

# Managing Lung Cancer during Coronavirus Disease 2019 Pandemic

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## Abstract

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been declared as a pandemic by the World Health Organization. As this disease continues to spread worldwide, it has posed enormous challenges on the healthcare of several diseases, especially cancer, because hospital facilities have invested health resources for patients with COVID-19. Indeed, patients with lung cancer are particularly vulnerable because of their poor baseline lung function and cancer-related treatment. In addition, once infected, they are at an increased risk of pulmonary complications from COVID-19. Oncologists are thus facing a challenge as how to balance the treatment plans to control the disease while protecting the patients with lung cancer from COVID-19. In fact, it is crucial to provide individualized treatment recommendations to limit the risks during these difficult times. This review highlights the key challenges that oncologists face when diagnosing COVID-19 among patients with lung cancer and examines the current recommendations from available literature, clinical expertise, and expert opinions regarding managing lung cancer in the era of COVID-19. It also explores the treatment approach recommended for patients with lung cancer while avoiding putting them at excessive risk of contracting COVID-19 infection.

**KEYWORDS:** Coronavirus disease 2019, lung cancer, prevention and control, therapy

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## INTRODUCTION

One of the major pathogens that target the human respiratory system is the coronavirus (1)]. Previous studies have shown six subtypes of coronaviruses that can cause disease in humans and that includes the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus that can cause severe infections (2, 3). In Wuhan, China, during late December 2019, there were several cases of patients who had “unknown fever with pneumonia” (4) which were identified on January 7, 2020 as cases of a disease caused by new coronavirus whose genetic sequence was rapidly analyzed with the development of a detection method (5, 6). This virus that was first detected in China is now spreading around the world reaching its highest numbers in the United States of America, Italy, Spain, and China. It is known as SARS-CoV-2 and represents the causative agent of a potentially fatal disease named 2019 novel (new) coronavirus disease and abbreviated as COVID-19 (by World Health Organization [WHO] on February 11, 2020). COVID-19 has been declared by WHO as a pandemic (7). SARS-CoV-2 is highly contagious and is transmissible through sneezing, coughing droplets, aerosols, and contaminated surfaces (8). Although various countries have been implementing strict measures of control and protection and integrating all forces to curb the infection, the virus is still spreading (9). Moreover, COVID-19 brings a huge burden on healthcare facilities, especially in patients with comorbidities. Many chronic diseases have been affected to variable degrees, one of which is cancer (10). It is known that patients with cancer are more vulnerable to the infection because of their immunosuppressive state owing to their malignancy and anticancer treatments, whether it is chemotherapy, radiation, or surgery (11). Patients with lung cancer are even more vulnerable because of their baseline lung disease and poor lung function (11). Several medical societies and organizations have proposed guidelines for the management of patients with lung cancer during the COVID-19 pandemic. This article reviews the available literature regarding the management and outcomes of COVID-19 infections in patients with lung cancer diagnosis and treatment. The recommendations that are mentioned are extracted from the available literature, expert opinions, and few studies and may not be the optimum standard of care but can be considered during the COVID-19 pandemic.

## CLINICAL AND RESEARCH CONSEQUENCES

### COVID-19 Infection in Patients with Lung Cancer

#### **Risk factors**

Patients with lung cancer have multiple risk factors that put them at higher risk of contracting the SARS-CoV-2 virus and developing complications from it. In a retrospective analysis that included 1,572 patients with COVID-19 in Chi-

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na, patients with cancer who got infected with COVID-19 were older, had a history of smoking, and had more severe baseline computed tomography (CT) manifestations. Interestingly, of the people who had cancer and got infected with COVID-19, the most common cancer was lung cancer (12), which can be explained by the fact that the patients with cancer have a poor baseline lung function because of their disease and treatment (11). Patients with lung cancer share several risk factors for COVID-19 complications, such as old age, smoking-related lung damage, and treatment-related immune impairment or suppression (13).

