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REVIEW

Cancer management during the COVID-19 world pandemic

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Abstract

Since 2019, the world has been experiencing an outbreak of a novel beta-coronavirus, severe acute respiratory syndrome coronavirus (SARS-CoV)-2. The worldwide spread of this virus has been a severe challenge for public health, and the World Health Organization declared the outbreak a public health emergency of international concern. As of June 8, 2023, the virus' rapid spread had caused over 767 million infections and more than 6.94 million deaths worldwide. Unlike previous SARS-CoV-1 and Middle East respiratory syndrome coronavirus outbreaks, the COVID-19 outbreak has led to a high death rate in infected patients; this has been caused by multiorgan failure, which might be due to the widespread presence of angiotensin-converting enzyme 2 (ACE2) receptors—functional receptors of SARS-CoV-2—in multiple organs. Patients with cancer may be particularly susceptible to COVID-19 because cancer treatments (e.g., chemotherapy, immunotherapy) suppress the immune system. Thus, patients with cancer and COVID-19 may have a poor prognosis. Knowing how to manage the treatment of patients with cancer who may be infected with SARS-CoV-2 is essential. Treatment decisions must be made on a case-by-case basis, and patient stratification is necessary during COVID-19 outbreaks. Here, we review the management of COVID-19 in patients with cancer and focus on the measures that should be adopted for these patients on the basis of the organs or tissues affected by cancer and by the tumor stage.

Keywords COVID-19 outbreak · Infection · Cancer management · Therapy · Immune system · SARS-CoV-2 · mRNA vaccines

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Abbreviations

AE	Adverse events
ALC	Absolute lymphocyte count
ORR	Overall response rate
SAE	Serious adverse event

Introduction

Since 2019, when the severe acute respiratory syndrome coronavirus (SARS-CoV)-2 virus was discovered, COVID-19 has spread around the world and shaped cancer therapy in previously unimaginable ways. Many studies have been conducted to understand the way the disease spreads and mutates, how therapies could be deployed to improve the condition of patients, and—most importantly—how vaccines could prevent this terrible outbreak. Although the death rate from the disease is below 5% on average, the infectiveness of the disease is problematic (e.g., in regard to the number of people hospitalized with COVID-19). Accordingly, knowing how to prioritize patients with very difficult health

conditions like cancer is of paramount importance. The current standard of care for patients with cancer and COVID-19 involves the use of personal preventive measures (e.g., gloves and FFP2 masks) to prevent the spread of infection, the use of symptomatic therapies (oral or intravenous) to alleviate the symptoms of the disease, and—in extreme cases—intubation for patients in intensive care who are struggling to breathe (Fig. 1). Many studies have shown the effects that of COVID-19 on cancer therapy and the treatment of patients. Systemic reviews and meta-analyses of published data from clinical trials are accepted as means of guiding evidence-based decisions in clinical practice.

From the beginning of the COVID-19 outbreak, it was evident that patients with cancer represent a group of special concern. Their risk of contracting SARS-CoV-2 has been estimated to be 2 times higher than that of the general population [1] because of their systemic immunocompromised state caused by the malignancy and anticancer treatments such as chemotherapy, radiotherapy, immunotherapy, or surgery. Compared with patients without cancer, they also have an increased risk of severe infections and an approximately 3.5-fold increase in the risk of needing mechanical ventilation or intensive care unit (ICU) admission if infected with the virus [2–6]. Thus, these patients might be at increased risk for COVID-19 and may have a poor prognosis. The need for a timely cancer diagnosis, surgical treatment, and radiotherapy, even during the pandemic, meant that patients with cancer had an increased need for hospital visits and an increased risk of being exposed to COVID-19 compared to the general population. On the other hand, the high demand for medical staff and healthcare facilities during COVID-19 limited patients' access to health care and their ability to receive necessary medical services, and this became the primary risk for patients with cancer [7]. It became clear that practical approaches were needed to manage the challenges of treating patients with cancer without putting their care at risk [6].

In this review, we discuss the effects of COVID-19 on the treatment of patients with cancer. We examine treatment choices and COVID-19's impact on cancer diagnoses and patient outcomes during the pandemic.

A brief illustration of COVID-19 pathogenesis

COVID-19 remains a serious challenge for health systems worldwide. This infection is associated with cytokine storm syndrome (CSS), which is related to severe acute respiratory distress syndrome [8] and which is characterized by a dysregulated immune response and hyperinflammation with constitutional symptoms and systemic inflammation. If left untreated, CSS may lead to multiorgan failure [9, 10]. The abnormal activation of the immune system associated with CSS may correlate with raised levels of several inflammatory cytokines, chemokines, and adhesion molecules [11]. Specifically, an analysis of cytokine levels in the plasma of 41 Chinese patients with confirmed COVID-19 cases (the first virus variants) showed higher levels of interleukin (IL)-1β, IL-7, IL-8, IL-9, IL-10, fibroblast growth factor, granulocyte colony-stimulating factor, granulocyte–macrophage colony-stimulating factor, interferon-γ, interferon-γ-induced protein 10, monocyte chemoattractant protein-1, macrophage inflammatory protein-1A, macrophage inflammatory protein-1B, platelet-derived growth factor, tumor necrosis factor-α, and vascular endothelial growth factor

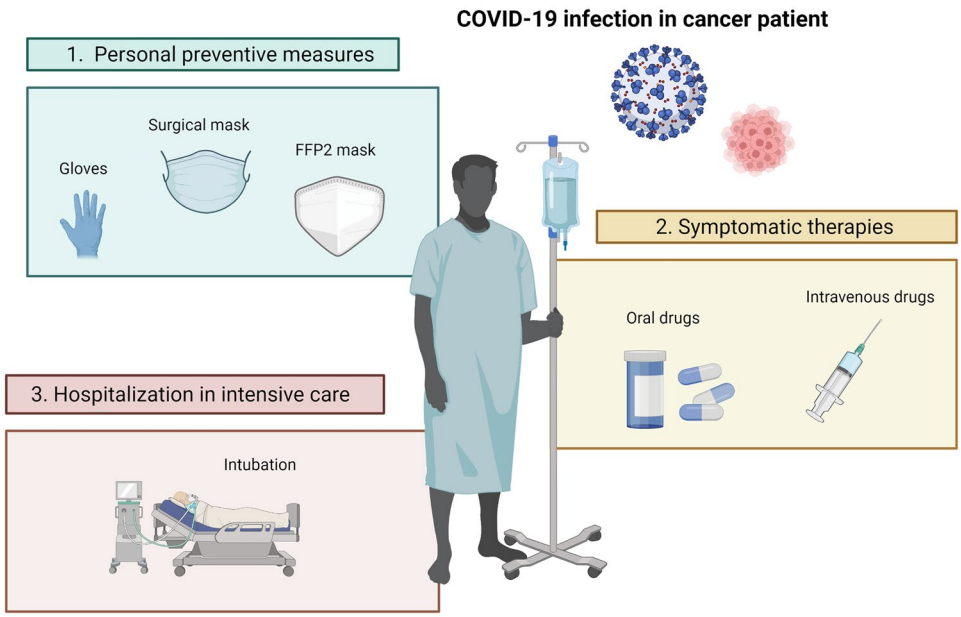

Fig. 1 Three main strategies to treat COVID-19-infected patients with cancer. These include personal protection measures in hospitals, symptomatic therapies (oral or intravenous) to alleviate COVID-19 symptoms, and—in worst-case scenarios in which patients cannot breathe—intubation

in ICU-admitted and non-ICU-admitted patients than were found in healthy adults. In addition, all the patients enrolled in the study had pneumonia; one-third were admitted to the ICU, of whom 6 died [12].

