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COVID-19 and lung cancer: update on the latest screening, diagnosis, management and challenges

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Abstract

Lung cancer, considered one of the most common causes of cancer deaths worldwide, is a complex disease with its own challenges. The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), compounded these challenges and forced the medical healthcare system to alter its approach to lung cancer. This narrative review aims to identify the effect of the COVID-19 pandemic on lung cancer screening, diagnosis and management. During this public health crisis, various medical societies have worked on developing guidelines to protect patients with lung cancer from the deleterious effects of SARS-CoV-2 infection, as well as from the complications imposed by treatment delays. The different therapeutic approaches, such as surgery, radiation oncology and immune checkpoint inhibitor therapy, along with the latest international recommendations, will be discussed. Protecting patients with lung cancer from COVID-19 complications, while avoiding barriers in treatment delays, has brought unique challenges to healthcare facilities. Prompt modifications to guidelines, and constant evaluation of their efficacy, are thus needed.

Keywords

COVID-19, lung cancer, management, screening, diagnosis, immune checkpoint inhibitors

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Introduction

The World Health Organization officially declared the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel beta-coronavirus that causes coronavirus disease 2019 (COVID-19), as a global pandemic on 11 March 2020. As of 4 September 2022, the cumulative number of cases reported internationally exceeded 600 million and the number of global deaths was approaching 6.4 million.[1]

This global pandemic has had tremendous consequences on patients with cancer. The American Society of Clinical Oncology published an article in the Journal of Clinical Oncology showing results from a pooled meta-analysis that found a 2% overall pooled prevalence of cancer in patients with COVID-19 infection.[2] Emphasis on patients with cancer diagnosed with COVID-19 should always be warranted, as these patients are shown to have worse prognosis compared with the general population, and are at risk of sudden deterioration.[3]

Ever since the designation of COVID-19 as a pandemic, many studies have been conducted to assess different aspects of the disease in patients with cancer. A large-scale retrospective case–control analysis of data from 73.4 million patients, collected electronically across 50 US states, showed that patients who had cancer, at any point during their life, had a 1.46 times higher chance of becoming infected with COVID-19, while those diagnosed within the last year had a 7 times greater likelihood of becoming infected, compared with patients who had never had cancer. In addition, this same study found that the risk of infection among patients with cancer was highest in those with leukemia, non-Hodgkin lymphoma, and lung cancer.[4] In another retrospective single-institution review, performed in Madrid, Spain, in 1069 patients with cancer, a higher cumulative incidence of COVID-19 infection and a higher mortality rate was reported among patients with cancer compared with the public; 4.2% of the study participants were diagnosed with COVID-19, among whom, lung cancer was the most common cancer type. Moreover, a similar overall survival was found between patients with and without active treatment.[5] Two other studies conducted in China, and a meta-analysis of 32 studies from Asia, Europe, and the US, also demonstrated a higher COVID-19 mortality rate in patients with cancer.[3,6,7]

One of the leading causes of this increased incidence of COVID-19 in patients with cancer is their immunosuppressed state, which is due to their underlying malignancy, as well as different treatment modalities, such as surgery and chemotherapy. A study performed in Italy showed that, among 355 deaths attributable to COVID-19, 71 patients were found to have active cancer.[8] Regarding disease severity, Luo et al.[9] demonstrated that patient-specific features, such as smoking status and history of chronic obstructive pulmonary disease (COPD), had COVID-19-related consequences that were much more aggravating than cancer-specific features. Similarly, Passaro et al.[10] stated that smoking increased both the incidence and severity of COVID-19 infections, while another study reported that the severity of COVID-19 infection was linked to patient age, smoking status, and history of hypertension, COPD and congestive heart failure (CHF).[11] Furthermore, reduced smoking and absence of COPD or CHF has been shown to increase the odds of recovery.[11]

Of the various cancer types, lung cancer specifically has been associated with many challenges since the beginning of the pandemic. Therefore, a global registry, The Thoracic Cancers International COVID-19 Collaboration (TERAVOLT), was formed to characterize the effects of COVID-19 in patients with thoracic cancer. Data from

eight different countries were analyzed and mortality in patients with thoracic cancer was suggested to be 33%, with smoking being attributed to higher death rates.[12]

Furthermore, since patients with lung cancer may have additional comorbidities, including pre-existing lung disease, similarities in clinical symptoms and radiological findings between both disease entities increased the challenges in managing patients with lung cancer during the pandemic. In addition, immune checkpoint inhibitor (ICI)-related pneumonitis may also mimic radiological findings of COVID-19, adding more complexity to diagnosis and management. Combining these factors, one could assume that treatment of patients with lung cancer was destined to change during the pandemic.[13]

The aim of the present study was to review and analyze the current literature, in order to investigate the effects of the COVID-19 pandemic on lung cancer diagnosis, treatment and prognosis.