### Presentation

The most prevalent manifestations of COVID-19 infection are fever (88.7%), cough (57.6%), and dyspnea (45.6%) that may be accompanied by fatigue and myalgia (9). These are common symptoms in patients with lung cancer caused by their underlying lung dysfunction and lung disease. Oncologists taking care of patients with lung cancer face a challenge when trying to figure out whether the symptoms that the patients have are due to possible COVID-19 infection or due to lung cancer and its treatment. To help differentiate, it is important to keep a wide differential diagnosis and fully assess the different possibilities that can explain the exacerbation of respiratory symptoms in these patients. One way is by considering a good contact history in addition to combining related laboratory test results (reverse transcriptase–polymerase chain reaction [RT-PCR]) with imaging (chest CT) to exclude COVID-19 [11]. Chest CT has shown to have a higher sensitivity (97%) for diagnosis of COVID-19 than initial RT-PCR (14). CT imaging has also shown an earlier detection rate because 60% to 93% of patients had an initial positive chest CT before the initial positive RT-PCR results, and 42% showed improvement of follow-up chest CT scan before the RT-PCR results turned negative [14]. In COVID-19, the typical chest CT findings are usually ground-glass opacities, crazy-paving pattern, and consolidations that are predominantly subplural (15). However, exceptions are still possible. In one case report by Jinrong et al. (11) an atypical presentation of COVID-19 was described in a patient with lung adenocarcinoma where the chest CT did not present the typical signs of COVID-19. Instead, chest CT images showed irregular diffuse ground-glass nodular opacities bilaterally. Moreover, it is advised that patients with a negative swab test accompanied with a CT scan demonstrating new ground-glass opacities to undergo a bronchoscopy to increase the testing sensitivity regardless of whether they are having new respiratory

symptoms(13). Nonetheless, oncologists, radiologists, and physicians of infectious diseases should keep in mind the similarities between the symptoms of COVID-19 and the symptoms that can be due to the treatment of lung cancer or lung cancer progression itself. For example, pneumonitis from immunotherapy or radiation therapy can manifest similar to COVID-19 not only with regard to the symptoms but also on imaging (11). According to Yang Lu (10), the patient's epidemiological history and pathogenic tests should help to further identify the cause.

### Complications

According to the current investigations, most patients with COVID-19 have a good prognosis and only few become critically ill (16). The patients who become ill are mainly the elderly and those with underlying chronic diseases (16, 17). These patients develop acute respiratory distress and septic shock (17) that can lead to death. In one epidemiological study conducted in China, 107 (0.5%) patients had a history of malignant tumor out of 72,314 patients with COVID-19 with a crude death rate of 5.6%, which is more than that of the overall population (2.3%) (16). In another retrospective analysis that included 1,572 patients with COVID-19 in China, results showed that patients with COVID-19 and cancer were observed to have a higher risk of severe events (the endpoint in the study was the percentage of patients who died or were admitted to the intensive care unit and required invasive ventilation) than patients without cancer (39% and 8%, respectively,  $p=0.0003$ ). This means that patients with cancer infected with COVID-19 have worse outcomes than the general population. Moreover, the health of patients with cancer deteriorated more rapidly (13 days versus 43 days) than that of patients without cancer ( $p<0.001$ ). When comparing the probability of severe events between the different types of cancer, patients with lung cancer had a higher probability of severe events than patients with other cancer types (20% and 62%, respectively), but this did not reach statistical significance because of the small sample size ( $p=0.294$ ). The study also showed that patients with cancer who underwent surgery or chemotherapy in the past month had a higher risk of clinically severe events than those who did not (3 of 4 patients [75%] and 6 of 14 patients [43%], respectively) (10, 12). Moreover, a new global consortium has been launched to collect data on patients with thoracic malignancies. It included a total of 295 patients across 59 centers. Their data showed that patients with thoracic malignancies are at a high risk of hospitalization in the ongoing global pandemic of COVID-19 (18). This can be explained by the fact that their immune systems will be weaker; thus, the possibility of having infections is more likely. In the light of these results, it is important to issue guidelines and recommendations for patients with lung cancer during the COVID-19 outbreak on the basis of their disease stage and the necessary treatment to ensure the most optimal medical care in terms of controlling their disease and protecting them from COVID-19.