From a clinical point of view, a CSS is a critical, life-threatening condition demanding ICU admission, and it is associated with a high mortality rate [13]. Recent studies have determined that patients with COVID-19 may develop a CSS, which is directly related to lung injury and an unfavorable prognosis [10, 12–14]. Because of the prognostic and therapeutic implications of a CS, rapid treatment of the condition is extremely important. Different biological agents targeting cytokines have been developed for this purpose. Kyriazopoulou et al. [15] showed that early blockade of the cytokine IL-1 via the recombinant human IL-1 receptor antagonist anakinra in patients with moderate and severe COVID-19 significantly reduced the risk of worse clinical outcomes at day 28. Another placebo-controlled trial examined the role of canakinumab, a monoclonal antibody targeting IL-1β, in the treatment of 454 hospitalized, hypoxemic patients with COVID-19 pneumonia before mechanical ventilation. Although the study showed a trend toward improved survival in the patients who received canakinumab compared with those who received placebo, it did not find a significantly greater likelihood of survival among the patients who received canakinumab [16]. Moreover, as higher levels of IL-6 have been positively correlated with cases of critical and severe COVID-19, the anti-IL-6 receptor antibody tocilizumab has been evaluated in a global phase 3 trial (EMPACTA) [17]. The study found that tocilizumab reduced the likelihood of progression to the composite outcome of mechanical ventilation or death, but without improving survival [17]. Although many clinical trials have explored the role IL-6 inhibition with monoclonal antibodies to either IL-6 or the IL-6 receptor, randomized, placebo-controlled, blinded trials have not shown any survival benefits associated with this treatment [18].

The challenge of targeting cytokines in severe COVID-19 pneumonia

Angiotensin-converting enzyme 2 (ACE2), which is often associated with COVID-19, may be overexpressed in some cancers, including renal carcinomas and cervical and pancreatic carcinomas [19, 20]. However, data from The Cancer Genome Atlas suggest decreased expression of ACE2 in breast, liver, and prostate cancers compared to normal surrounding tissues [21]. The chemotherapy dosage for patients with cancer with COVID-19 is not different from that for patients without COVID-19. One study of 1524 patients with cancer indicated that these patients had a higher susceptibility to develop COVID-19 than non-cancer patients and suggested that cancer patients should be isolated from non-cancer patients to mitigate the risk of SARS-CoV-2 infections in the general population [22]. Another study showed that a patient's response to COVID-19 infection probably influences the disease's pathogenesis, just as x influences y during chimeric antigen receptor T-cell therapy [12]. Corticosteroids were administered widely during the SARS-CoV-1 and Middle East respiratory syndrome coronavirus outbreaks and, in addition to other therapeutics, are being used in patients with COVID-19 [12, 23, 24], although administering corticosteroids to patients with cancer and COVID-19 to control excessive cytokine production and immune cell activation has become controversial [25, 26]. To target the inflammatory CS caused by IL-6 pathway activation, China has approved the use of tocilizumab and has included tocilizumab treatment in its latest guidelines for the diagnosis and treatment of COVID-19 [27]. Because anti-programmed cell death protein 1 (PD-1) therapy has been useful in the treatment of chronic viral or bacterial infections or tumors, the use of camrelizumab (a PD-1 immune checkpoint inhibitor) is being investigated in patients with cancer [28].

In conclusion, knowing when to target cytokines and which ones to target in severe COVID-19 pneumonia remains a challenge. Future therapeutic approaches to treating COVID-19 CSs may reduce COVID-19-associated morbidity and mortality [29] (Fig. 2). Meanwhile, strong efforts to prevent the spread and development of severe SARS-CoV-2 infections, combined with the administration of safe and effective vaccines, are mandatory [52].

Effects of COVID-19 on patients with cancer

Worldwide, SARS-CoV-2 infections have disrupted all aspects of health care, especially the treatment of cancer [30]. Since the beginning of the pandemic, multiple changes in treatment schedules (changes in therapy, treatment deferrals, or medications omissions), have been pointed out by multiple professional bodies and commissioners of services [31, 32]. The inevitable delay between the onset of the pandemic and the release of treatment guidelines from cancer societies and networks and pertinent clinical data to guide decision-making in the era of COVID-19 has led to variations in the standard treatments and treatment modifications in individual treatment centers. The major concern for oncologists has been whether to delay chemotherapeutic treatment for patients with cancer who are ready to begin chemotherapy with curative intent and for those already undergoing treatment.

According to a study by Liang et al., patients with cancer, as a highly vulnerable group, showed a higher risk of collateral effects from COVID-19 than patients without cancer

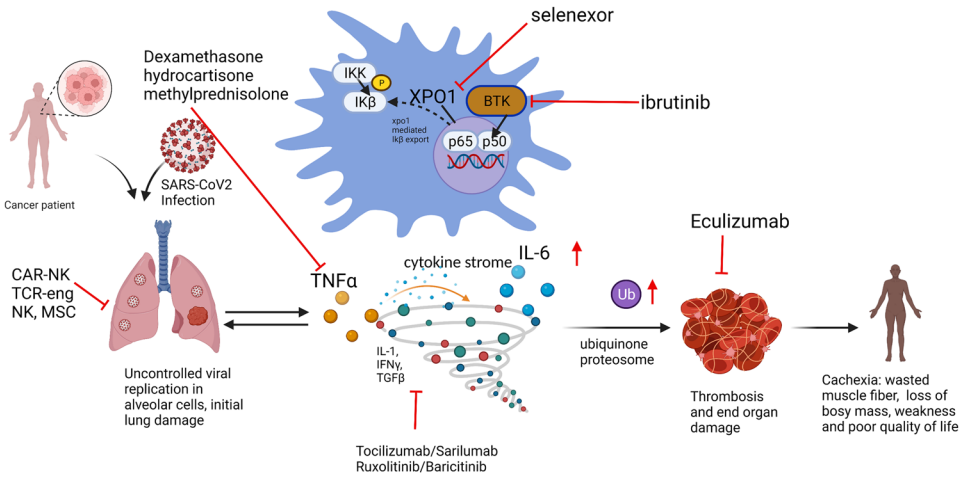

Fig. 2 Cytokine Storm. Patients infected with SARS-CoV2 can undergo an auto-immune cytokine storm leading to organ damage and/or failure