Materials and methods

This narrative review was conducted to assess the particularities of COVID-19 in patients with lung cancer. The PubMed database was searched for articles published between 2004 and 2022, using the following keywords: 'lung cancer', 'lung neoplasm', 'lung malignancy' in combination with 'novel coronavirus', 'COVID-19' and 'SARS-CoV-2'. Only relevant articles in English were included. There was no restriction on article type and reference lists of potentially relevant papers were not searched for further relevant articles.

The following topics regarding lung cancer and COVID-19 infection were targeted for inclusion in this review: epidemiological features; clinical and radiographic findings; cancer patient management; outcomes; and COVID-19 vaccination and its implications.

Titles and abstracts of identified citations were first screened independently by four reviewers. Then, full texts of potentially eligible citations were screened.

Expert recommendations on the management of patients with lung cancer during the novel coronavirus pandemic were reviewed and discussed.

Results

Initial search results yielded more than 100 articles that were collected and screened, with duplicates removed. Of these, 83 articles were judged as relevant according to the inclusion/exclusion criteria following full-text review.

Discussion

Diagnosis and screening

COVID-19 diagnosis in patients with lung cancer.

COVID-19 may interfere with the diagnostic and therapeutic management of patients with lung cancer. Radiological manifestations of COVID-19-induced pneumonia may be similar to the computed tomography (CT) findings found in patients with lung cancer disease progression or concomitant pneumonia.[14]

A retrospective study that included 157 patients with COVID-19 and 374 patients with early lung cancer compared radiological characteristics between the two groups using propensity score-matched (PSM) analysis.[15] Ground glass opacities were featured in both diseases, and a solitary lesion was characteristic in 89% of patients with lung cancer versus 17% with COVID-19 infection. COVID-19-related lesions tended to be multilobar and multisegmental ($P < 0.0001$).[15]

Similarly, Passaro et al.[16] reported that, although ICIs and tyrosine kinase inhibitors (TKIs) have not been proven to impact the risk and course of COVID-19,

radiological characteristics of these treatments may also show ground-glass opacities, mimicking the features of COVID-19. Data regarding the higher sensitivity of radiographic findings compared with nasopharyngeal swabs in diagnosing COVID-19 are under investigation. Given that patients with lung cancer periodically undergo follow-up CT scans, a higher amount of COVID-19-suspicious imaging findings in asymptomatic patients is thus expected.[17]

In patients with lung cancer receiving ICIs, the finding of pneumonitis constitutes a major challenge in identifying the correct diagnosis. Hence, a rapid and systematic differential diagnosis, focusing on drug-induced pulmonary toxicity, tumor progression and SARS-CoV-2–induced pneumonitis is needed.[18] The risk of developing ICI-related pneumonitis in patients with advanced non-small cell lung cancer (NSCLC) ranges from 2.5% to 5% with anti-programmed cell death 1 (PD-1)/programmed cell death 1 ligand 1 (PDL1) use alone, and from 7% to 10% with anti-cytotoxic T-lymphocyte protein 4 (CTLA-4)/anti-PD-1 combination. This complication leads to a high mortality rate, with up to 35% of toxic deaths related to immunotherapy.[19,20]

Symptoms of ICI-related interstitial lung disease (ICI-ILD) are usually nonspecific and include dry cough, progressive dyspnea, and fine inspiratory crackles. Radiological patterns of ICI-ILD include organizing pneumonitis in 65.5% of cases, non-specific interstitial pneumonitis in 15% and hypersensitivity pneumonitis pattern in 10%.[21] Therefore, due to the overlap of clinical symptoms, and the lack of definitive radiological standard to distinguish between these two entities, COVID-19 diagnosis becomes more and more complex.