### Lung Cancer Treatment Recommendations in the COVID-19 Pandemic Era

Due to the fast-evolving pandemic, various countries adopted strict control policies and prevention strategies at the individual and hospital levels. Personal protective equipment

#### MAIN POINTS

- Patients with lung cancer have multiple risk factors that put them at higher risk of contracting the severe acute respiratory syndrome coronavirus 2 and developing complications from it.
- Individualized management is crucial to protect patients with lung cancer from Coronavirus disease 2019 while controlling their disease.
- Challenging decisions should be communicated with the patients and most importantly with the medical ethicist and palliative care teams.

(PPE) plays a crucial role in preventing the transmission of COVID-19. Because the patients with lung cancer are highly susceptible to COVID-19 infection, prevention is a top priority. Hence, stronger personal protection provisions should be considered in this group of patients (12, 19). Moreover, patients with lung cancer should stay home; practice hand washing, especially before meals and after using the toilet; reduce the number of hospital visits; and get help from healthy young patients regarding purchasing necessary medications or daily needs. If patients with lung cancer need to go out, they must take good personal protection by wearing masks properly and gloves when needed. Their house should be ventilated at least twice a day for 30 minutes and surfaces disinfected after daily use. It is also necessary that patients with cancer ensure adequate sleep, try their best to exercise, find methods to relieve anxiety and tension, and have a good balanced diet to stay healthy (20). In Italy, this group of patients is called the off-treatment group, and their care should focus on prevention by delaying “well” visits and follow-up appointments in the absence of active disease and contacting doctors through phone or telemedicine consultations. A phone triage line should be established for patients with mild symptoms in the community to minimize the exposure in clinic and to help them avoid visits to the emergency departments (19, 21). Moreover, patients with caregivers or family members who have tested positive for COVID-19 should be tested before and during any cancer treatment. In the case of a patient who tests positive and is asymptomatic, there should be a 28-day delay, and two negative tests at a 1-week interval should be obtained before resuming the treatment (22). In addition to prevention, oncologists have to take treatment decisions for patients with lung cancer where several variables should be considered, such as the risk of infection of the individual, status of cancer, the patient’s comorbidities, extent of the epidemic, and the healthcare infrastructure and its capacity. According to Banna G et al. (22), all regimens with a survival benefit should be maintained and prioritized whenever possible. Risk/benefit ratio should be considered for every treatment. For instance, for adjuvant treatment, it may be better not to give therapy when the survival benefit is modest. In contrast, giving neoadjuvant chemotherapy may help to give time and delay the need for surgery if these services are interrupted.

In patients receiving active treatments, treatment during the critical period of COVID-19 should be on the basis of avoiding the infection, staying safe, and striving to ensure a controlled disease state in clinically stable patients (10). Moreover, difficult decisions should be taken about proceeding or delaying treatment. For patients with early stage cancer in a curative setting (surgery, adjuvant treatment, neoadjuvant treatment), it is advised to proceed with treatment despite the threat of COVID-19 during the treatment (21). In these cases, it may be beneficial to consider increasing the use of granulocyte colony-stimulating factor (G-CSF) to limit neutropenia and to choose 3-week regimens instead of weekly regimens (8). In Italy, patients with cancer are being taken care of in hub centers within a COVID-free clinical pathway with very close monitoring for potential toxicity and for COVID symptoms (19). Early identification of individuals with respiratory symptoms occurs through screening of all patients, visitors, and staff before en-

tering outpatient clinics and hospital, and symptomatic patients are then diverted to a separate secondary screening area for consideration of COVID-19 testing (21). Moreover, in the Lombardy area, four hub cancer centers have been designated where patients can be transferred to receive their indicated treatment. To regulate the access to the hub center, patients should pass through checkpoint areas that detect potentially infectious persons. The clinical staff at these checkpoints wear PPE, and if there is any suspicion of a person requiring isolation, the person will be placed in a private room until the COVID-19 test result is available (19). Moreover, consultations for second opinions when patients are already under treatment in another system have been deferred [21].