and were more likely to die or to require intensive care or invasive ventilation [22]. The authors suggested postponing adjuvant chemotherapy and elective surgery for patients with stable disease who live in areas in which COVID-19 is endemic [22]. In contrast, Zhang et al., in a retrospective case study conducted in cancer patients infected with COVID-19, in Wuhan, did not support delaying antitumor therapy to reduce the risk of COVID-19 infection [33]. In their point of view, patients with cancer should undergo whatever treatment is necessary, but only after careful research of the infection, comprising a chest CT scan and nucleic acid testing Similarly, Jindal et al. suggested maintaining adjuvant chemotherapy with a curative intent while taking precautionary measures, to reduce the risk of COVID-19 transmission [34]. For instance, the authors recommended that patients receiving chemotherapy must isolate themselves for at least 7 days before chemotherapy to avoid receiving chemotherapy during COVID-19 incubation [34]. Moreover, after weighing the risks vs. the benefits of continuing adjuvant chemotherapy they established that such treatment should be continued, but in conjunction with careful precautions to reduce COVID-19 transmission, such as self-isolation, minimization of the number of hospitalizations, and meticulous screening of patients and staff. The authors also advocated reducing patients' risk of neutropenia to limit the risk of simultaneous COVID-19 and bacterial septicemia.

A prospective observational study conducted in the UK and describing COVID-19 mortality in patients with cancer demonstrated that, compared with patients who did not receive cytotoxic chemotherapy within 4 weeks before a confirmed COVID-19 diagnosis, those who did receive cytotoxic chemotherapy did not have a significantly greater risk of more severe disease or death from COVID-19 [35]. Similar results were found for patients undergoing treatment with immunotherapy, hormonal therapy, radiotherapy, and targeted therapies [35]. Hanna T et al. considered the possibility of converting intravenous to oral systemic regimens and of stopping or reducing the frequency of long-duration or maintenance treatment to safely reduce the number of hospital visits and consequent risks [36]. Thus, in their center, they planned to move from 2-weekly to 4-weekly administrations of durvalumab as consolidation therapy and to eventually stop using pemetrexed as maintenance therapy in patients with non-small cell lung cancer. Interestingly, they proposed a conceptual framework to help oncologists to prioritize cancer treatments, including radiotherapy and systemic therapy, during the COVID-19 pandemic. For instance, according to this framework, postponing treatment in patients with low-risk prostate cancer or basal cell carcinomas may be acceptable because postponement does not seem to impact cancer outcomes in many of these individuals. Otherwise, it is straightforward that, in specific cases, treatment delays may impact patient outcomes.

In a meta-analysis of patients with breast cancer (BC), Raphael et al. showed that increased waiting time from surgery to the beginning of adjuvant chemotherapy was associated with a significant decrease in survival [37]. Therefore, they suggested making waiting times for adjuvant chemotherapy as short as prudently possible. Similarly, in a prospective study, Farolfi et al. found that poorer prognoses are associated with longer times between receiving a cancer diagnosis and the initiation of adjuvant chemotherapy, especially in patients with rapidly proliferating, early BC [38]. On the other hand, cancer care guidelines promulgated during the COVID-19 pandemic have recommended delaying surgery, when reasonably achievable, by initiating neoadjuvant chemotherapy in some patients with early-stage, estrogen receptor-positive (ER+) and human epidermal growth factor receptor 2 (HER2)-negative (HER2−), HER2+, or triple-negative BC [38–40]. Likewise, the treatment recommendations provided by Dietz et al. suggested treating patients with neoadjuvant endocrine therapies (NETs) for 6 to 12 months,

postponing surgery in patients with ER+HER2−BC, and periodically evaluating patients to confirm the absence of tumor progression [41]. In relation to this, Di Lena et al. conducted a multi-institutional matched historical cohort study in which they compared various clinical investigations of treatments for the same type of patients before and after the start of the pandemic. When they matched 28 patients who received NET with 48 control patients, they found that treatment was delayed 2.5 times longer in the patients who received NET. Moreover, they pointed out that patients with early-stage, ER + BC who received NET did not have pathological upstaging during the pandemic [42]. Interestingly, their findings suggested that, in similar patients, NET should be administered if surgery must be delayed [42].

A survey performed by Papautsky et al. revealed that, at the outbreak of the COVID-19 pandemic, nearly half of BC survivors experienced delays in cancer treatments (e.g., injections for ovarian suppression) because of clinic closures or the consolidation of services in a different clinic. Other patients described modifications in their treatment protocol (e.g., longer times between injections or the use of an alternative therapy [e.g., tamoxifen] that could be self-administered [43]. Younger respondents experienced a higher incidence of delays than older respondents, but there were no significant differences between groups in regard to race, insurance, site of care, or cancer stage [43]. However, studies have shown that the treatments used to treat BC (e.g., chemotherapy, tyrosine kinase inhibitors [44], cyclin-dependent kinase 4/6 inhibitors [45, 46]) have no impact on the risk of COVID-19 complications and that BC treatment should therefore be modified as little as possible to increase the likelihood of a good outcome [47].

Abundant clinical evidence also indicates that delays in initiating radiotherapy hurt outcomes in patients with head and neck squamous cell carcinomas [48]. Jensen et al. demonstrated the negative impact of a lengthy waiting time before radiotherapy in these patients [49] Similarly, a systematic review by Huang et al. showed that a delay in initiating radiotherapy worsened the 5-year local recurrence rate for BC and head and neck squamous cell carcinoma tumors [12]. A multicenter survey by the UK National Cancer Research Institute's Head and Neck Clinical Studies Group observed a clear trend toward centers adjusting radiotherapy treatments during the pandemic by increasing the radiation dose per fraction, reducing the number of treatments, and omitting cisplatin chemotherapy from radical radiotherapy regimes [50]. Many centers in which concomitant therapy with cisplatin was maintained chose to reduce total dose or dose density, switched to a regime believed to be less immunosuppressive, added granulocyte colony-stimulating factor or TKi-EGFR combined targeted treatment to reduce the perceived risks to patients [51].

A meta-analysis by Hanna et al. reported that, across all 3 major treatment modalities (surgery, systemic treatment, and radiotherapy), a 4-week treatment delay increased the risk of death among patients with the 7 most common tumor types (bladder, breast, colon, rectum, lung, cervix, and head and neck) [52]. In addition, the risk of death was considerably higher for some patients whose radiotherapy or systemic treatment was delayed. For example, among patients with colorectal cancer, the risk of death was increased by 9% and 13% for definitive radiotherapy and adjuvant systemic treatment, respectively [52]. In a single-center retrospective study of patients in Kyoto with lung cancer, 9.1% of patients experienced a delay in their treatment during the COVID-19 pandemic. The study found that the patients whose treatment was delayed were significantly more likely to be treated with immunotherapy agents than were the patients whose treatment was not delayed (who were more likely to be treated with targeted agents) [53].

