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## Review

## Cancer treatment in the coronavirus disease pandemic

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## ABSTRACT

Half a year after its emergence, severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) has resulted in a pandemic, with cases continuing to increase in nearly every country. Surges in coronavirus disease of 2019 (COVID-19) cases have clearly had profound effects on current cancer treatment paradigms. Considering the effect of antineoplastic treatment and the immunosuppressive properties of cancer itself, cancer patients are deemed to be more vulnerable to SARS-CoV-2. Hence, the specific risk of SARS-CoV-2 must be carefully weighed against the benefit of antineoplastic treatment for cancer patients in the COVID-19 era. In this review, we discuss the current evidence in this important field, and in particular, the effect of SARS-CoV-2 on antineoplastic treatment.

## 1. Introduction

Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) is a novel beta-coronavirus and the causative agent of coronavirus disease 2019 (COVID-19) [1,2]. As of 26 July 2020, over 16 million cases of COVID-19 have been confirmed globally, with nearly 650,000 deaths [3]. Recently, several studies revealed a recurrent pattern of D614 G mutation of SARS-CoV-2 at multiple geographic levels, which enhances viral transmission ability [4–6]. This implies that the virus will probably persist for the long term.

Approximately 7%–8% of hospitalized COVID-19 infected patients also had a malignant disease [7–12]. Additionally, these included cancer patients with advanced age, coexistent comorbidities, and immunocompromised conditions, which are all established factors associated with COVID-19 risk [8,13,14]. Hence, in the past few months of the COVID-19 era, treatment for cancer patients has received increasing attention from oncologists [15,16]. Studies on cancer patients with COVID-19 have already been published. A literature search was performed in PubMed using the following descriptors “COVID-19”, “SARS-CoV-2”, “Cancer” and “Tumor”. Based on these data, we have drafted some clinical characteristics of cancer patients with COVID-19 and reassessed the specific risk of SARS-CoV-2 in cancer treatment.

## 2. Clinical observations

## 2.1. Clinical outcomes

In February 2020, an early report from Liang et al. [17]. reported a cancer prevalence of 1% (95% confidence interval [CI], 0.61% to 1.65%) among 1,590 patients with COVID-19, and these patients had a higher risk of severe events compared with those without cancer (39% vs. 8%,  $p = 0.0026$ ). It is currently believed that patients with cancer show a more critical COVID-19 situation than individuals without cancer. This may result from the following factors: (1) the majority of cancer patients present with advanced age and coexistent comorbidities, which have been confirmed as high-risk factors [8,10,13,18]; (2) the immunosuppressive properties of cancer itself; and (3) treatment options, such as chemotherapy and steroid therapy, could induce systemic immunosuppressive states. Therefore, an increasing number of research teams from different regions are joining the effort to explore the specific relationships between COVID-19 and cancer more deeply (Table 1).

Currently, the global COVID-19 mortality rate is about 4.1%, while the data show four-fold to five-fold differences between the countries with the highest and lowest rates [3]. Even so, COVID-19 patients with a cancer history showed significantly worse prognosis than those without cancer. The short-term mortality for COVID-19 patients with cancer was approximately 11% to 28% (Table 1). Moreover, it seems that the mortality rate did not qualitatively change with different enrolment

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time periods and geographical distribution.

Other prognostic factors, including cancer state and cancer type, are worthy of concern. It is easy to understand that metastatic stage or active cancer patients have a significantly worse prognosis than early stage or remission cancer patients. Indeed, according to results from the COVID-19 and Cancer Consortium registry database, active cancer (progressing vs remission) was an independent factor associated with increased 30-day mortality (odds ratio = 5.20, 95% CI: 2.77–9.77) [19]. Similar results were observed in the COVID study [20]. As previously mentioned, a multi-center retrospective study showed that, in COVID-19 cases, confirmed time since cancer diagnosis (1–5 years vs. < 1 year) was significantly associated with non-severe disease outcome (hazard ratio = 0.227, 95% CI: 0.116–0.446,  $p < 0.0001$ ) [21]. This suggests that the more active the tumor, the more serious the COVID-19 condition. In addition, there is controversy regarding whether specific cancer type is associated with the COVID-19 clinical outcome. As summarized in Table 1, several retrospective studies pointed out that hematologic cancer and lung cancer were associated with worse prognosis than other cancer types [22–26]. However, results from the CCC19 cohort demonstrated a negative association between cancer type and the COVID-19 clinical outcome [19,27].

