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COMMENTARY

Cancer Treatment and Research During the COVID-19 Pandemic: Experience of the First 6 Months

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ABSTRACT

The coronavirus disease-2019 (COVID-19) pandemic has had a significant impact on patients with underlying malignancy. In this article, we summarize emerging data related to patients with cancer and COVID-19. Among patients with COVID-19, a higher proportion have an underlying diagnosis of cancer than seen in the general population. Also, patients with malignancy are likely to be more vulnerable than the general population to contracting COVID-19. Mortality is significantly higher in patients with both cancer and COVID-19 compared with the

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overall COVID-19-positive population. The early months of the pandemic saw a decrease in cancer screening and diagnosis, as well as postponement of standard treatments, which could lead to excess deaths from cancer in the future.

Keywords: Cancer; Coronavirus; COVID-19; Immuno-oncology; Malignancy; Mortality; Pandemic; Risk; SARS-CoV-2; Therapy

Key Summary Points

Pooled analyses show that approximately 1–3.9% of patients with COVID-19 have cancer. The proportion of patients with underlying malignancy was found to be much higher (7.3–20.3%) in subsets of patients with COVID-19 who were critically ill or died.

Patients with cancer have a higher risk (0.79–8.3%) of developing SARS-CoV-2 infection than the general population.

Patients with cancer who develop COVID-19 tend to have much worse outcomes (mortality ranging from 11.4% to 35.5%) compared with those without cancer.

There are conflicting data regarding the impact of recent systemic anticancer therapy on the outcome of SARS-CoV-2 infection.

The pandemic has had a negative impact on cancer clinical trials.

The use of technology, including telemedicine, has increased since the start of the pandemic.

Shunting of healthcare resources to frontline management of COVID-19 has resulted in a decrease in cancer screening and has also impacted cancer treatment. This could manifest in excess mortality from cancer in the near future.

BACKGROUND

The novel coronavirus disease of 2019 (COVID-19), caused by the beta-coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was initially reported in December 2019 from Wuhan, China. It was soon declared a pandemic, rapidly spreading around the world and greatly impacting human society, especially the healthcare systems. The incidence of new cases of COVID-19 has recently declined in many countries in Europe, Australia, and New Zealand, but continues to be high in other countries such as the USA, Brazil, India, and Russia. Further, some countries are again reporting an increase in the number of new cases after a period of control.

Cancer care and research too have been severely disrupted as a result of COVID-19 [1]. This article summarizes key observations and lessons from the impact of the pandemic on cancer treatment and trials during the first 6 months since its outbreak.

WHAT PROPORTION OF PATIENTS WITH COVID-19 HAVE UNDERLYING CANCER?

Emerging data show that among patients with COVID-19, a higher proportion have an underlying diagnosis of cancer than seen in the general population. Among 1590 patients with COVID-19 in a Chinese hospital, 18 (1%; 95% confidence interval [CI] 0.61–1.65) had a history of cancer, which was higher than the incidence of cancer in the overall Chinese population [2]. An analysis of 11 early retrospective studies from China involving 3661 patients showed that the overall pooled prevalence of cancer in patients with COVID-19 was 2% (95% CI, 2.0–3.0) [3], while a larger meta-analysis involving a total of 32,404 patients from nine countries estimated that the pooled prevalence of cancer among the COVID-19-infected population was 3.5% (95% CI 1.70–5.80) [4]. Another meta-analysis of 18 studies with14,558 patients with COVID-19 showed

that 3.9% (95% CI 2.5–5.4) of them had cancer [5].

The proportion of patients with underlying malignancy was found to be much higher in subsets of patients with COVID-19 who were critically ill or died. Among 1591 patients with COVID-19 admitted to intensive care units in Lombardy, Italy, 81 (8%) had underlying malignancy [6]. Among 82 Chinese patients who died of COVID-19, cancer was found to be present in 7.3% [7]. A chart review of 355 patients in Italy who had died of COVID-19 showed that 72 (20.3%) had active cancer [8].

WHAT PROPORTION OF PATIENTS WITH CANCER DEVELOP COVID-19?

Patients with active malignancy are likely to be more vulnerable than the general population to infections, including those caused by respiratory viruses [9]. There could be several reasons for this, including an immunocompromised state brought about by the disease itself [10], or by cancer treatment [11].