Nasopharyngeal swabs, bronchoalveolar lavage, and serological tests may be used to confirm the diagnosis of COVID-19, however, although these tests have a very high specificity, they lack reliable sensitivity.[12,21,22]

In short, ICI-ILD and COVID-19-related pneumonia differ in their initial etiology. While ICI-ILD is a result of excessive dysregulation in the T-cell mediated immune pathway leading to pneumonitis,[23] COVID-19-related pneumonia is viral in etiology. With this clinical and radiological overlap, a polymerase chain reaction (PCR) test should be used to definitively rule-out COVID-19 infection.[21]

Furthermore, in-depth interviews and clinical examinations are of high importance, as they can determine the presence of specific signs or symptoms that are common in COVID-19 patients but are generally not reported in drug-induced pneumonia and vice versa.[24]

Diagnostic and accessibility challenges impacting the delay in lung cancer diagnosis. The COVID-19 pandemic has brought unprecedented pressures on healthcare services, and its impact has been strongly affecting the entire clinical and patient care processes from presentation to diagnosis and treatment.[25,26]

Lung cancer is a considerable disease burden worldwide, with more than 2 million cases globally.[27] The survival rate remains very low, and early diagnosis is crucial.[28,29] Indeed, timely diagnosis and access to treatment are key factors to improve the prognosis of lung cancer.[26]

Access to healthcare services during the COVID-19 pandemic poses serious challenges.[30] The presenting symptoms of COVID-19, such as cough (57.6%), dyspnea (45.6%), and hemoptysis (5%), are potential symptoms of lung cancer, making it clinically difficult for primary care physicians to distinguish between the two entities.[31–33]

Furthermore, the collateral impact of the COVID-19 pandemic on healthcare systems has affected healthcare providers and

patients in several ways. As higher numbers of patients with COVID-19 require hospitalization, the redistribution of human resources is becoming a common phenomenon among many medical institutions.[34] Clinical investigations necessary for diagnosing and treating various diseases, including cancer, are put at risk of being disrupted. For example, Park et al. studied three teaching hospitals affiliated with Hallym University Medical Center in Korea and noted that staff in the field of general cancer diagnosis were relocated to COVID-19 screening wards to address the shortage of nursing staff.[35] Additionally, in a report on the impact of COVID-19 on cancer diagnosis, the registration of new cancer patients in the Netherlands National Cancer Registry was shown to be reduced by about 25% between March and May of 2020.[36] In the UK alone, referrals for suspected cancer cases have dropped by about 80% during the pandemic.[37,38]

Another challenge arising from the current pandemic is the risk of being exposed to SARS-CoV-2 while seeking healthcare for diagnostics and treatment purposes, making patients more reluctant to visit a health care facility out of fear of infection. This is especially true in patients at risk of, or diagnosed with, lung cancer, who present with multiple comorbidities, advanced age and a smoking history.[39]

Patients with severe lung disease belong to the group with the highest independent risks of COVID-19 and lung cancer,[40,41] and fall into 'shielding categories', making their access to healthcare more difficult.[42]

In a survey of patients with lung cancer who participated in a clinical trial in Taiwan during the pandemic, around 64% of patients were reported to be unwilling to attend hospital for fear of infection, and about 4% decided to suspend all treatment.[43]

In addition, the UK Lung Cancer Coalition report suggests that the UK government's advice against seeking non-emergency medical care during the COVID-19 crisis has strongly affected the motivation and willingness of patients to seek medical services.[44]

Socially disadvantaged groups, ethnic minorities and the elderly population may also be unevenly affected by COVID-19, through multiple barriers that hinder access to medical services, thus increasing inequality. For example, patients who depend on public transport may face additional sanitary, practical, and economic challenges related to accessing cancer diagnostic and treatment facilities.[45]

Impact of COVID-19 on delay in lung cancer diagnosis. Park et al.[35] analyzed the impact of COVID-19 on lung cancer diagnosis in Korea by comparing the number and medical characteristics of newly diagnosed lung cancer cases in three teaching hospitals affiliated with Hallym University Medical Center during the pandemic with those diagnosed during the same period in the preceding 3 years. The proportion of patients with stage III–IV NSCLC had increased significantly (2020, 74.7% versus 2017, 57.9%; 2018, 66.7%; and 2019, 62.7%; $P = 0.011$), while the percentage of patients with earlier stages of cancer decreased during the pandemic. These data suggest an existing delay in NSCLC diagnosis during the COVID-19 pandemic. Consequently, patients in symptomatic stage I or II lung cancer may have been diagnosed at an advanced stage after the disease had progressed.[35]