Thus far, these studies clearly indicate that COVID-19 patients with cancer had a 2.5- to 7-fold increase in risk of death and severe outcomes

compared to those without cancer. Particular attention should be given to patients with metastatic stage or active cancer.

## 2.2. Antineoplastic treatment and COVID-19

Whether recent antineoplastic treatment would aggravate the COVID-19 condition is another important question. The qualitative results of the prognostic value of recent antineoplastic treatment for COVID-19 patients are summarized in Table 2. Interestingly, contradictory results have been observed.

Some possible explanations for the apparent discrepancies are as follows: first, the observed heterogeneity between studies, especially the proportion of stage IV patients and patients receiving antineoplastic treatment. It is interesting to note that studies with negative findings had a higher proportion of patients who recently received antineoplastic treatment. Second, positive findings were obtained from retrospective cohort studies with an early enrolled time period in China. All enrolled patients were from the Hubei province, the early stage epicenter of the pandemic in China. Hence, selection bias in these retrospective studies should not be ignored. Moreover, based on phylogenetic network analysis, the prevalence and genotype distribution of SARS-CoV-2 in East Asians, Europeans, and Americans varies [31,32]. Different genomic clusters of SARS-CoV-2 may cause different prognostic effects

**Table 1**  
Recent studies investigating the clinical outcomes and risk factors of COVID-19 patients with cancer.

Ref.	Region	Study design	Time period	Sample size	Mortality	Primary endpoint	Cancer stage	Cancer type	Other findings
Dai et al. [22]	Hubei, China	Retrospective	1 Jan 2020–24 Feb 2020	105	11.4%	Severe outcomes <sup>#</sup>	Metastatic cancer/ stage IV (HR = 2.48, $p = 0.01$ )	- Hematologic cancer (HR = 6.30, $p < 0.01$ ) - Lung cancer (HR = 2.59, $p < 0.01$ )	Lung metastases (HR = 2.58, $p < 0.01$ )
Zhang et al. [28]	Hubei, China	Retrospective	13 Jan 2020–26 Feb 2020	28	28.6%	Severe outcomes <sup>#</sup>	Metastatic cancer/ stage IV (HR = 0.509, $p = 0.194$ )	–	Patchy consolidation (HR = 5.438, $p = 0.01$ )
Tian et al. [21]	Hubei, China	Retrospective	13 Jan 2020–18 Mar 2020	232	20%	Severe outcomes <sup>#</sup>	Stage IV (multivariable OR = 2.60, $p = 0.039$ )	–	Time since diagnosis (multivariable HR = 0.029, $p < 0.001$ )
Yang et al. [23]	Hubei, China	Retrospective	13 Jan 2020–24 Mar 2020	205	19.5%	Mortality	Stage III/IV (univariable OR = 3.38, $p = 0.011$ )	Hematologic cancer (HR = 3.28, $p = 0.0009$ )	Male sex (multivariable OR = 3.86, $p = 0.0033$ )
Kuderer and Rivera et al (CCC19) [19, 27]	USA, Canada, and Spain	Prospective	17 March 2020–26 June 2020	2186	15%	Mortality	Active cancer/ progressing (multivariable OR = 5.20)	No specific cancer type was associated with mortality	–
Mehta et al. [24]	New York, USA	Retrospective	18 March 2020–8 April 2020	218	28%	Mortality	Metastatic stage ( $p = 0.06$ )	- Lung cancer (mortality rate: 55%) - Hematologic cancer (mortality rate: 25%)	–
Lee et al. (UKCCMP) [25,26]	UK	Prospective	18 March 2020–8 May 2020	1044	30.6%	Mortality	Metastatic stage (multivariable OR = 1.34, $p = 0.579$ )	Hematologic cancer (OR = 1.74, $p < 0.01$ )	Age ( $p < 0.0001$ )
Garassino et al. (TERAVOLT) [29,30]	International multicenter	Retrospective	26 March 2020–11 Sep 2020	326 (thoracic cancer)	32%	Mortality	Metastatic cancer/ stage IV (OR = 1.9, $p < 0.001$ )	–	Smoking history (multivariable OR = 1.8)
Pinato et al. (OnCOVID) [20]	European	Retrospective	26 February 2020–7 May 2020	890	33.6%	Mortality	Active cancer (multivariable HR = 1.81, $p < 0.0001$ )	- Genitourinary cancer (mean OS: 22 days) - Hematologic cancer (mean OS: 24 days)	–

