

## Impact of COVID 19 on different aspects of oncology

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### Abstract

All fields of medicine have had to change and adapt in response to the COVID-19 pandemic. In this respect, frail and immunocompromised patients have been particularly affected. Such patients are commonly treated in oncology, a field that has witnessed a revolution in its protocols, as physicians and institutions address this new situation.

This paper details the aspects of oncology that have been affected by the pandemic, in areas such as chemotherapy, surgery and radiotherapy, together with the sharp rise in the use of telemedicine.

Some of these changes will probably be permanent and may even come to be seen as a positive outcome of the pandemic.

**Keywords:** Oncology; Radiotherapy; COVID-19; Pandemic

### 1. Introduction

The emergence in China in late 2019 of SARS-CoV-2, a new severe acute respiratory syndrome coronavirus, and its rapid elevation to pandemic status provoked a global health emergency (1). Coronavirus disease (COVID-19) causes fever, dry cough, dyspnoea, loss of smell and other, nonspecific, symptoms, making it difficult to differentiate COVID-19 from other infectious diseases (2).

The first cases identified were traced epidemiologically to the Huanan Seafood and Wet Animal Wholesale Market in Wuhan, Hubei Province, China (3).

The initial timeline of the COVID-19 pandemic is controversial, but the first cases were reported in late December 2019; from 18 December to 29 December, five patients were hospitalised and one died (1,4).

An important clinical concern is whether cancer patients, if infected with COVID-19, are more likely to develop life-threatening complications and die from the disease. Patients receiving active cancer treatment may be more vulnerable to infection for several reasons. Chemotherapy can induce neutropaenia and lymphopaenia, predisposing the patient to a greater chance of becoming infected. In addition, radiation therapy can limit the bone marrow reserve and cause pneumonitis, leading to increased complications if a patient develops COVID-19-related lung disease.

During the COVID-19 pandemic, hospital oncology services have been challenged by the need to adapt their facilities, in a very short period of time, to respond to a sudden increase in cancer patients presenting with symptoms of COVID-19.

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In this article, we review the impact of COVID-19 in medical areas related to cancer patients. Specifically, we examine the modifications that have had to be made to adapt health services to the pandemic, assess its effect on the morbidity and mortality of cancer patients, and describe the overall changes brought about in oncology by the emergence of COVID-19.

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## 2. The impact of COVID-19 on cancer patients

Cancer patients are known to be at increased risk of contracting community-acquired respiratory viruses, such as influenza, due to the immunocompromised state that is frequently observed (5). For this vulnerable population, the spread of SARS-CoV-2 has been of particular concern.

At the start of the pandemic, there was a sharp decrease in the number of patients receiving oncology services, due to the new priority of maximising intensive care and inpatient capacity, thus freeing up hospital beds (6). In consequence, there was a 30% reduction in the number of patients receiving chemotherapy, among those told not to come to hospital and those who voluntarily postponed treatment. For these reasons, and the suspension of certain protocols in primary care, oncology departments recorded a fall of over 50% in the presentation of new patients referred by general practitioners (6).

In the first data reported from Wuhan, China, an analysis of 105 COVID-19 patients with cancer and 536 control patients, with COVID-19 but no cancer, showed that the cancer patients had higher mortality rates, higher ICU admission rates, a greater chance of developing severe symptoms and a twofold greater chance of requiring invasive mechanical ventilation. However, the cancer patients were also more likely to be smokers and had experienced more hospital infections, which may have been a contributing factor in the statistical differences (7).

Similar results were reported in another series of cases from Wuhan (8), where the lethality in patients with cancer was notably higher than that of patients without cancer, at 5.6% compared to 2.1% in the total sample.

In a retrospective study of 1,590 patients with COVID-19, conducted in 575 Chinese hospitals (9), multivariate analysis after adjusting for age, sex and comorbidities showed that a diagnosis of cancer was associated with an increased risk of developing severe sequelae of COVID-19 (i.e., the need for mechanical ventilation and/or death) (OR = 5.399,  $p = 0.003$ ), with a median time to progression of 13 vs. 43 days in patients without cancer ( $P < 0.0001$ ; instantaneous hazard ratio = 3.56; and 95% confidence interval = 1.65-7.69). These results show that the diagnosis of cancer is an important comorbidity factor, associated with a higher rate of admissions to intensive care. A similar retrospective analysis in Italy of case fatality statistics for 355 patients who died of COVID-19 showed that 20.3% had active cancers (10).

In two later studies, 13-28% of cancer patients with confirmed cases of COVID-19 died (11,12). Risk factors associated with higher mortality included older age, being male, the presence of comorbidities, being a former smoker and having a poorer functional status.