On the other hand, the work by Sha et al. investigating the impact of COVID-19 on patients with lung cancer suggested that the continuation of in-hospital treatment with curative intent may be reasonable during periods of COVID-19-related quarantine. However, the authors suggested this option only if proper protections against the spread of COVID-19, are combined with a switch from intravenous to oral chemotherapy/molecular targeted therapy [54]. Despite the foundational importance of this study, the real impact of treatment delays on long-term outcomes such as cancer-specific mortality and local recurrence has not been determined in a standardized way. This information may become available in the next years and will be essential for the reassessment of cancer care systems, pathways, and models of care that deliver affordable and equitable outcomes [55]. In the meantime, the decision to begin or delay cancer treatment must be made on a patient-by-patient basis and should not be based on data from the small early studies reporting outcomes in patients with cancer during the initial phase of a pandemic. Instead, while the pandemic is still underway, it may be useful to make treatment decisions based on precautionary principles established through evidence-based data and information presented in virtual, multidisciplinary case conferences.

The challenges of providing immunotherapy and chemotherapy treatments to patients with cancer during the COVID-19 pandemic

As discussed above, the existing data indicate that, overall, the incidence of, risk of serious infection from, and death rate from COVID-19 is higher among patients with cancer than in the general population. It also appears that the treatments used to manage cancer, such as immunotherapy and chemotherapy, may play a role in increasing risks in

these patients, although better studies are needed to confirm this. Therefore, when a patient with cancer tests positive for SARS-CoV-2, decisions regarding the use and timing of anticancer therapy should be individualized and should make use of the following general principles. Oncology societies around the world, namely the European Society of Medical Oncology (ESMO), American Society of Clinical Oncology, National Comprehensive Cancer Network (NCCN), and many more, developed guidelines to mitigate the negative effects of the COVID-19 pandemic on the diagnosis and treatment of patients with cancer [56]. The NICE guideline provided many recommendations based on the available evidence regarding many COVID-19-related and cancer-related issues, including communicating with patients, managing patients with confirmed or suspected COVID-19, staff who are self-isolating, prioritizing patients for treatment, modifications to usual service, and treatment breaks. The common theme of these proposed guidelines was to categorize patients into high, medium, or low priority based on the Ontario Health Cancer Care Ontario criteria to plan their management course accordingly [57, 58]. In addition to these suggested priority-driven guidelines, hospitals around the world have issued internal guidelines for oncologists, aiming to decrease patient exposure to COVID-19. Given the immunocompromised nature of the patient population, cancer centers implemented strict infection control guidelines, in inpatient and outpatient settings. In the UK, clinical layouts were changed to create foot traffic in a single direction, physical distances were increased in waiting areas, and outpatient visits, including ambulatory clinic and chemotherapy infusion visits, were reduced. In addition, preference was given to oral therapy regimens rather than parenteral anticancer therapies if the 2 options were considered equivalent. As a result, patients' risk of exposure to SARS-CoV-2 and of compromised oncological outcomes was reduced.

Systemic therapy

Systemic anticancer therapy includes a spectrum of pharmacologic agents, such as chemotherapy drugs, hormonal therapies, targeted agents, and immunotherapies, administered for curative and palliative purposes to increase life expectancy in patients or reduce symptoms. The long-term management of patients with cancer is complicated by the patients' increased exposure to drugs with various side effects, such as immunosuppressive drugs, and to healthcare settings. In patients who have been exposed to many such drugs, receiving systemic therapy may be associated with worsening outcomes during COVID-19 infection. The major concern is whether patients with cancer and a confirmed COVID-19 infection should stop their anticancer therapy or not, and the issue is still debated.

None of these therapeutic regimen changes, which were made in accordance with new National Institute for Health and Care Excellence guidelines for the treatment of cancer, were associated with a higher risk of disease severity and mortality, although the sample size was relatively small. In parallel, some studies have reported a greater likelihood of dying from COVID-19 infection in patients with cancer receiving systemic chemotherapy (odds ratio [OR] 9.84; 95% CI 5.73–16.9) compared with those receiving other types of treatment. It has also been reported that the risk of developing COVID-19 is greater in patients who received chemotherapy (OR 2.99; 95% CI 1.72–5.21), especially at higher doses (OR 2.36; 95% CI 1.35–6.48) than in patients who received x. Similarly, in another cohort study, a history of systemic chemotherapy within 60 days of COVID-19 diagnosis was correlated with an increased risk of death (hazard ratio 2.30; 95% CI 1.16–4.6; $p = 0.02$) (94). These concerns have prompted institutions to recommend self-isolation for patients with cancer who are highly vulnerable to prioritizing cancer treatment [22, 59]. However, the most common approach is to discontinue immunotherapy or chemotherapy treatment for most patients with COVID-19, regardless of whether they display COVID-19 symptoms [60, 61].

Chemotherapy

Since the advent of the pandemic, concerns about the impact of chemotherapy on COVID-19 mortality have dramatically increased [62]. As previously stated, the data relating to the association between chemotherapy treatment and COVID-19 are controversial.

Several studies have reported an increased risk of mortality in COVID-19 patients receiving chemotherapy [19, 20], but others have not found an increased risk of mortality in patients undergoing chemotherapy within 4 weeks before a positive COVID-19 test [59, 60]. Another study did not find an association between cytotoxic chemotherapy treatment and adverse COVID-19 outcomes [60, 61, 63]. It is worth mentioning that COVID-19-related consequences have been shown to affect nearly 15% of patients with cancer and to have a negative impact on survival in general [64]. Moreover, patients' oncological outcomes are adversely affected after COVID-19 infection because of inadequate therapy administration after recovery. Therefore, for patients with COVID-19 infection, chemotherapy interventions must be personalized while keeping in mind the balance between the risks and benefits of chemotherapy in this population [65].

A study by Liang et al. reported that patients with cancer have a higher likelihood of being infected with COVID-19 [22]. So far, most COVID-19 infections are mild to severe, and there are no specific steps that patients with cancer should take to protect themselves, although they are at risk.

Because of the severe clinical deterioration associated with COVID-19 in patients with cancer, 3 essential strategies may be used to mitigate the COVID-19 crisis, or any future infection affecting patients with cancer. The first strategy is postponing chemotherapy treatment or elective surgical procedures in stable cancer cases at high-risk locations. The second is implementing strict personal precautions for patients with cancer or cancer survivors. The third strategy is providing more intensive care and treatment to COVID-19-infected patients with cancer who are old or have other comorbidities [66]. Kutikov et al. [67] proposed specific recommendations which can be used to guide the decision process on delaying or continuing cancer treatment during the COVID-19 pandemic. The proposed guide is based mainly on categorizing patients into low, medium, or high risk of disease progression with cancer treatment delay. For example, it is considered safe to delay treatment for > 3 months with a low risk of disease progression in patients with chronic hematologic cancers.

