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# Lung cancer and COVID-19

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**Abstract:**

Patients with cancer are more susceptible to an infection during the viral epidemic owing to their immunocompromised status. Furthermore, mortality was found to be higher in patients diagnosed with cancer infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It is a problem managing a process including diagnosis, staging, and treatment for patients with lung cancer. The clinical symptoms of coronavirus disease 2019 (COVID-19) patients and lung cancer patients are easy to be confused, which will bring great difficulties to the differential diagnosis. Management of patients with cancer at home should be encouraged. This includes telemedicine and phone calls to replace safety visits, as well as replacement of intravenous drugs with oral drugs where possible, along with substructure and coordination to allow home administration of intravenous and subcutaneous anticancer agents. By giving priority to the centers designated as corona-free, the consultation among physicians should be carried out online, and the diagnosis and treatment process of the patients should be continued in a way to minimize the risk of virus transmission. Patients should be evaluated during coronavirus pandemic for antitumor treatment with considering clinical status, stage of cancer, and status of suspected or confirmed COVID-19 infection.

**Keywords:**

Coronavirus, lung cancer, pandemic, telemedicine

## Introduction

Coronavirus disease 2019 (COVID-19) is an emerging and rapidly evolving problem for global public health whose pathogen is severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Transmission of infectious diseases can take place under three conditions: sources of infection, routes of transmission, and susceptible hosts.

Human-to-human transmission has been considered as a major transmission mode. It spreads mainly through respiratory droplets or close contact.[1] Nosocomial transmission was a severe problem to COVID-19, and even worse. A recent retrospective study indicated that a total of 1716 health workers were infected, accounting for 3.84% of total cases.[2] Nosocomial infections extremely burdened the health system and hindered early infected individuals from getting immediate medical supports, therefore resulting in high-case fatality rate. In Wuhan alone, 1080 health workers were infected; in return, case fatality rate of Wuhan is the highest. Wang et al. reported that among 138 hospitalized patients with COVID-19, 41% of patients were suspected to be infected via hospital-related transmission, About 26% of the patients received intensive care unit care, and mortality was 4.3%.[3] A lot of respiratory treatments for critically ill patients are deemed as high-risk factors for nosocomial transmission, such as intubation, manual ventilation by resuscitator, noninvasive ventilation,

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high-flow nasal cannula, bronchoscopy examination, suction, and patient transportation.[4] A large portion of nosocomial transmissions occurred through contacts between clinicians and visitors with no or mild symptoms of COVID-19.

## Why is Coronavirus Disease 2019 Major Concern in Lung Cancer Patients?

A study from Wuhan revealed that fatal cases with COVID-19 infection had male predominance, and the median age of them was 65.8 years.[5] Furthermore, it is concluded that older patients (>60 years) with nonsmall-cell lung cancer (NSCLC) are at risk of COVID-19 infection.[6] Similarly, we know that the frequency of lung cancer is higher in the sixth decade and male gender.[7] Considering both similar demographic features of these two mortal diseases, the probability of crossing of cases increases.

Patients with cancer are more susceptible to an infection during the viral epidemic owing to their immunocompromised status. Their systemic immunosuppressive state was caused by the malignancy and anticancer treatments. In a report from China, 18 of 1590 COVID-19 cases (1.13%) had a history of cancer, which was higher than the incidence of cancer in the overall Chinese population (0.29%) according to the 2015 cancer epidemiology statistics. Among patients with a history of malignant tumors, lung cancer (5/18, 28%) is the most common cancer.[8,9] However, the risk of severe events was found to be similar between patients with lung cancer and other types of cancer. Antitumor treatment within 14 days of COVID-19 diagnosis and having patchy consolidation on computed tomography (CT) scan (admission) independently increased the risk of developing severe events.[10] Furthermore, during this COVID-19 outbreak, the major risk for patients with cancer is the inability to receive necessary medical services. Based on all of these data, it is expected that mortality was higher in cancer patients infected with COVID-19. In China, among patients with COVID-19, while mortality is 2.3% in all patients, it has been reached 5.6% in cancer patients.[11]