Although the evidence base is limited, a cross-sectional study conducted in Wuhan, China (13) found that a sample of 1,524 cancer patients hospitalised over a six-week period had an infection rate of 0.79%, significantly higher than the cumulative incidence of 0.37% recorded for all hospital patients. On the other hand, all of these hospitalised cancer patients were in a sufficiently poor condition to warrant admission, which in itself is a poor prognostic factor for risk of infection. In addition, the number of cancer patients in the community was not recorded.

Also noteworthy are the relatively high rates of many of the symptoms related to COVID-19 among cancer patients. Thus, symptoms such as headache, muscle aches, severe fatigue or tiredness, and difficulty finding words, which are on the list of symptoms related to COVID-19, are commonly associated with cancer and its treatment (14,15).

Another factor producing a significant impact on oncology services is the accumulation of complementary tests that were delayed or interrupted due to the outbreak of the pandemic.

Cancer patients also suffer negative outcomes due to the distraction effect, i.e. the fact that hospital ICUs are committed to managing patients with COVID-19 and hence are not available to provide adequate care to those affected with cancer (16).

### 3. Adaptation of oncological services in response to COVID-19

In the UK, when the pandemic appeared, the National Institute for Health and Care Excellence (NICE) developed a triage system to categorise patients based on their chances of surviving treatment, and thus help clinicians make the most appropriate decisions (17). One outcome of this was that patients with cancer who required hospital treatment, such as surgery, were referred to COVID-free cancer centres for the procedure to be performed.

In this unprecedented context, the question arises: what frameworks should be used to inform decisions about how to modify cancer treatment, based on patient and cancer-specific factors? In response, the NICE recommendations for oncology care established four categories.

The first is that of patients whose care is not time dependent, or which can be delivered remotely, or both cases. This includes patients who have completed cancer treatment and do not have acute symptoms suggesting a recurrence. For example, low-risk patients receiving hormonal or oral chemotherapy can usually be evaluated remotely and, in most cases, blood tests and imaging studies may be postponed until the capacity of the health system has been restored.

The second is that of patients whose care cannot be delivered remotely, but for whom any omission or delay in treatment would have only a marginal effect on the quality or quantity of life. When clinical trial data demonstrate that the incremental survival benefit of therapy is limited, then omission or delay is appropriate, given the balance between the potential benefit of treatment and the risk if the patient becomes infected with SARS-CoV-2. For example, with most metastatic solid tumours, chemotherapy beyond the third regimen does not improve survival by more than a few weeks (18).

The third category is that of situations in which delay has a moderate and clinically important adverse influence on the quality of life or survival. In these cases, oncologists should reasonably prescribe marginally less effective regimens that have a lower risk of precipitating hospitalisation.

Fourth, and most evident, is the case of cancer treatment that has the potential to cure and cannot be safely delayed. This includes most patients with newly diagnosed acute leukaemia, high-grade lymphoma and those with tumours that respond to chemotherapy, such as testicular, ovarian or small cell lung cancer.

Due to the impact of the pandemic on the organisation of oncology services and/or on patients' personal choices, between March and April 2020 fewer patients received chemotherapy and fewer new patients presented or were referred for suspected cancer diagnosis (6). In the intervening period, essential and urgent cancer care continued, while other services were postponed or transformed to enable home delivery (19), in the view that cancer patients were more likely to be immunosuppressed, and so their risk of exposure to SARS-CoV-2 should be minimised. Among other strategies adopted, staff and patients were required to wear personal protective equipment to prevent viral transmission, and home delivery was initiated for certain systemic cancer therapies, such as the provision of tyrosine kinase inhibitors or herceptin, administered subcutaneously (17, 20-21).

Another measure recommended by NICE, in response to the pandemic, was that patients should attend appointments alone, without family members or caregivers, in order to reduce the risk of their contracting COVID-19. Moreover, health personnel should minimise the time spent by patients in the hospital or clinic waiting room, through effective scheduling. Another strategy often adopted was that patients were asked to wait outside or in their cars, and were informed by text message when the doctor was ready to see them (17).

A further, and novel, approach was to divide treatment rooms into two types, one for patients with confirmed or suspected COVID-19, and one for all other patients.

As a specific example, that of durvalumab, a drug prescribed for patients with non-small cell lung cancer, the UK National Health Service protocol suggests reducing the number of treatment visits, and hence potential exposure to the virus, by prescribing treatment every four weeks, instead of fortnightly (20). Table 1 summarises another approach, the WHO recommendations for adapting cancer treatment to the pandemic situation (22,23).