In a retrospective study, Malhotra et al.[46] analyzed all suspected lung cancer referrals received before the period between 1 January and 22 March 2020, and after the period between 23 March and 30 June 2020, the latter coinciding with the implementation of national lockdown in the UK due to the COVID-19 pandemic, with the aim of comparing referrals and outcomes for key stages in the lung cancer pathway over

a 3-month period. The authors observed a 7.6% increase in patients presenting with stage III disease, with a corresponding reduction in stage II disease. In an attempt to maintain timely diagnosis and treatment of patients with lung cancer, and despite the implementation of new COVID measures by St Helens and Knowsley Teaching Hospitals NHS Trust, an overall 7% fewer patients receiving radical treatment was observed.[28]

Moreover, Reyes et al.[47] are currently conducting a bicenter retrospective cohort study of patients with NSCLC and small cell lung cancer (SCLC) who were newly diagnosed before (January–June 2019) and during COVID-19 (January–June 2020) in Spain. Preliminary results showed that the number of newly diagnosed cases decreased by 38% (43 NSCLC; 19 SCLC) during COVID compared with the pre-COVID period (67 NSCLC; 33 SCLC). However, more new symptomatic cases were diagnosed during the period of the pandemic (between January and June 2020), compared with the pre-COVID period (between January and June 2019), which appears to be associated with poorer outcomes.[47]

In England, it has been estimated that the delay in diagnosis due to COVID-19 may have caused more than 1000 deaths from lung cancer within 5 years after diagnosis, potentially reversing the progress made in lung cancer survival rates in recent years.[37]

Screening of lung cancer during the pandemic and the impact of screening delay. Guideline recommendations for lung cancer screening and evaluation of lung nodules have changed during the pandemic due to the need for resource reallocation and, most importantly, the added risks from potential exposure to COVID-19. An American College of Chest Physicians (CHEST) expert group of pulmonologists, thoracic surgeons and thoracic radiologists was formed to review existing guidelines to provide guidance on screening for lung cancer and management of pulmonary nodules detected during the pandemic.[48] Baseline and annual lung cancer screening should be deferred, and surveillance of previously detected nodule should be delayed for nodules less than 8 mm in size. For nodules measuring more than 8 mm, with a probability of malignancy $\leq$25%, there was consensus that evaluation could be delayed by 3 to 6 months. However, when the probability for malignancy is between 25% and 85%, evaluation with positron emission tomography or nonsurgical biopsy and referral for treatment, if needed, should not be delayed. If the probability of malignancy was more than 85%, proceeding to treatment with no additional diagnostic testing is justified. Concerning stage I NSCLC, there was a universal consensus that treatment should be delayed. However, some recommendations regarding the tumor growth rate, the patient's characteristics, and patient preferences should be considered. Patient management should be based on a balance of benefits and harms of management approaches. The statements concurred with the recommendations from the Centers for Disease Control and Prevention (CDC) to defer non-urgent care and provide reallocation of resources and minimization of unnecessary exposure during the pandemic. These statements were expected to remain valid for 3 to 6 months at least in most countries.

Furthermore, a statement by The American Association for Bronchology and Interventional Pulmonology was issued regarding the safe and effective use of bronchoscopy in patients with suspected or confirmed COVID-19.[49] The statement emphasized that bronchoscopy should only play a role when less invasive tests to confirm COVID-19 are inconclusive, when alternative diagnoses that may affect clinical management are suspected, or in the

case of urgent vital intervention. Elective bronchoscopy for the management of lung or bronchial mass, mediastinal or hilar lymphadenopathy, or lung infiltrates, should be postponed until after full recovery from the infection. Urgent or emergent bronchoscopy for evaluation of massive hemoptysis, benign or malignant severe airway stenosis, or suspicion of an alternative or secondary etiology of endobronchial obstruction, should be performed with full precautionary measures.[49]

The Society of Interventional Radiology has classified all procedures into three categories: elective, urgent and emergent.[50] Delaying or rescheduling procedures in cases of worsening local infection should be individualized.

In light of CHEST panel recommendations to delay initiation of screening for new individuals and delay annual low-dose CT (LDCT) for patients in lung cancer screening protocols, Van Haren et al.[51] conducted a study to assess the short- and long-term outcomes of screening delays in this population of patients. The researchers retrospectively reviewed their lung screening database at the University of Cincinnati and compared it to their data upon resuming operations. Despite complete reopening of LDCT screening services, monthly rates of new patient LDCTs remained low. The 'no show' rate increased significantly during COVID from baseline (15% at baseline versus 40%; $P < 0.04$). Even more worrisome, the proportion of patients with pulmonary nodules suspicious for malignancy (Lung-RADS 4) significantly increased once screenings resumed (8% versus 29%; $P < 0.01$).[51] This analysis represents possible unintended consequences of delaying screening during the pandemic on lung cancer prognosis.