## Diagnosis

It is a problem managing a process including diagnosis, staging, and treatment for patients with a preliminary diagnosis of lung cancer. At first, the clinical symptoms of COVID-19 patients and lung cancer patients are easy to be confused, which will bring great difficulties to the differential diagnosis. There are many questions about how doctors and patients work together under the new COVID-19 epidemic. Given the failure of the health system in many countries, it is quite difficult to address cancer patients in a separate health center. Strict protections are required to prevent these patients from virus transmission, either from other COVID-19 positive patients or health-care providers who are asymptomatic carriers. In this context, to minimize inhospital transmission, there is a vital technical guidance prepared by the World Health Organization that all health centers should take into account.[12]

Another problem that clinicians should deal with in practice is a differential diagnosis because cough, fatigue, dyspnea, and even fever are symptoms that associated with both lung cancer and COVID-19 pneumonia. Moreover, considering the radiological similarities, there is a confusing overlap. We observed that there were lung cancer patients presenting with unilateral/bilateral patchy infiltrates on chest CT.[13] Similarly, as we follow the evolving literature on the novel coronavirus, it appears that its most prominent radiological features are rapidly progressive bilateral patchy infiltrates and ground-glass opacities.[14] Therefore, it is important to know the detailed epidemiological history and clinical symptoms of the patients. During this pandemic, for newly diagnosed lung cancer patients, physicians may use "*New Coronavirus Infection Pneumonia Diagnosis and Treatment Plan (Trial Sixth Edition)*" that is a reference source for differential diagnosis.[15] As its own data accumulates, each country can modify the patient approach with their own guides, as in our country, Turkey.[16] After careful analysis, further diagnostic procedures such as histopathological analyzes and positron-emission tomography (PET) should be performed if necessary. If the novel coronavirus is present in a patient who is planned to undergo a diagnosis of lung cancer, early diagnosis of the virus is the most challenging point. New coronavirus pandemic has led many restrictions in the management of lung cancer as other chronic diseases. The diagnostic processes should not be delayed as much as possible depending on the adequacy and capabilities of the health systems of countries. By giving priority to the centers designated as corona-free, the consultation among physicians should be carried out online, and the diagnosis and treatment process of the patients should be continued in a way to minimize the risk of virus transmission.

## Cancer Care during a Pandemic

Managing lung cancer patients with COVID-19 is difficult during this epidemic. Immunosuppression due to malignancy and anti-tumor therapy can cause severe COVID-19 complications. Otherwise, postponing antitumor treatment can also cause tumor progression. Management of patients with cancer at home should be encouraged. This includes telemedicine and phone calls to replace safety visits, as well as replacement of intravenous drugs with oral drugs (e.g.,

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chemotherapy and hormone therapies) where possible, along with substructure and coordination to allow home administration of intravenous and subcutaneous anticancer agents. Although it is difficult to apply, chemotherapy infusions can be performed at home if appropriate conditions are available.[17] Blood analyses before cytotoxic therapies or to evaluate hematological complications can be obtained at home to minimize hospital visit if feasible.[18]

If COVID-19 is suspected or confirmed in a lung cancer patient, the patient should be transferred to the hospital department specially prepared for the outbreak.[16] However, it should be noted that because of the possibility of false-negative virus detection, if the first detection of the new coronavirus nucleic acid is negative and clinically cannot be excluded, the new coronavirus should be re-tested after at least 24 h.[19] Along with COVID-19 tests are in progress, other etiologies such as other viral/bacterial infections, radiation pneumonia, immune-checkpoint inhibitor-associated pneumonia, or other noninfectious reasons (tumor progression, pulmonary embolism, cardiac insufficiency, etc.) should be considered in differential diagnosis. Lung cancer patients infected with SARS-CoV-2 can continue maintenance after 2 weeks of clinical stability. If COVID-19 is excluded, initiation of treatments for other infectious agents should not be delayed.

## Management of Thoracic Surgery

Curative treatments like surgery should not be delayed in lung cancer patients at early stages. However, in this serious condition, the timing of the surgery is critical. We should assess patient case by case. According to the requirements of the country's overall prevention and control plan, there are preliminary recommendations for thoracic surgery from China.[20] Certainly, these must be updated according to the changes in the epidemic situation and further understanding of the disease behavior.