**Table 1** Updated guidelines for management of cancer in the COVID-19 pandemic, adapted from Al-Shamsi et al. (22,23)

<b>Infectious Pandemic</b>			
<b>Patients with suspected cancer</b>	<b>Patients with established cancer</b>	<b>Cancer patients with suspected COVID-19</b>	<b>Cancer patients with confirmed COVID-19</b>
<ul style="list-style-type: none"> <li>Staging and diagnosis should not be compromised</li> </ul>	<ul style="list-style-type: none"> <li>Minimize hospital visits and elective admissions</li> </ul>	<ul style="list-style-type: none"> <li>Isolation and infection control as per WHO and CDC recommendations</li> </ul>	<ul style="list-style-type: none"> <li>Evaluate for admission or discharge, infection control and screen contacts as per WHO and CDC recommendations</li> </ul>
<ul style="list-style-type: none"> <li>Minimize hospital visits and elective admissions</li> </ul>	<ul style="list-style-type: none"> <li>Consider surveillance for early stage cancer with low risk of progression and if active anticancer therapy has not begun</li> </ul>	<ul style="list-style-type: none"> <li>Hold any active anticancer therapy</li> </ul>	<ul style="list-style-type: none"> <li>Hold any active anticancer therapy</li> </ul>
<ul style="list-style-type: none"> <li>Consider surveillance for early stage cancer with low risk of progression</li> </ul>	<ul style="list-style-type: none"> <li>Consider delaying surgical procedure</li> </ul>	<ul style="list-style-type: none"> <li>Postpone any surgical interventions /procedures</li> </ul>	<ul style="list-style-type: none"> <li>Postpone any surgical interventions / procedures</li> </ul>
	<ul style="list-style-type: none"> <li>Consider postponing adjuvant chemotherapy and radiation therapy</li> <li>For all patients on active anticancer therapy remain vigilant for COVID-19 symptoms</li> </ul>	<ul style="list-style-type: none"> <li>Keep the differential diagnosis broad including possible adverse events from the anticancer therapy and other infectious causes</li> </ul>	<ul style="list-style-type: none"> <li>Follow up as indicated to evaluate for:               <ul style="list-style-type: none"> <li>- Resolution of active infection</li> <li>- Restarting active anticancer therapy</li> </ul> </li> </ul>

Abbreviations: WHO- World Health Organisation; CDC- Centre for Disease Control and Prevention

It is imperative to prevent cancer patients from congregating in the proximity of potential carriers of SARS-CoV-2, which means the use of waiting rooms and treatment areas should be carefully controlled. In this respect, guidelines have been published for the prevention of respiratory viral spread among cancer patients in healthcare settings (24,25), and both the Centers for Disease Control (CDC) and the WHO regularly update their recommendations (26,27). These include screening patients for symptoms on admission, ensuring any positive cases are immediately isolated and maximising contact precautions for patients suspected of being infected (28,29).

Another aspect of this question is the introduction of new immuno-oncology drugs. A total of 4,720 were being developed in 2020 (30), which was 22% more than the 3,876 in development in 2019 and 233% more than in 2017. After a moderate increase of 15% in 2019 (compared to one of 68% between 2017 and 2018), this 22% expansion suggests a resurgence of interest in immuno-oncology, despite the impact of the COVID-19 pandemic.

Finally, long-term questions are also being considered, such as the challenge of maintaining social distancing, the safety of prolonged treatment at home and safety issues related to the ability to remotely monitor drug toxicity.

#### **4. Changes in approaches to surgical treatment**

From the start of the pandemic, hospital managers scheduling the treatment of cancer patients were well aware of the increase in perioperative mortality among COVID-19 patients and that surgery and anaesthesia posed a high risk of contagion for healthcare personnel.

Another issue considered was that of epidemiological conditions and resources within the treatment area. These factors made it necessary to carefully select the oncological patients who would undergo surgery. The American College of Surgeons (31) recommended that cases should be individualised, noting that the patient's status and prognosis should be taken into account. For example, some patients were offered a tumour resection for colon cancer without immediate reconstruction (temporary colostomy) during the most severe period of the pandemic, due to the shortage of ICU beds needed to ensure the availability of care in case of anastomotic leak (32).

To determine the type of patients who should be scheduled for treatment, according to the current intensity of the pandemic, the Spanish Association of Surgeons recommended a scale of considerations (33) (Table 2), based on five scenarios depending on the percentage of patients who were hospitalised and in the ICU, the emergency triage situation, the resources available and the current level of surgical activity.