Out of 1524 patients with cancer at a single institution in China, 12 (0.79%) were found to be positive for SARS-CoV-2, proportionately higher than the general population [12]. At a single institution in Spain, COVID-19 was diagnosed in 45 out of 1069 (4.2%) patients with cancer [13]. Out of 200 pediatric patients on anticancer therapy tested for SARS-CoV-2, nine (4.5%) were found to be positive for the infection [14]. Among 24 patients with castration-resistant prostate cancer in a single center in Italy, two (8.3%) were found to be positive for COVID-19 [15].

To summarize the intersection of the incidence of cancer and COVID-19, there is evidence that a significant subset of patients with COVID-19 have underlying malignancy, and patients with cancer have a higher risk of developing SARS-CoV-2 infection than the general population. However, given our inadequate capacity for systematic testing at a population scale, limited availability of published data, asymptomatic nature of the SARS-CoV-2 infection in a significant proportion of affected people, and the false-negative results of some of the tests performed, there are insufficient data to make a firm conclusion regarding the quantum of excess risk.

DO PATIENTS WITH COVID-19 AND UNDERLYING MALIGNANCY HAVE WORSE OUTCOMES?

The case fatality ratio (CFR) of COVID-19 in the overall population is not precisely known [16]. Current estimates range from 0.25% to 3.0% [17], although a meta-analysis of 73 studies involving 10,402 patients estimated a higher mortality rate of 7% [18]. In contrast, patients with cancer who develop COVID-19 tend to have much worse outcomes, with mortality ranging from 11.4% to 35.5% (see Table 1) in selected retrospective studies.

A study from nine hospitals in Wuhan which included 232 patients with cancer and COVID-19 found that patients with cancer were more likely to have severe infection than patients without cancer, with an odds ratio (OR) of 3.61 (95% CI 2.59–5.04) [19].

In an analysis from a New York hospital system of patients with COVID-19 and underlying malignancy, a CFR of 25% (41/164) was noted for solid cancers and 37% (20/54) for hematological malignancies, with older age, multiple comorbidities, need for intensive care support, and elevated levels of D-dimer, lactate dehydrogenase, and lactate being significantly associated with mortality [20].

There is also evidence that COVID-19 patients with hematological malignancies are generally at greater risk than those with solid cancers, and those with recently diagnosed cancer have worse outcomes than those with a remote diagnosis. A recent analysis of medical records of 10,926 adults in England with linked COVID-19 deaths found that the age- and sex-adjusted hazard ratio for COVID-19 death among patients with hematological malignancy diagnosed within the past year was 3.02 (95% CI 2.24–4.08), decreasing to 2.56 (95% CI 2.17–3.06) if the diagnosis was made 1–4.9 years ago; among those with a diagnosis of non-hematologic malignancy within the past year, the

Table 1 Mortality data from selected studies on patients with cancer and COVID-19

Geographical area	Total number of patients with cancer and COVID-19	Number of deaths	Death rate	Time period of study (2020)	References
COVID-19 and Cancer Consortium (CCC19), USA, Canada, Spain	928	121	13%	17 Mar–16 Apr	Kuderer et al. [29]
Italy	909	150	16.5%	Up to 30 Mar	Trapani et al. [64]
UK Coronavirus Cancer Monitoring Project (UKCCMP)	800	226	28%	18 Mar–26 Apr	Lee et al. [27]
New York, USA	423	51	12%	10 Mar–7 Apr	Robilotti et al. [65]
TERAVOLT Registry (8 countries)—thoracic malignancies	400	141	35.5%	26 Mar–12 Apr	Horn et al. [66]
New York, USA	218	61	28%	18 Mar–8 Apr	Mehta et al. [20]
9 Hospitals in Hubei, China	205	30	15%	13 Jan–18 Mar	Yang et al. [31]
Europe—chronic lymphatic leukemia	190	55		28 Mar–22 May	Scarfo et al. [67]
Brazilian National Cancer Institute	181	60	33.1	30 Apr–26 May	De Melo et al. (Preprint) [53]
Guys Hospital, London, UK	156	34	22%	29 Feb–12 May	Russel et al. (Preprint) [68]
Gustave Roussy Cancer Campus, Villejuif, France	137	20	14.6	14 Mar–15 Apr	Barlesi et al. [32]
5 Hospitals in Wuhan, China	107	23	21.5%	5 Jan–18 Mar	Zhang et al. [69]
14 Hospitals in Hubei, China	105	12	11.4%	1 Jan–24 Feb	Dai et al. [22]
New York, USA—lung cancer	102	25	25%	12 Mar–6 May	Luo et al. [70]

hazard ratio was 1.81 (95% CI 1.58–2.07), which decreased to 1.20 (95% CI 1.10–1.32) if the diagnosis was made 1–4.9 years ago [21].