#### **Patients with localized disease**

The COVID-19 pandemic has forced many hospitals to reduce or cancel the elective surgeries to minimize disease transmission and preserve PPEs to care for patients with COVID-19. Decisions taking regarding patients with lung cancer are particularly difficult because patients with thoracic malignancies are considered a high-risk group for having poor outcomes with COVID-19. The most crucial step is to have a multidisciplinary team that includes the oncologists and surgeons to make a shared decision while being transparent regarding the potential risks of deferring or proceeding with surgeries (23). Physicians should fully explain the risks of delaying the surgery versus the possibility of contracting COVID-19 infection by patients with stage I or II lung cancer. If surgery is recommended in the guideline care, then surgery is always preferred over nonsurgical therapy even during the COVID-19 pandemic. However, surgeries of patients with clinical stage IA1 can be deferred for 2–3 months, whereas patients with clinical stage IA2 to stage IIB and stage IIIA (T3, N1 or T4, N0) should proceed to surgery within 1 month, if feasible within local hospital resources. In addition, patients with clinical stage IIIA (T1-2, N2) with a single-station and a non-bulky mediastinal nodal disease can be considered for induction chemotherapy after restaging and surgical resection or definitive chemoradiation alone, whereas patients with bulky mediastinal nodal disease should proceed with definitive chemoradiation without surgery (24). Patients who plan to undergo surgery should be screened for any respiratory symptoms. If there is a suspicion or confirmed case of COVID-19, these patients should be isolated and treated in local hospitals until complete recovery. These patients can then reconsider surgery if they are stable after medical observation of at least 2 weeks. If the patient is asymptomatic but lives in an epidemic area or has a history of exposure in an infected area, the patient will be asked to be isolated for 14 days before surgery and to record daily temperatures and presence of any symptoms. It is advised that only one chosen family member is allowed to accompany the patient, and this family member should also be self-isolated at home with daily temperature recordings (11). If it is decided to delay or defer the surgery, these patients should be tracked and follow-up should be ensured to decide on the best timing for the surgery (23).

#### **Postoperative care**

Postoperative care of patients with early stage non-small-cell lung cancer (NSCLC) relies heavily on the patient’s risk factors

for being infected with COVID-19, prognostic indicators, and the stage of the disease (Table 1) (25). After surgery, patients with NSCLC stage IA do not need any postoperative adjuvant therapy (26), but regular follow-up visits should be ensured (10), which can be done over the phone. Stage IB-IIA NSCLC may need adjuvant treatment after surgery, but that decision depends on the age, risk factors, and the physical condition of the patient, and all of this can be communicated with the physicians through online platforms. Patients with stage IIB-III A NSCLC require adjuvant therapy. The dilemma is how soon the patient should start the therapy. In a large prospective study, results showed that delaying adjuvant therapy for up to 4 months after surgery does not change the effect of the treatment (27). This means that during this pandemic period, this category of patients can extend the time to receive the necessary adjuvant chemotherapy and rest at home while staying safe from the possibility of getting infected. To note, patients with driver mutations are recommended to stay at home during the pandemic, and they may be administered oral targeted drug therapy (11, 25). If the patients taking the targeted drug are stable, they can continue taking the drug treatment, follow-up through online communication, and if possible, postpone the follow-up imaging date. If the clinical symptoms worsen and the patient's disease progresses rapidly, it is recommended to visit the hospital, exclude COVID-19 infection, and try to determine the reason for drug resistance through blood or tissue genetic testing, if the local hospital condition permits. It is of crucial importance that the patients be aware and informed about the adverse reactions of these targeted drugs, such as skin reactions, diarrhea, and other adverse effects. Moreover, the patients should be educated about how to deal with such adverse effects by symptomatic prevention (25). Regarding surveillance imaging, it may be reasonable to lengthen the interval of surveillance imaging to decrease the risk of getting infected with COVID-19 (24).