**Table 2** Dynamic scale of hospital response scenarios during the pandemic and impact on surgical activity

Scenario	I (almost normal)	II (initial alert)	III (moderate alert)	IV (high-level alert)	V (emergency)
% of hospital beds occupied by COVID-19 patients	< 5	5-25	25-50	50-75	> 75
Hospital resources	No impact	No impact, but precautionary reserve of resources	Some impact on resources, with precautionary reserve of beds	Some impact on resources and on healthcare personnel	Significant impact with limited access to beds and ventilatory support
Surgical activity	Normal	Emergencies, cancer pathologies and preferential benign pathologies	Emergencies and cancer pathologies for which a 3-mo delay would worsen the prognosis	Only emergencies	Only non-deferrable emergency attention. Status assessment by the hospital's ethics committee

COVID-19: Coronavirus disease 2019. (Reference 33)

A controversial issue in this respect is the type of surgery to be employed. At first, laparoscopy was said to pose a high risk of contagion, because the procedure may release contaminant gases. Later, it was observed that in open surgery, when an electric scalpel is used, aerosolisation can occur in the digestive tract, a process that can be highly contagious. Therefore, the least bad option seems to be laparoscopy with constant pressure and gas extraction through a virus filter (34).

Other measures that have been taken during the pandemic period include the creation of an independent circuit for surgery for patients with COVID, limiting the number of staff in the operating room, using disposable material whenever possible, keeping doors and dividers closed, and using protective equipment.

In the latter respect, protective equipment was initially used when treating all patients (when there were no tests to detect the virus). When PCR testing came into widespread use, the equipment was reserved for treating patients who tested positive.

## 5. Changes in approaches to chemotherapy

The implications of COVID-19 are unprecedented and have created new challenges for health systems worldwide. Very clearly, permanent changes will be made, reshaping how medicine is practised in the future.

Different countries have developed various systems to reduce the risk of infection and to optimise cancer treatment options, as an essential support for patients' psychological and medical well-being. However, in most cases, if a cancer patient is known or suspected to have COVID-19, and treatment is deemed urgent and essential, it will be offered. Otherwise, patients are recommended to postpone all cancer treatment until they have received at least one negative test, according to the NICE criteria (17). This recommendation contrasts with most others, which generally suggest a

minimum delay of 14 days from the onset of COVID-19 symptoms or before treatment or relocating it to the patient's home (35).

Another recommendation is to discontinue maintenance chemotherapy, usually given in combination with maintenance immunotherapy, and to continue with immunotherapy alone. Alternatively, oral chemotherapy may be administered at home, thus reducing the frequency of hospital visits (20). However, there is conflicting evidence on immunotherapy; some have argued that, with the exceptions of ibrutinib and a tyrosine kinase inhibitor, it mitigates patients' risks of contracting or becoming seriously ill with COVID-19 (21). Another common practice is daily prophylactic treatment with granulocyte colony-stimulating factor to reduce the risk of neutropaenic fever, thus reducing hospital admissions.

Although the NICE Guidelines recommend these provisional adaptations of cancer treatments, the decision may be challenging for clinicians, who must determine the best treatment options but in the present context have limited data and clinical experience with which to guide patients through their treatment pathways. It is clearly necessary to transfer some treatments to the home setting, although patient safety is a concern, as treatment toxicity would then need to be monitored remotely. The home delivery of treatments certainly has its benefits, but it is not without challenges, and the advent of the global pandemic has accelerated these changes in clinical practice. Nevertheless, it will require close monitoring to ensure there are no increased risks to patient health and wellbeing.

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## 6. Changes in approaches to radiotherapy

In general, pandemic-related adjustments to systemic and radiation treatment should be discussed on a case-by-case basis, with input from multidisciplinary teams.

Radiotherapy and other services for cancer patients may continue to be subject to pandemic-related delay even if new consultations are postponed, because patients may require active treatment for many weeks (36). The cancellation of elective procedures will only reduce the number of cases to a limited degree, since active procedures continue to be performed. In consequence, efficient detection and classification protocols must be maintained in order to reduce COVID-19 risks for patients and health personnel. Accordingly, it may be necessary to reschedule non-essential follow-up visits or to divert them to a telemedicine service, if available (37). Rescheduling visits has also been considered for patients with no evidence of disease or worrying symptoms in the last five years, if the clinical, laboratory and imaging data suggest a low risk of recurrence. Finally, the question of remote working by non-essential members of the clinical team should be considered.

Another issue to be addressed is that of shared treatment machines. Some treatments are received on machines that are shared by many patients every day. Therefore, it is imperative that radiation oncology clinics review their infection control protocols and adapt them as necessary to the unique demands of the present pandemic, taking into account CDC recommendations.

