

# Lung Cancer Management in COVID-19 Pandemic

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## Abstract

In studies published in China, lung cancer patients were identified as the greatest risk group during the COVID-19 pandemic due to their diseases and immunosuppressive treatments. Poor prognosis is anticipated if COVID-19 pneumonia is detected in lung cancer patients. Oncology associations and specialists from countries such as China and Italy have published suggestions that allow patients to experience the pandemic with minimal harm. It is recommended that patients stay in their homes and not visit the hospital. This may mean postponing treatments, switching to oral form of treatments that must continue, and extending the intervals between IV treatments or reducing the number of cycles. When surgery is required, neoadjuvant chemotherapies are preferred. It is difficult to differentiate the symptoms or radiological images of the lung cancer patient with COVID 19 pneumonia vs cancer progression or treatment-related complications. Therefore, careful examination is key. In this article, we have compiled recommendations for the management of lung cancer during the COVID 19 pandemic.

**KEYWORDS:** COVID 19, lung and pleural malignancies, lung cancer management, pandemic

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## INTRODUCTION

Lung cancer is still the most common cancer in the world with the highest mortality rate. According to the Globocan 2018 data, the number of new patients worldwide is over 2 million, and the number of patients lost is close to 2 million [1]. It is estimated that patients with lung cancer will be adversely affected by pandemic. In the studies published in China, patients with lung cancer were identified as the highest risk group during the coronavirus disease 2019 (COVID-19) pandemic owing to their disease and immunosuppressive treatments. Poor prognosis is anticipated if COVID-19 pneumonia is detected in these patients. Oncology associations and specialists from countries such as China and Italy have published suggestions that allow the patients to experience the pandemic with minimal harm. It is recommended that the patients stay in their homes and do not visit the hospital. This may mean postponing treatments, switching to the oral form of treatments that must continue, and extending the intervals between intravenous (IV) treatments or reducing the number of cycles. When surgery is required, neoadjuvant chemotherapies are preferred but it is also stated that the surgeries will continue by taking precautions in healthcare centers without COVID. With symptoms or radiological images of a patient with lung cancer, it is difficult to distinguish COVID-19 pneumonia from cancer progression or treatment-related complications. Therefore, a careful examination is necessary. In this review, recommendations for the management of lung cancer during the COVID-19 pandemic was compiled.

## CLINICAL AND RESEARCH CONSEQUENCES

In December 2019, a disease caused by a new coronavirus derivative, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was detected in Wuhan, Hubei province of China, causing pneumonia and respiratory failure. It was called COVID-19 pneumonia [2-4]. This disease, which is endemic to the Wuhan region, was observed first in China and then worldwide and was declared as a pandemic by the World Health Organization (WHO) [5, 6].

One of the patient groups adversely affected by the coronavirus disease 2019 (COVID-19) pandemic is patients with lung cancer. Older individuals and those with comorbidities such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and cancer were adversely affected [7]. In a study conducted in China, it was stated that patients with cancer with COVID-19 had a higher risk for serious clinical events than patients without cancer [8]. In the first retrospective study published in Wuhan, 1,524 patients with cancer who applied to Zhongnan Hospital, Radiation and Medical Oncology Department between December 30, 2019 and February 17, 2020 were scanned ret-

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respectively. COVID-19 was diagnosed in 12 patients (95% confidence interval: 0.3–1.2); 7 of the 12 patients (58.3%) had non-small cell lung carcinoma (NSCLC), and 5 (41.7%) had chemotherapy with or without immunotherapy (n=3) or radiotherapy (n=2). It was observed that these results were higher than the cumulative incidence of all the patients diagnosed with COVID-19 in the city of Wuhan during the same timeframe. The total number of patients with NSCLC followed at the same center was 228, 7 of whom were diagnosed with COVID-19, and 5 of the patients were over 60 years. Hospitalization and recurrent hospital admissions have been reported to be the potential risk factors for SARS-CoV-2 infection [9].

In another study, where 3 hospitals were scanned retrospectively, 28 of 1,276 patients with COVID-19 were diagnosed with cancer; 7 of whom had lung cancer. Six patients (21.4%) who received at least one type of cancer treatment within 14 days of being diagnosed with COVID-19 were found to have a higher risk of developing serious events than those who did not receive cancer treatment. It was also stated that the observation of patchy consolidation areas rather than ground-glass densities was associated with a worse prognosis in thoracic computed tomography (CT) at the time of diagnosis. Although the study is retrospective and reflects a small sample, it is important for showing that patients with cancer are at risk during the pandemic. Therefore, it is recommended to postpone cancer treatment and elective surgery [10].