Hence, to minimize the chances of patients with cancer becoming infected with COVID-19, we recommend that clinics screen patients for COVID-19 signs and symptoms; consider chemotherapy regimens with low toxicity and myelosuppression levels; use chemotherapy regimens that minimize the exposure of patients with cancer to healthcare settings (e.g., administer chemotherapy orally instead of intravenously); and discontinue palliative chemotherapy when it cannot improve a patient's survival [12].

Immunotherapy

Immunotherapy, including treatment with immune checkpoint inhibitors, monoclonal antibodies, cancer vaccines, chimeric antigen receptor T-cell therapy, and immunomodulators, plays a vital role in cancer management and forms the first-line treatment option for several types of malignancies [24]. However, certain immune-related adverse events could favor more severe forms of COVID-19 infections in patients with cancer by increasing mortality rates. In particular, the co-occurrence of immunotherapy-related pneumonia and COVID-19 may correlate with increased mortality from end-stage respiratory failure [24], and hypogammaglobulinemia and immune-related neutropenia are of great concern in COVID-19-infected patients with chronic lymphocytic leukemia [25].

Overall, treatment with immune checkpoint inhibitors can be considered in the active phases of the COVID-19 pandemic. In a recent single-center multiobservational study of 69 outpatients with lung cancer with COVID-19 positive cases, the severity of COVID-19 was comparable among those who received PD-1 inhibitor treatment and who had not received PD-1 inhibitor [68, 69]. Pembrolizumab can be administered less frequently at 400 mg every six weeks, which is approved by the US FDA. This treatment schedule has similar efficacy and safety as a previously approved dose of 200 mg every three weeks. Decisions regarding whether it is appropriate to use a combination of immunotherapy Vs single-agent immunotherapy needs to be individualized. The risks of immunotherapy treatment regimens should be weighed against the diminished efficacy of single-agent therapy in an individual setting. Lymphopenia is a specific risk factor for COVID-19 [69–71]. A critical re-evaluation of the drugs that inhibit B cells like anti-CD-20 monoclonal antibodies during active treatment of COVID-19, especially in the treatment of follicular lymphoma [72]. Some have discontinued the usage of rituximab, especially in older patients and younger patients with low immunoglobulin levels. Moreover, the neutrophile-to-lymphocyte ratio predicts early signs of COVID-19 and worse prognosis [73]. An additional study showed in a cohort of 1071 cancer patients infected with SARS-CoV-2 that systemic inflammation is a validated prognostic domain and that it can be used as a predictor of adverse outcomes. OnCovid Inflammatory Score (OIS) and lymphocytopenia are independent predictive markers of severe COVID-19 [74]. Therefore, OIS, NLR, and lymphocytopenia can be used to stratify patients based on their risks.

Other systemic treatments

Limited data have suggested that the administration of granulocyte colony-stimulating factor is associated with worse COVID-19 outcomes in patients with cancer. However, hormonal therapies and some non-immunosuppressive oral targeted therapies may be continued [75]. Many case reports have suggested safety with the continuation of anaplastic lymphoma kinase (ALK) and c-ROS oncogene 1 (ROS1)-targeted therapies among those with the relevant cancer genotypes and COVID-19 pneumonia [76]. Although very little data are available, observational studies in chronic leukemia suggested that BTK inhibitors may be associated with less severe infection and continuation of the treatment with this class of drugs should be considered on a case-by-case basis [42, 43]. Similarly, treatment options with systemic glucocorticoids must be individualized, depending on the dose and indication for glucocorticoid. For example, in patients with an immunotherapy-related adverse event, it may be appropriate to continue treatment with glucocorticoids. On the other hand, if patients are experiencing nausea, glucocorticoids should be discontinued, and alternative therapy offered.

Surgery

Surgery is another vital component in cancer management. Where possible, all elective surgeries were rescheduled

[77]. Evidence suggests that patients who received surgery and concomitantly contracted COVID-19 were at much higher risk of severe clinical events than those who did not have surgery [77]. But also, was important to consider resource availability, as surgeries often require postoperative care in the ICU. Given the current shortage of ICU beds, it is important to delegate resources efficiently. For early-stage cancers where surgery is often the first step in management, patients could be offered neoadjuvant therapy, and surgery can be postponed without compromising patient outcomes [40]. Evidence suggests that 60-day delays in the surgical intervention of early-stage BC have been documented without worsening oncological outcomes. In the UK, neoadjuvant chemotherapy was reserved for patients for whom no other treatment options were available, all patients with ER + BC were switched to neoadjuvant endocrine therapy, and surgery was offered only in so-called green centers (hospitals that treated only patients with cancer), in which all patients were screened for COVID-19 and isolated for 2 weeks before and after surgery during the pandemic outbreak [78]. An international study conducted in 24 countries/regions included all surgical patients with confirmed COVID-19 infection and assessed the mortality rate (the primary outcome) at 30 days after surgery together with the rates of pneumonia, respiratory distress syndrome, and acute respiratory and accidental ventilation (secondary outcomes). In patients with confirmed COVID-19 infection before surgery (26.1%), the 30-day mortality rate was 23.8%, and pulmonary complications occurred in 51.2% of patients with a 30-day mortality rate of 38% [79]. Another study defined the length of time that surgery could safely be postponed in different disease settings [80]. The authors reported a median palliative performance scale survival time of 3 weeks (6 weeks from diagnosis) for primary surgery and a median of 8 weeks (26 weeks from diagnosis) for neoadjuvant therapy [80]. On the basis of this study, it can be stated that most surgical operations can be postponed for at least 4 weeks without significantly affecting either the survival of the cancer patient or the likelihood of complete tumor resection.

Thus, although the risk of perioperative morbidity and mortality is increased in patients with COVID-19, the decision to perform surgery must be made after balancing the risks of delaying or avoiding the planned procedure. In principle, surgery can be delayed for some patients, including those with non-melanoma skin cancer, BC that is not locally advanced, low- or intermediate-risk prostate cancer, low-grade lymphoma, and other low-risk cancers, but delaying surgery is not recommended for patients at high risk of disease progression, including those with liver cancer, pancreatic cancer, colon cancer with obstruction, small cell lung cancer, suspected ovarian cancer, and other high-grade or aggressive cancers [81].