A remarkable and clinically significant observation from 14 hospitals in Hubei, China is that COVID-19-positive patients with cancer involving the lung (either primary or metastases) seem to have a poorer clinical outcome than those without tumoral lung involvement [22, 23]. A retrospective chart review of 1878

patients with COVID-19 at a Spanish hospital found that 17 had lung cancer, of whom 9 died [24].

Among 1018 patients with both COVID-19 and cancer, independent factors associated with increased 30-day mortality were age, male sex, former smoking, and worse Eastern Cooperative Oncology Group (ECOG) performance status [25].

Fortunately, pediatric cancer patients who test positive for SARS-CoV-2 tend to generally have a benign course of infection [26].

DOES RECENT ANTICANCER THERAPY IMPACT OUTCOMES OF PATIENTS WITH CANCER AND COVID-19?

There are conflicting data concerning the impact of recent systemic anticancer therapy on COVID-related mortality.

A prospective observational study from the UK Coronavirus Cancer Monitoring Project (UKCCMP) found that among 800 patients with active cancer and a positive SARS-CoV-2 real-time reverse transcription polymerase chain reaction (RT-PCR) assay, the receipt of cancer treatment (chemotherapy, immunotherapy, hormonal therapy, targeted therapy, or radiotherapy) within the past 4 weeks had no significant effect on mortality from COVID-19 after adjusting for variables such as age, gender, and comorbidities [27]. Similarly, a study from Madrid, one of the epicenters of the pandemic, showed that patients with COVID-19 and cancer who received chemotherapy did not have an increase in mortality, and the authors even hypothesized that chemotherapy could decrease COVID-19-induced inflammation [13]. Another study found that treatment with cytotoxic agents, anti-PD1/PDL1, anti-CD20, antiangiogenic tyrosine kinase inhibitors, or mTOR inhibitors were not associated with an increased risk of death in patients with cancer and SARS-CoV-2 positivity [28]. In a cohort study of 928 cancer patients from the COVID-19 and Cancer Consortium (CCC19) database, 30-day all-cause mortality in patients with cancer infected with SARS-CoV-19 was not found to be associated with the type of cancer, recent anticancer therapy, or recent surgery [29]. Intriguingly, initial data from the Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) registry indicate that patients on tyrosine kinase inhibitors appear to be at decreased risk for hospital admission [30].

On the other hand, a retrospective analysis from nine hospitals in Hubei, China, which included 205 patients with cancer and laboratory-confirmed SARS-CoV-2 infection, found that those receiving chemotherapy within 4 weeks before symptom onset had a higher risk of death during hospital admission [31]. The French experience at Gustave Roussy showed that those patients who had received chemotherapy within the past 3 months had a poorer outcome compared with patients who received either targeted agents or immunotherapy [32]. The TERAVOLT registry too reported that chemotherapy within 3 months of COVID-19 diagnosis was associated with increased risk of mortality [30].

In summary, there is evidence from retrospective analyses that COVID-19 patients with cancer have worse outcomes and more severe disease compared with COVID-19 patients without cancer. This could be especially true for patients with primary or secondary involvement of the lung, and those with hematological malignancy. However, because there are likely to be some confounding factors in these analyses, it is currently not possible to quantify with certainty the excess mortality in cancer patients over a propensity-matched control population.

IMPACT OF THE PANDEMIC ON CANCER TRIALS

The pandemic has had a considerable negative impact on cancer clinical trials, for several reasons [33, 34], including research staff being redeployed to frontline clinical activities, global travel restrictions, reduction in the numbers of eligible patients visiting hospitals, and other factors [35]. As the SARS-CoV-2 outbreak spread around the world, it resulted in a considerable dip in enrollment in ongoing studies, especially

during periods of high transmission. Unger et al. reported that while 1431 patients were enrolled in ongoing SWOG Cancer Research Network studies during weeks 1–11 of 2020, this number dropped to 439 during weeks 12–17, coinciding with increased COVID-19 incidence across the United States [36]. A global analysis found a 60% decrease in enrollment of new patients in oncology clinical trials in April 2020 compared with April 2019 [37]. On the other hand, a large number of COVID-19-related clinical trials have been launched, many of them testing repurposed anticancer drugs [38].

There could be increased protocol deviations as patients miss hospital visits, as well as delayed data reporting, potentially impacting patient safety. Of particular concern are immunotherapy trials, where fever and pneumonitis are expected complications of therapy [39] and might be difficult to discern from symptoms of COVID-19.