Relationship between COVID-19 and lung comorbidities affecting lung cancer. Pre-existing risk factors and comorbidities, such as smoking and COPD, are known to highly increase the risk of lung cancer.[52] For example, COPD, an obstructive lung disease highly related to smoking, is one of the main comorbidities associated with patients diagnosed with lung cancer with a prevalence of around 30 to 70%.[53] In the COVID-19 era, new concerns have been raised about the possible consequences of these comorbidities on the risk of severe COVID-19 infections and outcomes.[54] For example, COPD and smoking-related illnesses are shown to be linked to a four-fold increase in the risk of COVID-19,[55] and its associated severity and morbidity. This is mostly due to the increased expression of angiotensin-converting enzyme-2 receptors by type 2 pneumocytes in the lower respiratory tract, which provides a binding site and a port of entry for the viral particles.[56,57] Effective preventative measures are therefore necessary to reduce the risk of COVID-19 infection in patients with these comorbidities, knowing that they are already predisposed to develop other life-threatening diseases, such as lung cancer.[42,52]

Treatment and outcomes

The outbreak of COVID-19 forced physicians to be flexible in adjusting their routines, particularly when treating patients with cancer. The pandemic carried a recurrent dilemma regarding treatment of patients with lung cancer: whether it was better to start, postpone, or stop treatment altogether.[51]

In a meta-analysis focusing on clinical outcomes in patients with lung cancer and COVID-19, controversial results were reported concerning the risk of adverse outcomes depending on the type of cancer treatment received. The general consensus found no benefit in withholding treatment of lung cancer in patients with mild to moderate disease.[58]

Evidently, there is no universal solution to oncological management plans during the COVID-19 pandemic, and treatment decisions are best made by multidisciplinary teams. The focus should be risk versus benefit evaluation, with all regimens that have a survival benefit being prioritized whenever possible. Palliative treatments should be meticulously assessed by the physician and further discussed with the patient.

For adjuvant treatments, when survival benefit is of little importance, it may be more favorable for the patient to skip this regimen. On the other hand, neoadjuvant chemotherapy might demonstrate a particular advantage, particularly in helping to delay the need for surgery, when this latter treatment is not a current option.[59]

The main goal of lung cancer treatment during the pandemic is minimizing the risk of exposure to patients and staff whenever possible, as well as being able to promptly manage all life-threatening events.[60]

The European Society for Medical Oncology (ESMO) proposed recommendations for all aspects of lung cancer management during the COVID-19 pandemic. These recommendations are not meant to replace, but to adapt and improve the current guidelines in order to mitigate, as much as possible, the potential harm of the pandemic on patients with lung cancer. The ESMO established guidelines related to therapy, and cases were divided into three levels of priority: Tier 1, a high priority group of patients whose conditions are life-threatening, who are currently unstable, or whose treatment benefit heavily outweighs the risks when it comes to betterment of quality of life and/or survival time; Tier 2, a medium priority group, comprising non-critical patients whose overall outcome would not be significantly affected by an intervention delay that does not exceed 6–8 weeks; and lastly, Tier 3, a low priority group encompassing all stable patients whose treatment, in theory, can be delayed for the duration of the pandemic, and/or whose intervention would not significantly improve their survival or quality of life.[61]

Surgical treatment. Minimizing preoperative morbidity and mortality due to COVID-19 and lung cancer form common goals during the pandemic. In view of the fast progression of lung cancer, a surgical assessment should be of high priority in order to limit any delay that may affect the surgical outcome. In addition, significant symptomatic incidences necessitating surgical palliative approaches, such as stent insertion or thoracentesis, should also be given high priority. Improving the quality of life and prognosis of the patient is always the main goal. In short, all surgical indications should be individualized and discussed between physicians and their patients.[62]

When dealing specifically with NSCLC, according to a study from the National Cancer Database, an interval between diagnosis of stage I lung cancer and surgery of greater than 8 weeks was associated with a reduction in 5-year survival.[61] Regarding stage III NSCLC, for which management during the COVID-19 pandemic has shown to be particularly challenging, a 3-month delay or more of neoadjuvant therapy after surgery was associated with shortening of median survival. Moreover, given the significant curative potential, treatment of patients with stage III NSCLC, including non-surgical options, should be given high priority.[62,63]

