who died (10/11 patients died within 14 days of admission), all had received systemic

Table 1. Patient characteristics.

Characteristics	Cohort A (cancer)	Cohort B (non-cancer)
Number of patients	30	90
Age		
Median	74	74
IQR	(70–78)	(66–81)
Gender		
Male	20 (67%)	60 (67%)
Female	10 (33%)	30 (33%)
No. of comorbidities median (excluding malignancy) IQR	2 (1–2)	2 (1–4)
Admission duration median days	8	7
Number with severe event	11 (37%)	36 (40%)
Death	11 (37%)	32 (36%)
IQR, interquartile range.		

anti-cancer therapy; 55% (6/11) had received chemotherapy, 36% (4/11) had received targeted treatment and 9% (1/11) immunotherapy. Six had a history of prostate cancer, three lung cancer, one pancreatic cancer and one breast cancer. Of the 11 patients who died, 10 were being treated with palliative intent.

Discussion

To our knowledge, this is the first report comparing the outcomes of COVID-19 positive patients with a history of cancer with their non-cancer counterparts in the UK. This study demonstrates that COVID-19 infection carries a significant risk of morbidity and mortality for all patients regardless of their history of malignancy.

The results of the oncology-specific patients are comparable with literature from a similar series of patients with cancer and COVID-19 in Wuhan, China.^{12,13} In this study of 30 cancer patients, no significant increased risk of mortality or severe outcome (including ventilation or ITU admission) was demonstrated compared with an age/gender and comorbidity matched cohort of non-cancer patients.

Clinical features of both cohorts were consistent with previous studies. Typical laboratory features

Table 2. Characteristics of cancer patients.

Characteristics of cancer patients		Number (%)
Tumour Type	Prostate	7 (23%)
	Colorectal	5 (17%)
	Lung	5 (17%)
	Breast	4 (13%)
	Pancreatic	2 (7%)
	Testicular	1 (3%)
	Urothelial	1 (3%)
	Oesophageal	1 (3%)
	Skin (Merkel cell)	1 (3%)
	Nasopharyngeal	1 (3%)
	Cholangiocarcinoma	1 (3%)
	Diffuse large B cell lymphoma	1 (3%)
Treatment intent	Radical	20 (67%)
	Palliative	10 (33%)
Type of treatment	Chemotherapy	14 (47%)
	Targeted Treatment	7 (23%)
	Immunotherapy	2 (7%)
	Radiotherapy	1 (3%)
	Surgery Alone	1 (3%)
	None*	5 (17%)
Median time interval between recent anti-cancer therapy and admission (days)	–	8 days IQR (3–21)

**n* = 2 had treatment planned, but not yet commenced; *n* = 3 were considered unfit for further systemic therapy.
IQR, interquartile range.

in both groups included anaemia, lymphopenia and an elevated CRP; however, patients with cancer significantly more frequently had features of anaemia, hypokalaemia and hypoproteinaemia on presentation (although the former two may be a consequence of anti-cancer therapy and the latter a reflection of malnutrition associated with malignancy, advanced disease and frailty). These were features also reported in the cancer patients in Wuhan.¹²

The combined mortality of both cohorts (36%) is significantly higher than the current estimation of

mortality in hospitalised patients (>5%)^{16,17}; however, both groups of patients had significant co-morbidities, of the same median number (two excluding malignancy). A history of malignancy did not appear to increase the mortality rate compared with those without cancer, acknowledging that this cohort study has a small sample size. Of the 11 cancer patients who died, all had received anti-cancer therapy, and the majority in the palliative setting of advanced disease. Patients were more likely to die if treatment had been administered within 28 days of admission, corroborating Zhang *et al.*'s dataset, although our data has not

Table 3. Clinical features of patients based on investigations carried out at point of admission.

Clinical features	Cohort A (cancer) number (%)	Cohort B (non-cancer) number (%)
Anaemia	21 (70%)	29 (32%)
Lymphopenia	22 (73%)	70 (78%)
Neutropenia	8 (27%)	2 (2.2%)
Hypokalaemia	8 (27%)	9/85 (11%)
Elevated CRP	28 (93%)	87 (97%)
Median	100 (IQR 77–162)	122 (50–176)
Hypoalbuminaemia	12 (40%)	21 (23%)
Hypoproteinaemia	12/21 (57%)	8/85 (9.4%)
Abnormal Chest Radiograph	23/29 (79%)	82/89 (92%)

Chest radiographs were performed in 29/30 cancer patients and 89/90 of those without cancer.
CRP, C reactive protein; IQR, interquartile range.

shown a significant result.¹² During the course of the publication process of the current paper, we acknowledge another retrospective cohort study published with somewhat conflicting data¹³; however, this may be explained by the differences in the patient population of individuals in Wuhan compared with those in the UK and the retrospective nature of both studies.