In recent years, telemedicine solutions have been implemented in Australia to allow patients in more remote locations to have access and to boost recruitment to major adjuvant breast cancer trials such as MonarchE [40], a trend that is likely to intensify during the pandemic and to continue in the post-pandemic era.

There has also been a significant impact on trial processes [41], including monitoring and audit, with new remote systems being required and deployment of staff to working from home conditions. Consequently, the pandemic has generated calls to streamline cancer trial methodology and paperwork, and to reduce the number of mandatory hospital visits [42].

IMPACT OF THE PANDEMIC ON CANCER TREATMENT

Cancer clinics worldwide responded to the pandemic by implementing processes such as segregated workflow [43], prioritizing certain subgroups of cancer patients for immediate treatment while postponing therapy for other groups [44], modifying certain treatment protocols, [45, 46] incorporating telemedicine into their workflow [47], and other measures [48, 49]. Mauri et al. [50] reviewed 63 guidelines from professional societies around the world and summarized key recommendations.

In hospitals serving populations with a high caseload of SARS-CoV-2 infection, such as New Delhi, Mumbai, Milan, Madrid, and New York, medical resources were preferentially deployed to treat patients with COVID-19, potentially compromising routine activities such as cancer screening and therapy. Another concern that physicians in charge of metastatic cancer patients have had during the pandemic is in selecting the ideal systemic treatment from different available alternatives, keeping in view emerging data that hospital admission or recurrent hospital visits could be potential risk factors for cancer patients to acquire SARS-CoV-2 infection [12]. Patients with cancer being treated in low- and middle-income countries have faced particularly difficult challenges during the pandemic [51–53].

In the field of genitourinary tumors, where different treatment strategies including chemotherapy, targeted therapies, hormone therapies, immunotherapy, or radionuclides can be offered to patients, recommendations favor the use of regimens with lower rates of cytopenia during this pandemic [54].

Given their widespread use in oncology as well as their immunomodulatory properties, the use of checkpoint inhibitors during the pandemic has drawn attention. Initial data show that administering immunotherapeutic agents to patients with cancer may not worsen their outcomes [27]. However, additional research is needed, and careful patient selection and informed discussion should take place before using these agents [55].

INCREASED ADOPTION OF TELEMEDICINE

Rapid implementation of telehealth consultations, either by phone or video link, has allowed potentially vulnerable patients to be monitored and supported at home, rather than having to travel to hospitals for follow-up. Difficulties arise with the inability to fully examine patients, technology failures, and lack of training of clinical staff in the nuances of

communication at a distance, including maintaining privacy. Attention to appropriate positioning, eye contact, lighting, sound, and expressions of empathy can help patients have more satisfying interactions over video. Key to the success of telemedicine has been changes to reimbursement structures, as well as the development of suitable technology. It is important to ensure that the use of patient-centered measures such as telemedicine continues to be part of the standard oncology clinical practice and clinical trials even after the pandemic subsides [56].

COULD THERE BE AN EXCESS OF CANCER DEATHS IN THE NEAR FUTURE?

Emerging data indicate that fewer cases of cancer were diagnosed during the early phases of the pandemic [57], likely as a result of travel restrictions and the avoidance of hospital visits by patients for regular cancer screening or investigation of new symptoms. One analysis from England and Northern Ireland found a 45–66% reduction in admissions for chemotherapy and 70–89% decline in urgent referrals for early cancer diagnosis during the early phase of the pandemic [58]. This postponement of normal cancer screening activities and timely treatment could lead to excess deaths from cancer in the future, with one estimate suggesting a 1% increase in deaths from breast and colorectal cancer over the next decade in the USA alone, i.e. about 10,000 excess deaths [59].

There is an urgent need to implement policies and procedures to limit the collateral damage of COVID-19 on cancer screening, diagnosis, and treatment [60], especially since there are increasing data to show that careful patient selection and implementation of rigorous infection control measures may allow safe delivery of oncology therapy during the pandemic, with little additional risk to patients.

Efforts to collect large-scale and long-term data about the impact of COVID-19 on patients with cancer, such as the OnCovid observational study, should be encouraged [61].

FUTURE DIRECTIONS

This global pandemic has had an unprecedented impact on human society, culture, and medical practice. It is likely that future oncology care will increasingly incorporate digital pathology [62], telemedicine [63], and other technologies. Virtual multidisciplinary team meetings, supplemented by electronic patient-reported outcome measures, may allow patients with rarer cancers and their clinicians to receive expert input while reducing the impact of travel, and facilitate more equitable access to clinical trials.

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