#### **Patients with metastatic disease**

Patients with more advanced cancers are more critical because delays in treatment may lead to worsening of cancer and perhaps loss of a window to treat (21). Individualization of cases is a necessity because each case is different, and it is crucial to discuss the pros and cons with the patients. Indeed,

several approaches are available that include but not limited to continuing the treatment on schedule, prolongating treatment interval, or deferring doses. These approaches may be reasonable in the metastatic setting if it is not compromising disease control. According to the European Society for Medical Oncology, patients with metastatic lung cancer with high priority should proceed with chemotherapy (28). Oral therapies should be prioritized over intravenous chemotherapy when appropriate because they are often the standard of care in many targetable driver mutations (24). Furthermore, it is suggested to provide drug supplies for two or three courses with home monitoring if oral therapy is needed. It has also been recommended to prescribe prophylactic G-CSF to minimize the risk of febrile neutropenia and thus decreasing the visits to the emergency departments. Most importantly, it is crucial that physicians discuss with their patients, particularly those with metastatic disease, the code status and goals of care (24). With regard to the patients who are enrolled in clinical trials, enrollment is limited to those that would most likely benefit our patients. Nevertheless, it is crucial during these difficult times to have a proactive end of life and palliative case discussions with patients with cancer (21) because getting infected with COVID-19 carries a higher risk of complications and death.

For patients with advanced lung cancer needing chemotherapy, it is best recommended to proceed with treatment and to go to the nearest hospital with experience in chemotherapy while avoiding public transportation to decrease the risk of infection with COVID-19. The key to decrease the probability of getting infected by COVID-19 is to try to shorten the time spent in the hospital during patient visits and to simplify the review methods; then the patients can discuss with their oncologists, online or offline, to choose the appropriate follow-up treatment plan. Professional oncologists should try to figure out more convenient alternatives such as oral chemotherapy alternatives or targeted therapy to decrease the visits to the hospital and possible adverse side effects while maintaining the efficacy of the treatment. Nevertheless, the medical staff should monitor any adverse effects such as bone marrow suppression that can increase the risk of being infected by COVID-19, and the patients should have strict

**Table 1.** Treatment approach towards post-operative care of patients within each lung cancer stage

Type and Stage	Guidelines	Special Considerations in COVID pandemic period
IA NSCLC	No need for postoperative adjuvant therapy	Follow up visits over the phone or online platform. Minimize the number of medical visits
IB-IIA NSCLC	May need postoperative adjuvant therapy	Decision communicated between patients and physicians via online platform
IIB-III A NSCLC	Need adjuvant therapy	Can delay the adjuvant therapy up to 4 months after surgery with no change in the benefit of treatment <sup>1</sup>
IV NSCLC	Chemotherapy	Choose the nearest hospital with experience in chemotherapy Avoid taking public transportation to the hospital
SCLC	Chemotherapy as soon as possible	Mask is worn during the treatment Family member is accompanied <sup>2</sup>

<sup>1</sup>If patient has N2 mutation in EGFR gene, the patient can benefit from postoperative oral EGFR tyrosine kinase inhibitor as one of the adjuvant treatments options.

<sup>2</sup>If disease progresses, patients should consider online hospital consultation and a change in treatment plan (keep in mind the oral medication anlotinib).

protection when they go to the hospital for their routine blood tests. Nonetheless, the patients should try their best after chemotherapy to maintain a healthy lifestyle to maintain their immunity by moderate physical exercises and reasonable balanced diet (25).

Regarding the patients receiving immunotherapy, currently, there is no evidence whether prolonging the interval between treatments increases the risk of disease progression. Given the epidemic, it would be more favorable to postpone the set date of immunotherapy or if that is not possible, to extend the period between immunotherapies (10, 25) because of the potential pulmonary toxicity and lung injury that can be caused by immunotherapy drugs (1). Moreover, because SARS-CoV-2 affects macrophages and T cells, it may cause an immunological dysregulation that might interfere with the response to immunotherapy (29). Nevertheless, if immunotherapy is initiated, these patients need adequate personal protection, and they should pay attention to immunotherapy toxicity and side effects.