Radiation therapy

Radiation therapy, which is another essential part of cancer management, had its unique challenges during the pandemic. Given the nature of the treatment, patients have to attend radiotherapy sessions daily [82]. There are three potential strategies to reduce the demand for radiotherapy during the pandemic: omitting, delaying, and shortening the radiotherapy course [83]. Considering varied clinical scenarios, the American Society for Radiation Oncology (ASTRO) published brief guidelines for radiation oncologists dealing with the COVID-19 pandemic. As noted by ASTRO, if considered reasonable, hypofractionated schedules, a modification to classical radiation therapy schedule, are encouraged [82]. The Royal College of Radiologists (UK) established a clinical resource that included guidelines on the management of many cancers, including breast, upper and lower gastrointestinal, prostate, lung, central nervous system, sarcoma, thyroid, melanoma, gynecologic, and urethral cancers, during the COVID-19 pandemic. These guidelines provided detailed recommendations on treatment with radiotherapy, including types of radiotherapy; administered doses; and when to continue, delay, or stop radiotherapy [77]. This resulted in the lead author for the trial enabling the provision of important radiotherapy quality assurance materials and protocols, essentially enabling the revision of departmental radiotherapy protocols for BC within days. Data from the then-unpublished fast forward trial were used to move to hypofractionated radiotherapy for adjuvant BC.

Canceling or delaying radiotherapy is suggested for patients with cancer and COVID-19 before the beginning of radiotherapy. Other options such as hypofractionation may be considered. However, it is important to note that delayed or discontinued radiotherapy may contribute to worse local control and overall survival [84].

Combination therapy

Despite the recognized effectiveness of the individual treatment modalities discussed so far, their use in combination with other treatments may be more efficacious in patients with cancer. Immunotherapy and chemotherapy are often combined with each other or with local treatments such as radiotherapy. The synergistic effect of radiotherapy with immunotherapy not only improves local control of the tumor but also can keep the patient's immune response active, leading to the abscopal effect. This effect may also bolster patients' defenses against viral infections, including COVID-19, although the pandemic has strongly hindered its use [85]. In their observational cohort study, García-Suárez

et al. included 100,691 patients with hematologic malignancies who were receiving different anticancer therapies within 30 days of being diagnosed with COVID-19. They found that the patients who were receiving or who had recently received antineoplastic therapy with monoclonal antibodies were at an increased risk of death, whereas those receiving conventional or intensive cytotoxic therapy may have a higher risk of death, although the association between chemotherapies and an increased risk of death remains to be clarified [86].

In general, it was recommended that patients receiving curative cancer therapy should continue their treatment despite the potential risk of COVID-19 infection during anticancer therapy. Delaying treatment of metastatic disease results in deteriorated performance status, admission for symptom palliation, and progressive disease. Surgeries can be delayed in some cases based on the clinical treatment delay without major negative health consequences. Online medical counseling and appropriate diagnosis and treatment of critical cases to minimize patients' exposure to COVID-19 were utilized during the virus outbreak [66].Virtual health services, including telephone or online appointments, especially for routine check-ups or prescription refills, can also be implemented as appropriate to reduce crowding in healthcare facilities to reduce exposure and efficiently utilize clinical resources.

Finally, another major concern is that, once a patient with cancer is infected with COVID-19, the patient may have a severe form of the disease that requires ICU treatment [7]. Thus, it seems reasonable to suggest regular surveillance for infected patients. This surveillance should include monitoring of saturated oxygen levels and hospitalization for patients with chemotherapy-induced neutropenia. Importantly, all patients with cancer and COVID-19 must have access to ICU care.

The impact of COVID-19 on cancer diagnosis and access to care

The current impact of the COVID-19 pandemic on cancer care in the USA has resulted in decreases and delays in identifying new cancers and delivery of treatment. These problems, if unmitigated, will increase cancer morbidity and mortality for years to come [87]. A collaborative study with a total of 356 centers from 54 countries across six continents participated has been conducted between April 21 and May 8, 2020. These centers serve 716,979 new patients with cancer a year. Most of them (88.2%) reported facing challenges in delivering care during the pandemic. Although 55.34% reduced services as part of a preemptive strategy, other common reasons included an overwhelmed system (19.94%), lack of personal protective equipment (19.10%), staff shortage (17.98%), and restricted access to medications (9.83%). Missing at least one cycle of therapy by > 10% of patients was reported in 46.31% of the centers. Participants reported patient exposure to harm from interruption of cancer-specific care (36.52%) and non-cancer-related care (39.04%), with some centers estimating that up to 80% of their patients were exposed to harm [88]. New cancer diagnoses decreased by 13% to 23%. These drops varied by state and continued to accumulate despite reductions in pandemic-related restrictions [89]. COVID-19 disease has fundamentally disrupted the practice of oncology, shifting care onto virtual platforms, rearranging the logistics and economics of running a successful clinical practice and research, and in some contexts, redefining what treatments patients with cancer should and can receive [90]. In a study of 3776 patients (from 64 UK units), 2246 (59%) had 'COVID-altered' management. 'Bridging' endocrine therapy was used ($n = 951$) where the capacity of the hospital operating surgical room was reduced. There was increasing access to COVID-19 low-risk theaters during the study period (59%). In line with national guidance, immediate breast reconstruction was avoided ($n = 299$). Where adjuvant chemotherapy was omitted ($n = 81$), the median benefit was only 3% (IQR 2–9%) using 'NHS Predict.' There was the rapid adoption of new evidence-based hypofractionated radiotherapy ($n = 781$, from 46 units). Only 14 patients (1%) tested positive for SARS-CoV-2 during their treatment journey. The majority of 'COVID-altered' management decisions were largely in line with pre-COVID evidence-based guidelines, implying that BC survival outcomes are unlikely to be negatively impacted by the pandemic. However, in this study, the potential impact of delays to BC presentation or diagnosis remains unknown [91, 92]. We estimated that 1,489,237 women had screening delayed by around 2–7 months between July 2020 and June 2021, leaving 745,277 outstanding screens. Depending on how quickly this backlog is cleared, around 2500–4100 cancers would shift from screen-detected to symptomatic cancers, resulting in 148–452 additional BC deaths. There would be an additional 164–222 screen-detected tumor deaths and 71–97 deaths from DCIS that progresses to invasive cancer [93].

Outcomes in patients with cancer during the omicron outbreak in correlation with SARS-CoV-2 vaccination

During the pandemic, the outcomes of patients with cancer have been heavily influenced by COVID-19, and the differences in outcomes between vaccinated and unvaccinated people have been investigated. In early 2020, as the virus evolved, multiple outbreaks started across the world. The emergence of SARS-CoV-2 variants such as the omicron

(B.1.1.529) variant affected the virulence of the disease. Omicron, characterized by its high transmissibility, caused a surge in the pandemic in both Europe and the USA in early 2021. Even if the reduced cellular tropism for cells and lower respiratory tract that express at higher levels transmembrane protease serine 2 [94, 95]. The clinical course of the disease poses people who are considered vulnerable to be susceptible to COVID-19 [96] such as patients with cancer. The immune-escape potential of this variant poses an additional concern in patients in high risk [97, 98].