Abbreviations: COVID-19, coronavirus disease 2019; HR, hazard ratio; OR, odds ratio; OS, overall survival.

<sup>#</sup>Severe outcomes including admission to an ICU, development of severe or critical symptoms, the use of mechanical ventilation, or death.

**Table 2**  
Recent studies investigating the effect of recent antineoplastic treatment for COVID-19 patients with cancer.

Ref	Sample size	Outline of enrolled cancer patients	The prognostic role of antineoplastic treatment
Dai et al. [22]	105	- Stage IV: 21.0% - 36 patients (34.3%) received antineoplastic treatment ( $\leq 40$ days) #	- Immunotherapy: higher rate of death 33.3% - Surgery: higher rate of death 25.0%
Zhang et al. [28]	28	- Stage IV: 35.7% - 6 patients (21.4%) received antineoplastic treatment ( $\leq 14$ days) #	- If the last antineoplastic treatment was within 14 days, it significantly increased the risk of developing severe events (HR = 4.079, $p = 0.037$ )
Tian et al. [21]	232	- Stage IV: 15%	- Targeted therapy or immunotherapy (multivariable OR = 3.29, $p = 0.015$ ) - Time interval since last chemotherapy to hospital admission (multivariable HR = 3.51, $p = 0.046$ )
Yang et al. [23]	205	- Stage III/IV: 27% - 54 patients (26.3%) received antineoplastic treatment ( $\leq 28$ days)	- Chemotherapy (multivariable OR = 3.51, $p = 0.026$ )
Kuderer and Rivera et al (CCC19) [19, 27]	2186	- Present, progressive disease: 11% - 371 patients (40%) received antineoplastic treatment ( $\leq 28$ days)	- Type of antineoplastic therapy and recent surgery were not associated with mortality
Mehta et al. [24]	218	- Stage IV/metastatic: 19.3% - 47.1% patients received antineoplastic treatment ( $\leq 30$ days)	- Chemotherapy, radiotherapy, and immunotherapy were not associated with mortality
Lee et al. (UKCCMP) [25, 26]	1044	- Stage IV/metastatic: 43% - 66% patients received antineoplastic treatment ( $\leq 28$ days)	- Recent chemotherapy ( $\leq 4$ weeks) for patients with hematologic malignancies (OR = 2.09, $p = 0.028$ )
Garassino and Trama et al. (TERAVOLT) [29,30]	326 (thoracic cancer)	- Non-small cell lung cancer: 76% - 74% patients received antineoplastic at the time of COVID-19 diagnosis, and 37% received immune checkpoint inhibitors	- Type of antineoplastic therapy were not associated with mortality
Pinato et al. (OnCOVID) [20]	890	- Advanced stage: 39.4% - Active cancer: 62.5% - 53.8% patients were on antineoplastic therapy at the time of COVID-19 diagnosis	- Provision of chemotherapy, targeted therapy, and immunotherapy did not worsen mortality

COVID-19 = coronavirus disease, 2019. HR = hazard ratio. OR = odd ratio.

that remain unknown.