Worldwide, in countries where the pandemic continues, the most important problem experienced by patients with lung cancer has been the delay in their treatment and their inability to benefit from the health services as necessary. A total of 321 questionnaires, prepared by a group of researchers in China, "The Guide for the Diagnosis and Treatment of Patients with Advanced Stage Non-Small Cell Lung Cancer during the Epidemic Pneumonia," was published in March 2020 [11]. The guideline provides key points and recommendations for the management of patients with advanced NSCLC, strategies for the use of antitumor drugs, specific measures, drug reactions, and differential diagnosis of the patients with COVID-19 pneumonia. It has been recommended that the follow-up of patients with a diagnosis of NSCLC should be carried out in the closest centers where COVID-19 patients do not apply and where outpatient diagnosis and treatment can be performed. Patients should be monitored for symptoms associated with COVID-19, and close attention should be paid to the determination of tumor or treatment-induced adverse reactions. It is emphasized that appropriate treatment strategies should be selected to balance the effectiveness and toxicity of drugs in patients with NSCLC. It is recommended that chemotherapy drugs, which are immunosuppressants, should not be administered for a suitable period of time to the patients who need to receive chemotherapy or to continue; the drugs should be given only by the healthcare institution and healthcare staff who have not been exposed to the COVID-19 disease. It is also stated that this center should be located close to the patient's home to avoid traveling.

It is emphasized that tyrosine kinase inhibitors, which are called targeted therapies, are recommended at home because they can be taken peroral. Patients should be very mindful of the drug side effects, monitor their symptoms closely, contact their physicians via telephone or internet, and go to the hospital when necessary. Immunotherapy is not recommended because it can create diagnostic confusion with pneumonitis and suppress the immune system. It is recommended that the ongoing treatments be given in an experienced hospital close to their home under clean hospital conditions. Another recommendation on the basis of the practices of 321 specialists (192 personally treated patients with COVID 19) is to give cancer treatments at least 2-4 weeks after the patients, who have been diagnosed with COVID-19, have recovered [11].

Many publications highlight the importance of ensuring that patients who need treatment during the outbreak are not infected with COVID-19. Patients diagnosed with cancer who need treatment should be isolated for at least 14 days before the treatment, accompanied by a single companion if necessary. Fever and symptoms of patient and companion should be monitored during isolation. If COVID-19 is not suspected, treatment is indicated. If the patient and companion cannot be isolated at home, it is suggested that the patient be isolated and monitored in the hospital, avoiding contact with other patients and relatives during this period. Patients who can isolate at home are instructed to stay home and avoid going out and allow younger, healthier people living in the home to leave the house for essential activities with personal protective equipment.

For newly diagnosed patients who have not yet started treatment and for patients awaiting postoperative adjuvant chemotherapy, clinicians should consider pathological diagnosis and clinical stage, risk factors, and prognostic indicators. It has been determined that postoperative adjuvant chemotherapy can be delayed for the patients with earlier clinical stage and lung cancer with a good prognosis. For the patients with advanced lung cancer, in the presence of low tumor burden and stable disease, chemotherapy can be postponed for a moderate period or oral chemotherapy and targeted therapies can be arranged as home treatment. If the patient needs chemotherapy, it is recommended to choose the closest hospital with chemotherapy experience and to not contact any patients with suspected COVID-19. Patients receiving targeted therapies should stay at home, take the medication in oral form, closely monitor the side effects and blood pressure, and if acute symptoms occur, they should contact their health institution [12].

It has been reported that patients with lung cancer are vulnerable, and their prognosis is poor during the COVID-19 outbreak [13]. Compared with the general population, patients with cancer need to go to the hospital frequently, and hospitalization for treatment significantly increases the risk of exposure to the virus. It is also emphasized that after surgery, radiotherapy, or immunotherapy, a high risk of infection is expected owing to the weakening of the immune system [14]. Patients with cancer are typically older, in poor physical

condition, and often have more than one comorbid disease or other lung diseases. Patients with lung cancer have inadequate respiratory functions, and when COVID-19 pneumonia develops, it usually causes symptoms to be more severe with poor prognosis.

The differential diagnosis for COVID-19 is recommended in patients with lung cancer to assess if there are other possibilities for fever and respiratory symptoms and to rule out the infections other than COVID-19, such as radiation or immunotherapy pneumonitis. It is recommended to consider tumor progression or other diagnoses such as pulmonary embolism and pulmonary edema in the differential diagnosis [13].