COVID vaccines, including booster doses, have been an important tool in protecting patients with cancer from becoming infected with COVID-19. Since there are no large real-world studies providing evidence that taking the SARS-CoV-2 vaccine booster doses would affect the mortality of patients with cancer diagnosed with COVID-19. Pinato and colleagues [99] were the first to investigate the correlation between morbidity and mortality in vaccinated (with at least 1 dose of a SARS-CoV-2 vaccine) vs. unvaccinated European patients with cancer ($N = 3820$) who were diagnosed with COVID-19 and infected during the omicron outbreak vs. the alpha through delta outbreaks (before vaccines were available), respectively. Remarkably, the study found that, compared to patients who were infected in the pre-vaccination period, those vaccinated during the omicron period had significantly fewer fatalities at 14 days as well as COVID-19-related complications or the use of specific therapies, like oxygen therapies. The fatality rates at 14 days and 28 days, the rates of hospitalization because of COVID-19, and the rates of COVID-19 complications were similar for the patients diagnosed during the omicron vs. the alpha–delta phases.

Various small studies have shown that SARS-CoV-2 vaccines influence cancer outcomes and the efficacy of cancer therapeutics [100]. It is noteworthy that the clinical trials developing the SARS-CoV-2 vaccines did not test the vaccines in patients with advanced cancer and did not follow up with this population for a long time [101]. Pinato and colleagues presented important evidence in their large clinical study, which confirmed that SARS-CoV-2 vaccination and boosting help prevent COVID-19 -related outcomes in patients with cancer; this finding mirrored data for the general population and therefore emphasized the importance of giving the SARS-CoV-2 vaccine to all patients with cancer [102].

Our understanding of how COVID-19 in patients with cancer is influenced by vaccination is advancing noticeably as more data from large, patient-based studies become available. From a clinical point of view, CS is a critical life-threatening condition that demands intensive care admission, and it is associated with quite high mortality 6. Recent studies found out that patients with COVID-19 may develop CS, which is related directly to lung injury, and unfavorable prognosis [10, 12, 14, 103]. Due to its prognostic and therapeutic implications, the recognition of CS is extremely important for clinicians, and avoiding the condition through vaccination is critical, especially for patients with cancer.

Future studies comparing outcomes of vaccinated vs. unvaccinated patients with cancer who have variants of SARS-CoV-2 that appeared after omicron and who reside in other parts of the world are expected to support the solid data on large populations of European patients. In the long term, protection against SARS-CoV-2, obtained either by encountering the virus or through vaccination, is expected to reduce COVID-19-related deaths, complications, and therapy-related interventions among patients with cancer. Currently, the mRNA vaccine BNT162b2 was the first of its kind to be FDA-approved as safe and effective based on an international placebo-controlled clinical trial in 43,448 individuals (NCT04368728). The vaccine conferred protection in 95% of the people who received it at 16 years of age or at older age [104]. This fact revolutionized our appreciation of mRNA vaccines, making them always more of a valuable opportunity in vaccine discovery.

Moreover, many ongoing clinical trials are testing promising treatments for patients with cancer and COVID-19 to learn more about the disease's effects on patients with cancer. Table 1 shows the ongoing clinical trials that have enrolled patients with cancer and severe COVID-19.

COVID-19 risks and management for immunocompromised cancer patients

The Lancet Oncology recently published two significant studies examining the susceptibility and outcomes of cancer patients with COVID-19. In one study led by Kunyu Yang and colleagues, they explored the clinical characteristics and risk factors for mortality in 205 cancer patients with COVID-19. Out of the patients, 15% were transferred to intensive care units, and 20% died while hospitalized. Notably, the receipt of chemotherapy within four weeks of symptom onset was identified as a risk factor for in-hospital death [105].

Another study by Jianbo Tian and colleagues in The Lancet Oncology focused on 232 cancer patients with COVID-19, comparing them to COVID-19 patients without cancer. The researchers found that cancer patients had a higher risk of developing severe or critical COVID-19 compared to those without cancer. They also identified several novel predictors for poor prognosis, including advanced tumor stage, elevated tumor necrosis factor α, elevated N-terminal pro-B-type natriuretic peptide, and reduced CD4 + T cells [106].

These studies highlight the heightened susceptibility of immunosuppressed cancer patients to COVID-19 and emphasize the need for better management strategies.

Table 1 Clinical trials in patients with cancer and COVID-19

Clinical trial identifier code	Investigation plan	Viral vaccine/drug	Clinical setting/line	Primary endpoint	Stage of development	Clinical trial status
NCT04379518	64 participants, randomized parallel assignment, open label	Recombinant interferon alfa-2b and rintatolimod	First line	AE, kinetics of viral load	2	Recruiting
NCT04532372	30 participants, randomized sequential assignment, double	Leflunomide	First line	Toxicity, MTD, clinical activity	2	Recruiting
NCT04847050	220 participants, non-randomized parallel assignment, open label	mRNA-1273	First line	Safety and reacto-genicity	2	Recruiting
NCT04977024	240 participants, interventional, randomized parallel assignment, triple	Synthetic MVA-based SARS-CoV-2 vaccine COH04S1	Second line or later line	Biological response	2	Recruiting
NCT05028374	171 participants, interventional, single-group assignment, open label	Booster dose of the Moderna mRNA COVID-19 vaccine	First line	Evaluation of ORR, AEs, and SAEs	2	Recruiting
NCT04426201	10 participants, interventional, randomized parallel assignment, quadruple	CYT107, placebo	First line	Clinical improvement of ALC	2	Active, not recruiting
NCT05016622	100 participants, interventional, single-group assignment, open label	BNT162b2 vaccine	First line	Rate of serocon version for SARS-CoV-2 spike antibodies	2	Recruiting
NCT04439006	10 participants, interventional, randomized parallel assignment, open label	Ibrutinib	First line	% of patients with diminished respiratory failure, death	2	Active, not recruiting
NCT04565665	70 participants, interventional, randomized, parallel assignment, open label	Mesenchymal stem cells	First line	Incidence of SAEs, toxicity	2	Recruiting
NCT05438498	1500 participants, single-group assignment, open label	Evusheld (tixagevimab + cilgavimab), IM or IV	First line	AZD7442 serum concentration	3	Recruiting

Previous research has indicated that patients with both lung cancer and COVID-19 experience a longer infection course, more severe outcomes, and a higher risk of death compared to the general population [107, 108]. Additionally, patients with metastatic or stage IV cancers are more likely to exhibit severe COVID-19 symptoms than those with localized malignancies [109]. It has been observed that therapeutic approaches such as surgery, chemotherapy, radiotherapy, and immunotherapy can worsen COVID-19 outcomes among cancer patients [110].

Interestingly, there are similarities in the manifestations of COVID-19 and cancer. Both conditions involve the uncontrolled overproduction of cytokines, leading to a cytokine storm [12]. This common feature of immune dysregulation in COVID-19 and cancer has clinical relevance. Understanding the molecular connection between COVID-19 and cancer, particularly in cytokine, interferon, and immune checkpoint signaling, can assist healthcare providers in balancing the risks and benefits of various therapies and making informed decisions regarding treatment and timing.