Two retrospective studies from China found a significant correlation between time interval since last antineoplastic treatment and COVID-19 prognosis [21,28]. This suggests that shorter time intervals are associated with a greater effect on COVID-19 outcomes. This is consistent with findings that COVID-19 patients with active cancer status had a worse prognosis.

Overall, these studies revealed that no conclusion can be drawn as to whether recent antineoplastic treatment aggravates COVID-19 disease. However, there are reasons for caution with patients who received antineoplastic treatment within the previous two weeks, especially those with significant treatment-related side effects.

### 2.3. Immunotherapy and COVID-19

Given their profound immunomodulatory activity, concerns about immunotherapy interference with the clinical course of SARS-CoV-2 infection have been raised in the early phase of the outbreak [33,34]. Lovly et al. [35] reported a case of an extensive small cell lung cancer patient treated with carboplatin, etoposide, and atezolizumab. The patient developed rapidly fatal pneumonitis within three days of the first treatment dose. Unfortunately, no therapeutic benefits were observed in this patient after high-dose steroids and infliximab were administered out of concern for immune-related pneumonitis. The patient was later diagnosed with SARS-CoV-2 infection by nasal swab reverse transcription-polymerase chain reaction; the immunoglobulin M seropositivity for SARS-CoV-2 suggested that the viral infection occurred before the patient received antineoplastic treatment. Although the reason for the fatal pneumonitis is not known, the interaction between SARS-CoV-2 infection and immune checkpoint inhibitors should be considered.

In a recent retrospective study from the Memorial Sloan Kettering Cancer Center, Luo et al. [36] investigated 69 COVID-19 patients with lung cancer, where 59% had previously received programmed cell death protein 1 blockade therapy (median last dose to COVID-19 diagnosis 45 days, range 4–820 days). Moreover, 200 patients with COVID-19 and thoracic cancers were enrolled in the thoracic cancers international COVID-19 collaboration registry, an international cohort study. Seventy-four percent were on antineoplastic therapy at the time of COVID-19 diagnosis, 37% of which included immune checkpoint inhibitors. The multivariate analysis showed that any type of antineoplastic therapy, including immune checkpoint inhibitors, was associated with an increased risk of death. These results were consistent with the majority of studies shown in Table 2 and suggest that there was no significant difference in severity regardless of PD-1 blockade exposure.

## 3. Adjustments of cancer treatment paradigm in the COVID-19 era

### 3.1. Ethical prioritization strategy

Surges in COVID-19 cases are deemed to cause a shortage of medical resources. Not surprisingly, there was a significant decline in the number of cancer-related hospitalizations and operations during the pandemic [37–39]. Based on an analysis of the UK's National Endoscopy Database, the activity of endoscopy procedures in the COVID-19-impacted period decreased to 12% of pre-COVID-19 levels, and the number of cancers detected weekly decreased by 58% [40]. Moreover, according to a nationwide online survey of cancer patients in the Netherlands, treatment was postponed in 39 of 250 patients (16%) and in 279 of 2391 patients (12%) who were awaiting treatment [41]. Hence, the primary challenge of a cancer treatment paradigm in the COVID-19 era is to ensure that patients receive timely cancer diagnosis and treatment.

As the epidemic progresses, there is a growing body of guidelines, measures, and consensus that provide more or less formal instructions for adjusted cancer care in the context of the COVID-19 pandemic

[42–49]. A key issue in these guidelines concerns the ethical problems arising from scarce medical resources in a pandemic [50,51]. Hence, when assessing these guidelines, the crucial issue lies in determining the priority system of different diseases within the ethical framework. In April, the American Society of Clinical Oncology (ASCO) drafted several recommendations for the oncology community to observe during the COVID-19 pandemic, which highlighted that the allocation of scarce resources should be based on maximizing health benefits [52]. The ASCO recommended that a fair and consistent allocation policy should be developed based on acknowledged ethical frameworks [53,54]. Therefore, ethical and rational prioritization strategies were the most important aspects of these instructions, especially for cancer patients who require surgery. Reduced surgical and perioperative care capacities often lead to a delay in the time to surgery [55]. Therefore, different specialties have published several surgical recommendations or guidelines, such as head and neck surgery, thoracic surgery, and colorectal surgery [42,56–62]. Detailed prioritization strategies are embodied in these guidelines. Recently, to better overcome the clinical dilemmas in the COVID-19 era, a global consortium led by the European Society for Medical Oncology published 28 statements on the clinical and technical areas of uncertainty ranging from diagnosis to therapeutic planning [48]. Overall, the ethical approach to cancer patients in the COVID-19 era would follow these clinical practice guidelines and consensus after considering local disease prevalence and medical resources.