Our data show that outcomes between cancer and non-cancer patients were comparable. Whilst patients with cancer tend to have underlying immunosuppression from SACT, and therefore perhaps more inclined to contract infection, cytokine storm syndrome might be the primary reason for mortality in COVID-19 positive patients more generally.¹⁸ Contrary to the general hypothesis that patients on immunosuppressive regimes such as chemotherapy are at particular risk of adverse outcomes after contracting COVID-19, immunosuppression may paradoxically work in their favour, by dampening this cytokine storm response. A recent study suggested use of immunosuppressive therapies such as steroids, intravenous immunoglobulin, selective cytokine blockade (e.g. anakinra/tocilizumab) or Janus kinase (JAK) inhibition might act as potential therapeutic options.¹⁸

Based on the data presented here, there was no excess in mortality in the cancer cohort despite many patients being actively treated with

anti-cancer therapy. However, the majority of patients in the cancer cohort who died had received systemic anti-cancer therapy within the last 28 days. Thus, cautious consideration should be made of the risk/benefit profile of palliative SACT in the setting of the COVID-19 pandemic to minimise the potential risks of mortality in already vulnerable patients.

We acknowledge the limitations to this study, including the retrospective sample and small sample size. To address this, we increased the sample size of the non-cancer patients to a ratio of 1:3. Amongst the patients with cancer, there was significant heterogeneity between tumour types, including variability in stage and other clinicopathological factors. The prevalence of different tumour types admitted in this study is described in Table 3, with prostate cancer the most frequent, and colorectal and lung cancers the next most prevalent. Given the small sample size, we are unable to define a relation of severity of COVID-19 disease with different cancer types, and this cohort likely reflects the prevalence of cancers treated at these North London hospitals. Patient data was obtained from five different London hospitals, in which treatment may vary, and this therefore may have an impact on prognostic factors. Patients were age-, gender-, comorbidity- and date-matched to reduce selection bias. Our data suggested that systemic anti-cancer treatment within 28 days may increase the

risk of mortality from COVID-19 (although results were not significant). However, this result may be confounded by the fact that most of these patients were receiving treatment in the palliative setting and therefore perhaps may be suggestive of worse disease leading to death, rather than a treatment effect. We acknowledge the above limitations. Given the urgent timeline of an evolving and rapidly progressing pandemic, we elected not to wait for a larger sample size, as we prioritise the early release of data to assist global physicians and oncologists to make real-time decisions.

In the UK, at the time of writing, the government had closed all non-essential places of work, limited travel to key-workers only and was encouraging social distancing.¹⁹ Due to the significant burden on the National Health Service (NHS) over the coming months, and potential risks to cancer patients, the prioritisation of chemotherapy was recommended in March 2020 to meet capacity and mitigate the risks of COVID-19 on balance with optimally treating cancer, with a number of guidelines published.²⁰ Cancer remains a significant global cause of death, and consideration should be given to re-escalating cancer services to normal at the earliest opportunity. Further studies are required to evaluate the impact of the COVID-19 infection and the consequences of the slowdown of services on cancer outcomes.²¹

Conclusion

COVID-19 is a significant cause for healthcare, societal and economic concern globally. Previous work has demonstrated older patients and those with significant comorbidity are at greatest risk of morbidity and mortality from the virus. Patients with cancer are at higher risk of immunosuppression on cancer therapy, with possible increased incidence of infection based on data from China. Whilst acknowledging the limitations of the study, compared with patients without cancer, our study found no evidence that patients with cancer are more likely to have a severe outcome or mortality from COVID-19. Whilst extra caution is warranted in administration of SACT pertaining to risk of immunosuppression, this data does not demonstrate a higher risk to cancer patients compared with their non-cancer counterparts.

Author contributions

All authors approved the manuscript

Availability of data and materials

Datasets generated or analysed during the current study are available on request

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Consent for publication

No patient identifiable information was used in this study

Ethics approval and consent to participate

Research and development approval was sought from North Middlesex University Hospital where the study was primarily conducted (primary centre)

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Supplemental material

Supplemental material for this article is available online.

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