A huge effort has been made by different thoracic surgery societies and national authorities to guide surgeons in decision-making on lung cancer surgeries during the novel coronavirus outbreaks. The International Association for The Study of Lung Cancer agreed with providing safe lung surgery during the COVID-19 pandemic, along with offering treatment

according to the standard of care when possible.[51] In contrast, the Lung Cancer Center of the Oncology Institute of Southern Switzerland recommended exclusive non-surgical management in patients with high risk of cancer progression (stage T4 any N, N2 any T and oligometastases) and high risk of COVID-19 infection (age >70 years with immunosuppression or >2 associated diseases).[64]

A consensus statement from the Thoracic Surgery Outcomes Research Network, offering guidance for triage of thoracic surgeries during the pandemic, was published in May 2020. Three phases of hospital settings were defined according to COVID-19 infection prevalence and availability of hospital resources (Table 1).[65] First, in a phase I semi-urgent setting, surgeries should be restricted to patients for whom survival would be compromised if surgery was not performed within the next 3 months (such as solid lung cancer >2 cm and node positive lung cancer); Secondly, in a phase II urgent setting, surgeries should be performed when survival would be compromised if surgery was not performed within the next few days; And finally, in phase III, termed 'emergent operations', where all hospital resources are routed to COVID-19 patients, only surgeries with immediate effect on survival should be performed (threatened airway, tumor associated sepsis, and/or surgical complications in an unstable patient). For each setting, a list of examples of surgeries and alternatives was provided.[65]

Chemotherapy and immunotherapy. Despite an increased severity of disease and poorer prognosis in patients with lung cancer diagnosed with COVID-19, no increased risk of ICU admissions or deaths was shown in a study amongst patients receiving cytotoxic chemotherapy.[58] However, Elkrief et al.[66] showed that patients with active, or history of, malignancy, as well as patients receiving cytotoxic chemotherapy, are at higher risk of developing severe COVID-19. Chronic immunosuppressive state in these patients limits their immune response, resulting in a reduced number of plasmacytoid dendritic cells that can respond to infection.[17] As a result of this compromised immune response, patients with cancer may

Table 1. Three phases of hospital settings for triage of surgical interventions according to the Thoracic Surgery Outcomes Research Network.

	Hospital setting		
	Phase I: Semi-urgent	Phase II: Urgent	Phase 3: Emergent
Example	• Solid lung cancer >2 cm • Node positive lung cancer	• Management of surgical complications in stable patients	• Threatened airway • Tumor associated sepsis • Surgical complications in an unstable patient
Protocol	Surgery should be restricted to those for whom survival will be compromised if not performed within 3 months	Surgery should be performed if survival is compromised if surgery not performed within a few days	Only surgeries with immediate effect on survival should be performed

experience prolonged viral clearance, leading to prolonged illness and worse outcomes.

Data are generally conflicting regarding the use of ICIs during the pandemic, however, there is no proof to date of it being detrimental to patients. Therefore, whenever there is a survival benefit for patients, ICI treatments are better carried-out than withheld.

An ESMO multidisciplinary expert consensus on the management of patients with cancer during the COVID-19 pandemic stated that ICIs should not to be delayed or withheld in the absence of a COVID-19 infection, particularly where there is a significant survival benefit in cases of approved indication of (neo)adjuvant therapy, but in cases of confirmed infection, a delay of such treatments was preferrable. Moreover, for patients with NSCLC, even in the clear presence of a survival benefit, the recommendation was to withhold ICI treatment in the setting of a COVID-19 infection and restart it once complete resolution of infection is proven.[61] Conversely, multiple registries that focus on real-world data, such as TERAVOLT and the COVID-19 and Cancer Consortium (CCC19), suggest that chemotherapy combined with ICIs may prove detrimental in COVID-19-infected patients.[67]

When exploring PD-1 blockade, survival rates have been shown to improve in multiple cancers, however its impact on patients with cancer during the COVID-19 pandemic remains to be established.[68] A theoretical possibility is that blockade of PD-1 may worsen outcomes by augmenting the hyperactive immune phase of COVID-19. On the other hand, PD-1 blockade might enhance immunologic control of viral infections and improve outcomes.[69,70]

Lung cancer data have shown that immunotherapy treatment is not associated with worsened COVID-19 infection. In an observational single-center study of 69 outpatients with lung cancer, no association was found between receipt of prior anti-PD-1 therapy and COVID-19 severity.[71] Within the subset who had received PD-1 blockade, there were no consistent trends regarding proximity of exposure to PD-1 blockade and COVID-19 severity. Regarding TKIs in particular, withholding therapy during acute COVID-19 infections was found to be reasonable in cancer stable cases.[72]