In this respect, the CDC recommends routine cleaning and disinfection as appropriate for SARS-CoV-2 in the healthcare setting (38). Vulnerable areas in radiation oncology may include active breathing control devices, arm positioning handles, and any treatment table accessories that come into contact with the patient. Attention should also be paid to the time of day that patients with suspected COVID-19 are treated. High-risk patients should be treated at times that facilitate proper sterilisation and minimise patient and staff exposure.

Radiotherapy is also subject to treatment interruptions when cancer patients develop COVID-19, and are then required to effect a 14-day quarantine (or longer), in accordance with CDC recommendations (39). Such interruptions are of great concern in the case of high-risk tumours, for which treatment delay will significantly affect outcomes (40,41). This is the case, for example, of tumours of the head and neck, cervix or lung. Therefore, priority should be given to these patients.

The resulting burdens on radiation oncology clinics and services is of particular concern, due to the daily need to screen patients, together with treatment interruptions, delays in restarting treatment and reductions in health personnel.

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## 7. Impact of COVID-19 on teleoncology

The number of telehealth visits in oncology has increased during the pandemic (42), in line with international oncology guidelines which suggest that telemedicine should be considered to support cancer patients and reduce their exposure to COVID-19 (43).

According to the WHO and the American Telemedicine Association, telemedicine is the use of electronic information and communications technologies to remotely deliver clinical services (44). This treatment format is now playing a significantly greater role in the care of cancer patients.

Teleoncology offers an innovative and highly effective solution to the problem of caring for cancer patients in times such as the present pandemic. Many hospitals have adopted this approach, replacing in-person sessions with telephone consultations, and thus improving the risk-benefit ratio (45). This change has decreased the need for cancer patients to visit hospitals at a time when they are at high risk of death from SARS-CoV-2 infection (46).

Proper patient selection, depending on factors such as clinician experience, patient preference and case complexity, is an integral part of a well-functioning teleoncology service (47).

The European Society for Medical Oncology (ESMO) also recommends the use of telephone and online technology for toxicity assessment, dose adaptation and supportive care (48). ESMO suggests a multi-stage approach, in which stable (low priority) and non-critical (medium priority) patients will normally replace most of their hospital visits with the telemedicine option.

The introduction and adoption of teleoncology have been facilitated by technological advances such as voice consultation, telesynergy, video consultation and virtual telemicroscopy. Telemedicine can also be valuable in the triage of cancer patients with suspected COVID-19 infection. In this case, it is essential to make a list of symptoms (such as temperature, respiratory rate and coughing), to note the patient's recent risk of exposure and to perform an observational evaluation (49). Finally, teleoncology may be useful in the palliative care of cancer patients. For example, the US Drug Enforcement Administration allows palliative care professionals to dispense opioid prescriptions to cancer patients using teleoncology services (50)

One of the main limitations of teleoncology concerns the jurisdictional limits placed on physician practice, which are exacerbated by limited physical examinations and the need for appropriate training in telemedicine technology (51).

Another problem is that most cancer patients belong to the older generation and/or live in remote areas. In consequence, the use of teleoncology may be hampered by limited access to telemedicine platforms and/or lack of proficiency in the use of the internet. Nevertheless, patients who live in rural, remote or underserved areas are precisely those who would benefit most from the use of teleoncology, and therefore all possible effort should be made to make this service available to them.

Regarding patient satisfaction, a recent systematic review concluded that video consultations in oncology were effective (52), although some patients reported feelings of nervousness and anxiety around the use of new technologies. They also had some difficulty in communicating with health workers using screen-based systems.

Another study reported that although 86% of oncologists were aware of virtual assistance, the majority were undecided about this type of patient management, which was preferred by only 46% (53).

Finally, a pilot study of telemedicine reported suboptimal satisfaction among clinicians, due to the difficulties in observing patients' nonverbal behaviour and to the impossibility of conducting a physical examination (54).

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## 8. Conclusion

The COVID-19 pandemic has impacted on cancer patients in many ways, requiring significant changes in the medical services provided. In this respect, official bodies have issued important guidelines. Many of these changes are probably here to stay, and will permanently alter some routines in oncology practice. Another effect produced by the pandemic is the significant uptick observed in oncological research, greatly increasing the data available and contributing to the future generation of predictive models for high-risk populations in future pandemics.

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## Compliance with ethical standards

### *Disclosure of conflict of interest*

No conflict of interest to be disclosed.

### Author's contribution

FJ Pérez Lara: made a substantial contribution to the concept and design, drafted the article or revised it critically for important intellectual content, approved the version to be published.

- M.L. Hebrero Jimenez: approved the version to be published.
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