Patients who are planning to receive radiotherapy should travel as little as possible for treatment, hopefully within the same city. They should confirm their appointment time and arrive at the hospital at the time of the appointment (not too early) to reduce the time spent in the hospital and the contact with other patients. If a companion is needed, a single person is allowed but should be monitored with daily temperature and screening for cough, shortness of breath, diarrhea, or other symptoms. Body temperature and respiratory symptoms should be screened before initiating treatment at the hospital. Patients with respiratory symptoms should be directed to the appropriate clinic for COVID-19 pneumonia and should receive the treatment 2 weeks after full recovery.

Elective procedures and non-urgent operations should be deferred for the patients diagnosed with lung cancer if they are to be taken to the hospitals where patients with COVID-19 are being cared for. If a procedure is urgent and must be performed, the patient and a companion must be isolated for at least 14 days before the procedure. The procedure must be performed in a clean hospital, and it is recommended to perform the surgery only if there are no symptoms of COVID-19, and the patient's blood tests and thoracic CT are negative. Although the patient is deemed not to have COVID-19, it is recommended that all the healthcare personnel who come in contact with the patient should take maximum preventive measures by assuming that each patient is COVID-19 positive. If COVID-19 is suspected during or after the procedure, polymerase chain reaction (PCR) sampling of the patient is recommended. All the healthcare personnel who came in contact with the patient should be isolated for 14 days, and PCR tests should be performed for those who show symptoms. However, priority should be given to isolation and clinical, laboratory and radiological monitoring; It is also reminded that PCR-nucleic acid tests may mislead the process due to false-negative results [15]. It has been suggested that elective surgical procedures for lung cancer can be postponed for a period of 3 months, and neoadjuvant therapy can be given to the patients who are diagnosed and require surgery. For nodules less than 3 cm, a control CT should be performed after 1 month, and if there is a progression of more than 20%, surgery must be performed under suitable conditions. Control screening for ground-glass nodules should be performed by following the guidelines, and

the ground-glass nodules must be checked for at least 3 months with thoracic imaging [15].

Various oncology associations in the USA and Europe have published guides with similar recommendations regarding this pandemic process. During the pandemic, it is recommended to follow the patients through the telehealth system over the phone or the internet, that the patients stay at home as much as possible, and that the treatments are delayed for an appropriate period. Each case must be evaluated with multidisciplinary considerations. During the pandemic, as was the case in Italy, the personnel who provide oncology services may be called upon to care for patients with COVID-19, including retired physicians and medical school seniors who have been recruited to care for the patients [16].

In Italy, where the disease was the most prevalent after China, the Young Medical Oncologists Group published a statement emphasizing that the health system is under a heavy load and that patients with cancer will be affected the most by the current conditions [17]. The country's various oncology associations have come together to create the guidelines. They have made phone calls and online clinical evaluations and have tried to keep their patients in a safe environment for routine follow-up visits, avoiding the hospital. They also raised fears about delaying treatment and the progression of the disease and emphasized the importance of making multidisciplinary decisions for each patient. In addition, they emphasized that ongoing cancer research may be affected by this process and that necessary measures be taken [17].

"How do we treat patients with lung cancer during the SARS-CoV-2 outbreak: *primum non nocere*," an article published in ESMO Open, described the patients with lung cancer as a high-risk group during the COVID-19 outbreak, and recommendations were made for treatment [18] (Table 1). It is recommended that options such as the application of first-line treatment for advanced-stage small cell lung carcinoma (SCLC), concurrent chemoradiotherapy for limited-stage disease, or extrapulmonary palliative or ablative radiotherapy (SBRT) should not be stopped without a valid justification. In NSCLC, it is stated that adjuvant therapy may not be given after the risk/benefit ratio, survival benefit, and possible risks are carefully discussed with the patients. Neoadjuvant chemotherapies can be given to the patients with surgical indication to delay the process. In NSCLC, first-line treatment for metastatic disease, sequential or concurrent chemoradiotherapy for stage III disease, and SBRT treatments can be applied. Oral chemotherapies can be given instead of IV in patients with Eastern Cooperative Oncology Group 2. However, patients with the risks associated with COVID-19, who are in contact with people having a positive COVID-19 PCR test, should be tested before or during cancer treatment. If the patient is asymptomatic but COVID-19 PCR positive, the patient must be isolated, and before starting the treatment, it is recommended to have 2 negative PCR test results in the following 28 days. In addition, it is stated that the treatment intervals will be extended, and the number of chemotherapy courses will be reduced by informing the patients to reduce the frequency of hospital admission. It is recommended to use