According to ESMO experts, adjuvant chemotherapy in the presence of N1 or N2 disease should be considered in young fit patients but should be withheld in frail elderly patients with multiple comorbidities. Adjuvant chemotherapy is also recommended in young, fit patients with stages II and III NSCLC and no known comorbidities. Furthermore, neoadjuvant chemotherapy followed by surgery may be considered in select patients when there is lack of surgical resources, such as clinical stage II patients, in order to enable a surgery deferral by up to 3 months. Experts also noted that the local profile and intensity of the COVID-19 pandemic should be taken into consideration when making decisions about adjuvant chemotherapy, since the absolute survival benefit is not substantial in patients with lung cancer.[67]

In cases of newly diagnosed metastatic NSCLC, as per ESMO recommendations, first-line systemic therapy and second-line treatments for patients with progressive symptomatic disease should be prioritized and conducted as normal. This helps improve prognosis, symptoms, and quality of life, whereas any delay in treatment could potentially compromise patient survival.[62]

Other than the effects of postponing certain cancer treatments due to COVID-19 infections, studies have also reported data on confounding findings cause by such treatments. ICI-induced pneumonitis has been reported in 2% of patients with

cancer, with higher incidence in those with lung cancer.[68] Regarding radiological assessment of ICI-induced pneumonitis, findings are similar to COVID-19-induced pneumonia, and these similarities in presentation may pose a major challenge to clinicians in discriminating between the two clinical entities.[8,73]

Additionally, TKIs may also induce interstitial-like pneumonitis on CT; reported in 4% of lung cancer patients with epidermal growth factor mutation treated with Osimertinib.[74]

Radiotherapy. Radiotherapy is essential in treating all stages of lung cancer. During the COVID-19 pandemic, radiotherapy departments worldwide are facing challenges with delivering appropriate patient treatment while protecting this vulnerable population and their staff from the risk of infection. Delays in radiotherapy sessions, along with limitations in access to radiotherapy departments, may negatively affect the outcomes of patients with lung cancer.

Given their advanced age and comorbidities, and treatment side-effects, patients with lung cancer undergoing radiotherapy belong to the group of highest risk of severe complications and death from COVID-19. Therefore, use of reduce-fractionation radiotherapy should be discussed with the patient in order to find an appropriate risk-benefit balance.

In the case of diagnosed COVID-19 infection in a patient with lung cancer, ESMO experts recommend continuing the curative thoracic radiotherapy regimen, taking into consideration the risk of tumor recurrence/progression associated with treatment interruption, and severity of the COVID-19 clinical syndrome.[61]

A panel of international experts in lung cancer radiotherapy from the European Society for Radiotherapy and Oncology and the American Society for Radiation Oncology addressed common lung cancer scenarios during the COVID-19 pandemic. It was agreed that when radiotherapy resources remain available, guideline-recommended radiotherapy practice should be applied with postponement of treatment for COVID-19-positive patients, in order to protect patients with cancer and staff. However, when resources are reduced, important factors should be taken into consideration, including life expectancy, performance status, potential of cure and benefit of radiation.[75]

Another international panel of experts in lung cancer management shared their experience, and recommended systematic screening for every patient undergoing treatment and delaying postoperative radiation therapy in patients with NSCLC. They also recommended against 2-times daily treatments or prophylactic cranial irradiation for limited-stage SCLC, as well as using single fraction radiotherapy for palliative treatment of metastatic disease.[76] Guidance for hypofractionated radiotherapy in curative treatment of lung cancer has been provided by UK centers.[77]

The Spanish Society of Radiation Oncology and the Oncologic Group for the Study of Lung Cancer published an updated review in the World Journal of Clinical Oncology on the scientific evidence currently available, in order to establish recommendations for the treatment of different stages of SCLC and NSCLC during the pandemic.[78]

COVID-19 vaccination and recommendation in patients with lung cancer

The expansion of COVID-19 infections across the globe has prompted the need for a massive vaccination drive. Vaccines, which have proven to prevent severe illness, are becoming vital tools in the fight against cancer.[79]

In conjunction with a global collaborative, many countries have already developed ambitious vaccination programs designed to meet the challenge of vaccine production, maintaining safety and efficacy standards, and implementing vaccination strategies in their nations.[79]