Elevated cytokine levels, including IL-6, IL-1β, tumor necrosis factor α, and interferons, have been observed in COVID-19 patients, potentially resulting in a cytokine storm or cytokine release syndrome [111]. Importantly, elevated levels of IL-6 have been reported in the serum of both COVID-19 patients and various types of cancer [112, 113]. IL-6 serves as a driver of tumor progression and a biomarker for cancer diagnosis and prognosis [113]. For instance, in breast cancer, IL-6 promotes tumor stem cell self-renewal and metastasis [114].

In addition to carcinogen exposure, chimeric antigen receptor (CAR) T-cell therapy has been shown to generate IL-6, which drives the undesired 'cytokine storm' in the treatment of chemo refractory hematological malignancies [115]. Cytokine responses have been proposed as the cause of severe coronavirus infection in humans [116].

Recently, a retrospective cohort study compared the immunological characteristics of 93 COVID-19 patients with cancer and 1959 COVID-19 patients without cancer. COVID-19 patients with cancer were reported to have significantly elevated inflammatory cytokines, as well as decreased immune cells than those without cancer [117]. These observations revealed that the immunological alternation, especially cytokine storm, is a key indicator of COVID-19 deterioration.

Given that overproduction of plasma IL-6 levels was observed in patients with severe COVID-19, and also in patients with disseminated malignancies, it is conceivable that IL-6, or its downstream molecules, could be a promising target for the treatment of COVID-19. Therefore, drugs targeting the IL-6/JAK/STAT pathway with anticancer effects may be repurposed for the treatment of COVID-19, saving invaluable time, and allowing timely delivery of care.

Additionally, corticosteroids have been proven to exhibit anti-IL-6 activities. A clinical trial conducted in the UK showed that after dexamethasone treatment, decreased mortality rates were observed in patients developing COVID-19 [118]. Mechanistically, dexamethasone destabilizes IL-6 mRNA and inhibits TNF-α-mediated IL-6 mRNA expression and subsequent protein secretion. Notably, recently a meta-analysis of randomized clinical trials was conducted to evaluate the effect of corticosteroid therapy in patients with different disease severity. In this study, the researchers reckoned that corticosteroids may be considered in patients with critical COVID-19 rather than those not requiring oxygen therapy, as these two subgroups showed a significantly different effect on survival [119].

Tocilizumab, an antibody targeting human IL-6R, disrupts both the classic and trans-signaling pathways. Previous findings have demonstrated the validity of tocilizumab against many types of cancer, such as pancreatic, ovarian, and colitis-associated colorectal cancers [120].

Siltuximab, an alternative monoclonal antibody targeting IL-6R, has been widely studied in cancer. Preclinical studies have shown that siltuximab exerts antitumor activities accompanied by reduced levels of activated STAT3 and MAPK in some solid tumors. With regard to treating COVID-19, an observational study revealed the improvement of outcomes in most patients after receiving siltuximab, as demonstrated by a decrease in IL-6 and CRP levels.

Governments' COVID-19 guidelines for cancer care

Cancer is a recognized risk factor for COVID-19 infection, particularly among older individuals and those with comorbidities such as cancer [121]. A report from the Italian national medical council revealed a higher incidence of COVID-19 among cancer patients, accounting for 16.3% of infected individuals [122]. Consequently, oncologists and their patients are particularly concerned about the implications of COVID-19.

The Italian Association of Medical Oncologists (AIOM) recommends a case-by-case evaluation to determine the feasibility of treatment postponement, taking into account the biological aspects of cancer, patient characteristics, and potential health risks associated with COVID-19 [123]. Similarly, French guidelines propose a priority-based approach to clinical management, considering treatment intent, age, life expectancy, time since diagnosis, and symptoms [124]. These guidelines emphasize the need to maintain medical and radiation oncology units as 'COVID-19 sanctuaries,'

directing COVID-19-positive cancer patients to specialized COVID units instead of oncology departments.

The UK National Institute for Health and Care Excellence (NICE) guidelines suggest measures to minimize in-person contacts, such as telemedicine consultations, home delivery of medicines, and local services for blood tests [125]. Patients are encouraged to attend appointments alone to reduce infection risks. NICE introduced a priority scale for determining the intent of anticancer treatment, ensuring that treatment decisions are made by multidisciplinary teams and clearly communicated to patients and their families.

The ESMO (European Society for Medical Oncology) identifies cancer patients at potential risk for COVID-19 and provides health education on preventive measures [126]. Patients are categorized into two groups: those off therapy and those receiving treatment. For patients receiving active treatment, discussions about treatment benefits and risks, treatment timing prioritization, modified regimen schedules, and increased utilization of remote communication methods are recommended.

The American Society of Clinical Oncology (ASCO) offers comprehensive information on patient care during COVID-19, including guidance from organizations like the US Centers for Disease Control and Prevention (CDC) [127]. ASCO emphasizes the importance of limiting hospital access, implementing triage stations, maintaining physical distancing, and utilizing telemedicine for follow-up visits. They also highlight the risk of drug shortages and encourage judicious resource use.

These guidelines developed by various oncological societies provide recommendations for healthcare workers, patients, and their families during the COVID-19 pandemic, aiming to ensure optimal cancer care and minimize infection risks[128] (8).

Conclusions

The COVID-19 outbreak has changed the way medicine has operated in the past several years. Indeed, the initial increase in the numbers COVID patients mandated changes in the treatment of patients with cancer. There is a consensus that anticancer treatments should be continued in conjunction with careful measures to reduce COVID-19 transmission. It has been demonstrated that, compared to patients who had not received chemotherapy or immunotherapy, patients who underwent cytotoxic chemotherapy or immunotherapy 4 weeks before a confirmed COVID-19 diagnosis did not have an increase in severe disease or death from COVID-19. In patients with low-risk prostate cancer, basal cell carcinoma, or BC, postponing treatment is a viable option. On the other hand, in cases in which treatment delays could impact outcomes (e.g., head and neck squamous cell carcinomas), treatment should not be stopped because of the pandemic. In a recent investigation, 11 articles showed that postponing such investigations and treatments can actually protect cancer patients' health. On the other hand, 35 articles warned about the risk of delaying cancer screening and treatment [129]. Immune suppression is another aspect that deserves further consideration in cancer patients, for example, because of intensive chemotherapy. Of note, it is interesting clinically testing whether the use of immunotherapies in cancer patients could actually protect cancer patients from COVID-19. In our opinion, while these are some of the general guidelines outlined by different governments in the world that one may follow, a world-embracing understanding should be reach for which flexibility is important, and it is especially critical to make therapy decisions on a case-by-case basis with the help of a hospital-based multidisciplinary team.

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Declarations

Conflict of interest We declare that we do not have any conflicts of interest, whether of a financial or personal nature, that could potentially bias the outcomes or interpretations of this study.

Ethical approval This study is a review and did not need to obtain ethical approval from the relevant ethical committees and internal review boards.

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