**Table 1.** Practical suggestions to treat patients with lung cancer during the SARS-CoV-2 pandemic (18)

	<b>Non small cell lung cancer</b>	<b>Small cell lung cancer</b>
Should be started when possible**	NACHT for locally advanced resectable disease† Sequential/concurrent CHT/RT§¶ for stage III disease First-line treatment for metastatic disease Palliative or ablative radiotherapy (SBRT) outside the lung**	First-line treatment for extensive-stage disease Concurrent CHT/RT§ for limited-stage disease Palliative or ablative radiotherapy (SBRT) outside the lung**
Should not be stopped without justification	NACHT for locally advanced resectable disease‡ Sequential/concurrent CHT/RT§¶ for stage III disease First-line treatment for metastatic disease Maintenance ICI*	Concurrent CHT/RT§ for limited-stage disease First-line treatment for metastatic disease
Can be given preferentially	CT/RT for stage III disease Oral chemotherapy for ECOG PS 2 and elderly patients (instead of intravenous)	Oral rather than intravenous chemotherapy
Can be withheld or delayed after careful consideration††	Withhold ACHT in patients at significant COVID-19-related risk†† Delay ICI (within 42 days) for stage III disease after CHT/RT Withhold maintenance pemetrexed Prolong intervals of ICI*	Prolong intervals of ICI*
Should not be started without justification	Third and beyond lines of chemotherapy in patients at significant COVID-19-related risk††	PCI (favouring MRI surveillance) Thoracic consolidation radiotherapy extensive stage Third and beyond lines of chemotherapy in patients at significant COVID-19-related risk††

\* Regimens with longer interval (including ICI; ie, nivolumab 480 mg every 4 weeks or pembrolizumab 400 mg every 6 weeks) should be preferred

† Shorter duration of chemotherapy (ie, four cycles of chemotherapy instead of six) should be discussed with patients and use of prophylactic G-CSF should be considered.

‡ NACHT could be helpful to bridge time to surgery in case where surgery is not possible.

§ In patients with adequate respiratory function.

¶ Try to start RT on day 1 of chemotherapy, only two cycles will be needed, three cycles if starting RT with cycle 2, or sequential.

\*\*Exception: indicated if compression of airways or bleeding. Fractions of SBRT could be reduced if organ at risk constraints (from eight fractions to five or three) and palliative RT single or in two fractions (8–10 Gy or 17 Gy, respectively) should be used where possible.

†† Patients with family members or caregivers who tested positive for COVID-19 should be tested before or during any cancer treatment, whenever. If a patient results positive and is asymptomatic 28 days of delay should be considered before (re)starting the treatment. In the case of SARS-CoV-2, two negative tests at 1-week interval should be performed before (re)starting the treatment.

‡‡ Patients at significant COVID-19-related risk: aged ≥70, with ischaemic cardiac disease, atrial fibrillation, uncontrolled hypertension or diabetes, chronic kidney disease.

ACHT, adjuvant chemotherapy; CHT, chemotherapy; COVID-19, coronavirus disease; ECOG PS, Eastern Cooperative Oncology Group Performance Status; G-CSF, granulocyte colony-stimulating factor; ICI, immune checkpoint inhibitor; NACHT, neoadjuvant chemotherapy; PCI, prophylactic cranial irradiation; RT, radiotherapy; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SBRT, stereotactic body radiotherapy.

prophylactic granulocyte colony-stimulating factor and prescribe antibiotics at home for neutropenic fever [18].

Although there is no definitive data in our country, it is observed that hospitals that provide treatment services for patients with lung cancer have turned into pandemic hospitals, and healthcare professionals provide services in the field of pandemics. During the pandemic, treatment of patients with cancer is delayed if possible, but patients whose chemotherapy cannot be delayed, such as those suffering from SCLC, continue their treatment. It is stated that there are similar applications in the field of thoracic surgery where elective

operations were delayed, and in cases where urgent intervention is needed, such as massive hemoptysis and airway obstruction, the patient is treated with personal protective equipment, assuming that the patient is COVID-19 positive.

## CONCLUSION

It is estimated that the patients most adversely affected by the COVID-19 pandemic will be patients with lung cancer. The consensus during the pandemic is that patients with lung cancer will have a higher risk of infection and the prognosis will be worse. The recommendation is that the decision on how

to manage a patient with lung cancer during a pandemic is to be made multidisciplinary. The diagnosis (NSCLC or SCLC), stage of the disease (early or advanced), tumor burden, clinical (age, performance, symptom or comorbidity) and social status should be considered. It should also be remembered that lung cancer surgery is a semi-elective surgery. Therefore, it is recommended that the surgeries and treatments of lung cancer patients who can be cured continue in non-COVID healthcare centers.

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