Patients with lung cancer have been considered as a high priority group for COVID-19 vaccination,[80] and vaccination of cancer patients against COVID-19 has proven to be safe. A study involving 170 patients with cancer receiving ICI showed no additional safety concerns in receiving COVID-19 vaccination. Among the systemic serious events, fatigue (4%), headache (3%), myalgias (2%), and chills (1%) were comparable to those observed in the general healthy population.[81]

From March 2021 onwards, Regina Elena National Cancer Institute has been the first institution in Italy to begin vaccination of patients with cancer referred to its units. By conducting a large prospective cohort study, which included 816 patients with cancer at the institute, Di Noia et al.[82] assessed the immunogenicity and safety of the BNT162b2 COVID-19 vaccination (Pfizer–BioNTech) in patients with cancer compared with matched control groups of healthcare workers. The study concluded that BNT162b2 assures serologic immunization without clinically significant toxicity in patients with cancer, and a second dose of Pfizer vaccine was necessary to achieve a satisfactory humoral response in patients with cancer that was comparable to the general population.[82] Interestingly, Monin et al.[83] found a single dose of the BNT162b2 Pfizer–BioNTech COVID-19 vaccine to be poorly immunogenic in patients with malignancy, but immunogenicity improved substantially at 2 weeks after a second dose, administered at a 21-day interval. Delayed administration of the second dose was reported to negatively impact its efficacy.[83]

In the absence of contraindications, many cancer organizations recommend that vaccinations should be administered early, as COVID-19 infection can be deadly.[84]

The CDC interim clinical guidance recognizes the potential pitfall of limited safety and efficacy data, but continues to recommend vaccinations for patients with cancer, as it provides some benefits and reduces the severity of COVID-19. Additionally, the Society for Immunotherapy of Cancer has recommended that patients undergoing approved or investigational immunotherapy receive the SARS-CoV-2 vaccination, however, patients receiving steroids or tumor necrosis factor blockers, and those with B-cell deficiency, may not mount robust immune responses and may require further boosters.[79]

For patients with hematological malignancies, the benefits of vaccination likely outweigh the risk, as most cancer treatments currently adopted do not impair active immunity. A refined anti-cancer regimen, close monitoring of medical comorbidities, and optimization of function status are all possible considerations before vaccination is administered to patients with cancer.[80]

Given that fully vaccinated individuals may still become infected with SARS-CoV-2 and transmit the disease, recommendations for testing patients with cancer prior to surgical or medical (chemotherapy mainly) therapies remains unclear.[85] Routine testing of patients with cancer receiving therapy should be individualized since ‘successful immunization’ may differ between patients. Guandavda et al.[86] suggested that fully vaccinated patients with cancer may lose the immunity acquired by the vaccine due to suppressive therapy. Hence, preventive measures, including face masks and social distancing, are always required to decrease the patient’s risk of exposure. Patients expected to receive

immunosuppressive therapy are required to complete vaccination up to 3 weeks before initiation of cancer therapy.[86]

Further data on the effect of vaccination in patients with lung cancer, and its impact on the management of this population, are still required.

Conclusion and perspectives

In conclusion, the COVID-19 pandemic has generated an unprecedented strain on healthcare facilities and their abilities to care for patients with cancer in general and those with lung cancer particularly. This includes the variable challenges in diagnosis, delays, and accessibility to screening and treatment facilities, which all greatly affect patients and the progression of their disease. Therefore, during this public health crisis, medical societies around the world have worked on developing guidelines to protect patients with lung cancer from the adverse effects of SARS-CoV-2 infection, as well as from the complications of treatment delays. However, according to the evolution of COVID-19 and availability of facilities and resources, recommendations may change over time. The novel coronavirus continues to be a global threat to the vulnerable population of patients with cancer, and tremendous research efforts are needed to keep track of the evolving nature of the virus.

Ongoing research targeting the healthcare system's pandemic preparedness and response is already underway. We cannot anticipate when this pandemic will end, but we can learn from this experience and bolster the healthcare system for future challenges. All international guidelines should state the appropriate recommendations to be applied during a pandemic, particularly regarding vulnerable patients such as those with lung cancer. Recommendations should be in line with recent events, updated appropriately and regularly, and not forgotten, as we move on. Extensive comparative research evaluating the responses of different healthcare systems, and their impact on patients with lung cancer, is still needed to obtain the full picture and evaluate the wide effects of the COVID-19 pandemic on the pulmonary oncology sector.

Author contribution

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