#### ***Patients with small-cell lung cancer***

In patients with extensive stage small-cell lung cancer (SCLC), chemotherapy should be started as soon as possible, and if the disease progresses, these patients should consider online hospital consultation to discuss and change the treatment plan with the oncologist (10). Considering its poor prognosis and high chance of relapse, it is recommended to discuss the treatment plan with the physician through online consultation or hospital video consultation and to go to a local hospital if treatment is agreed upon and try as much as possible to avoid travel to decrease the risk of infection (10). It is advised to withhold chemotherapy and immunotherapy for patients who have poor performance (8). Moreover, magnetic resonance imaging surveillance could be considered as an alternative to prophylactic cranial irradiation for limited or extensive SCLC to reduce the number of visits (22).

#### ***Patients eligible for lung cancer screening***

During the COVID-19 pandemic, performing a screening examination and the evaluation of lung nodules is considered a risk for patients. Therefore, during these times, elective procedures and imaging are being cancelled, making it difficult to implement the guidelines. Current consensus is based on expert opinion, taking into consideration the current Centers for Disease Control and Prevention COVID-19 guidelines. In one article, an expert panel of 24 members was formed where they were asked to give consensus regarding several scenarios. For instance, it has been suggested to defer initiation of screening for lung cancer in eligible patients and in patients who have repeat annual chest CT screening examinations. If there is a need to follow-up regarding a nodule that is more likely to be an indolent cancer or has a low probability of being cancerous, it is preferable to delay the follow-up for at least 3–6 months. If the probability of malignancy is high, it would be acceptable to evaluate the patient with positron emission tomography scan and/or nonsurgical biopsy to ensure that there is a need to proceed to treatment. However, patient preferences should always be discussed before taking any decision (22).

#### **COVID-19 Treatment in Patients with Lung Cancer**

If a patient with lung cancer develops any fever or respiratory symptoms that can be suggestive of COVID-19 symptoms, it is necessary to visit a physician to perform the necessary tests and imaging for workup and diagnosis. If the patient turns out to be COVID-19 positive, it is important to visit the nearest medical unit instead of trying to go to the original medical unit or a higher-level hospital. These patients should be isolated and treated according to the COVID-19 treatment guidelines. If these patients have recovered from a new COVID-19 infection, there should be a comprehensive assessment of the patient's function, a moderate delay in tumor treatment, and selection of treatment drugs that have high efficiency and low toxicity (30). Case reports show the potential of continuing the targeted therapy in patients who are stable after COVID-19 infection (31).

Since the beginning of the outbreak, COVID-19 has not only affected the physical health of patients but also their mental health and their families (10). The general population and especially the patients with cancer are prone to suffer from psychological problems such as anxiety and depression because most people have realized the seriousness of the COVID-19 pandemic and the threat it imposes on their health (30). It is recommended that patients with lung cancer incorporate relaxation exercises to release all the tension and bad emotions, actively communicate with their families at home and their physicians regarding their fears, and perhaps have an online psychological consultation to overcome these difficult times (32).

#### **CONCLUSION**

In summary, with the ongoing increase in COVID-19 spread, patients with cancer, especially those with lung cancer, are fighting a huge battle. Moreover, the diagnosis and treatment of lung cancer has been restricted to varying degrees during this period (11). Individualized management is crucial to protect these vulnerable patients from COVID-19 while controlling their disease. Oncologists should carefully consider, in the light of the recommendations mentioned, the best treatment plan for each patient and who would benefit from the treatment when compared with the risk of getting infected with COVID-19. These challenging decisions should be communicated with the patients and most importantly with the medical ethicist and palliative care teams (19). With the combined efforts of doctors and patients, every effort should be made to help the patients with cancer to smoothly endure this difficult period of COVID-19. There is no easy universal solution during this crisis especially because the duration of this pandemic is hard to predict; thus, we need to continuously adapt and evolve rapidly to treat our patients in the most effective manner possible.

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