### 3.2. Some points for future cancer treatment paradigms

Taken together the results of previous studies provide several take home messages from the clinical perspective (Fig. 1). Besides, some key points are suggested to mitigate the massive challenges to future treatment paradigms caused by the pandemic. First, accelerate telehealth services development to ensure the quality of cancer care while avoiding face-to-face contact [63–65]. This is an essential strategy for mitigating the spread of SARS-CoV-2 [66]. In fact, a substantial proportion of hospitals have either partial or full implementation of computerized telehealth capabilities; the major barrier remains as to how to use it. Currently, medical telehealth service in China was limited to treatment decision making among doctors. We should expand the application scenario of telehealth, such as tele-consent, psychological guidance and non-treatment visits. Second, allow oncologists to return to cancer clinical trials and cancer research [67–69]. The pandemic has caused widespread disruption of cancer clinical trials, which could have a profound impact on the survival of cancer patients [70,71]. Prolonged clinical trial closure does not appear to be warranted. Third, early detection of cancer is crucial for secondary cancer prevention [72–74]. Screening for high-risk populations must be firmly implemented in accordance with the guidelines.

### 4. Conclusions

The COVID-19 pandemic has already had a profound effect on cancer treatment paradigms. As a vulnerable population, cancer patients require more caution in the COVID-19 era. Although many aspects of SARS-CoV-2 and cancer remain unclear, there is no conclusive evidence indicating that antineoplastic treatment aggravates COVID-19 disease. Hence, from a clinical viewpoint, when any kind of treatment represents the optimal choice, it seems unreasonable to deny it to cancer patients or to interrupt its administration due to fears of COVID-19 infection. Under this premise, we cannot stop providing the best available treatment for cancer patients. According to incomplete statistics, there are currently over 200 kinds of COVID-19 vaccine being developed [75], and ten of them has progressed to phase III clinical trials [76]. We hope that the mass vaccination programs could control and end this pandemic.

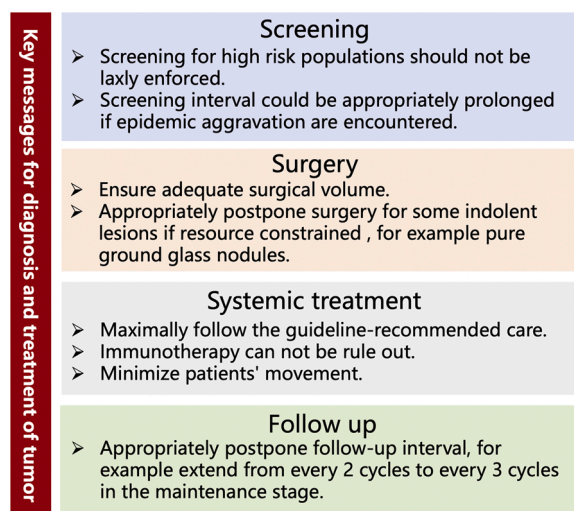


Fig. 1. Several take home messages for diagnosis and treatment of tumor in the COVID-19 era.

### 5. Authors contribution

JTZ, WZZ, and YLW designed the concept and outline of the original draft. JTZ wrote the original manuscript, WZZ and YLW reviewed and supported the editing of the original manuscript. YLW edited the final manuscript.

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### Declaration of Competing Interest

The authors have nothing to disclose.

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