1. If patients have respiratory symptoms suggesting COVID-19, they must be assessed in a hospital that is determined as a pandemic center by the government. If not, patients must be encouraged to visit local hospitals to minimize cross-infection caused by the flow of patients and their families
2. After examinations with PET-CT or percutaneous lung biopsy, if it is indicated as benign lesions, it is recommended that patients' elective surgery must be postponed up to 3 months (if possible after the epidemic is over or relatively stable)
3. After initial examinations, if it is indicated as malignant lesion and located in central, the patient is advised for neoadjuvant therapies than elective surgery that can be planned for a relatively stable time
4. For peripheral malignant lesions, recommendations change depending on the size. If its' diameter ≥3 cm, surgical treatment should be considered. For nodules with a diameter of ≤3 cm short-term follow-up is recommended (once a month)
5. For ground-glass nodules (GGNs) including pure GGNs, mixed GGNs, or multiple GGNs (multiple GGNs need to exclude new coronavirus infections) in the lungs, it is recommended to follow-up, not surgery. We should also give great importance to GGNs because the imaging features of the lungs of the new coronavirus pneumonia are ground glass-like changes. For newly discovered ground glass-like nodules or space-occupying lungs, there should be at least 3 months of follow-up to rule out the lung changes of new CoV pneumonia.

Briefly, these reports from China divide recommendations about thoracic surgery into two categories.

### Elective surgery

It is defined as surgery for lesions that can be observed for more than 3 months, including various GGNs with a diameter of <3 cm, and a benign possibility of more than 70% probability, nodules or space-occupying, benign lung diseases that can be treated conservatively, such as bronchiectasis with hemoptysis. Such operations are not recommended or performed with caution during the epidemic.

### Time-limited surgery

It is defined as surgery for lesions that can be best performed within 1 month. The lesions include clinically or clearly diagnosed as lung cancer and lesions with a diameter > 3 cm. Surgery should be performed for these lesions except patients having new coronavirus infection. Various types of emergency surgery are beyond the scope of this discussion.[20]

## Adjuvant Therapies when and to Whom?

After a successful lung cancer operation, adjuvant therapies and their timing are other confusing points. For Stage IA patients, there is no need for adjuvant therapy.[21] For patients with Stage IB-IIA requiring adjuvant therapy after surgery, in case of high-risk factors like the elderly patient and poor physical condition, the follow-up treatment plan should be comprehensively determined via the network platform with relevant physician.[22] During the epidemic period, patients with pathological Stage IIB-IIIA can be advised to extend the time of receiving adjuvant chemotherapy. Among them, N2 patients with epidermal growth factor receptor (EGFR) gene mutations may consider oral first-generation EGFR tyrosine kinase inhibitors (TKIs) as one of the adjuvant treatment options.[21-23]

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## Approach to Advanced Stage Lung Cancer Patients

Patients with advanced stage NSCLC having a targetable driver mutation may be considered for targeted drug therapy by choosing drugs with less adverse reactions. Few data are available about targeted therapy in COVID-19 outbreak. One case report published by Zhang *et al*.; 57-year male patient with COVID-19 infection and advanced EGFR L858R mutant NSCLC on osimertinib, treated with lopinavir/ritonavir and continued osimertinib was improved and discharged after 1 month of hospitalization.[24] During epidemic, follow-up imaging evaluation can be delayed, and to questionnaire patients' symptoms, online communication is recommended. If the patient has a slow radiological progress with stable clinical symptoms, relevant physician should consider continuing the original treatment under close observation. If a patient becomes symptomatic, it is recommended to communicate with the doctor online.[22] In case of rapidly progressive lesion with worsen clinical symptoms, the patient must visit a local hospital. If the patient's disease progresses rapidly and the clinical symptoms worsen progressively, it is recommended to visit a local hospital to exclude COVID-19. If a local hospital is available for further investigation (re-biopsy, re-staging, liquid biopsy etc.,) it is recommended to plan appropriate drug therapy (other generation of TKIs) to overcome drug resistance. The aim of all these efforts is to prevent patients from risk of infection by going to the hospital for systemic chemotherapy.[22]

For driver mutation negative and advanced stage NSCLC patients, decision of initiating or continuing of chemotherapy must be reconsidered. Having poor performance status/complications after few cycles of chemotherapy and being in the stage of consolidation chemotherapy are clinical situations to extend the interval of chemotherapy by close communication with physician.

If the capacity of pandemic hospitals for COVID-19 is restricted, prioritization of patients with COVID-19 for chemotherapy during this pandemic is very crucial. For chemotherapy, the classification of patients of priority is shown in Table 1.[25]

**Table 1: Priority chemotherapy treatments**

| Order of priority | Treatment |
|---|---|
| 1 | Curative therapy with high (>50%) chance of success |
| 2 | Curative therapy with an intermediate (15%-50%) chance of success |
| 3 | Noncurative treatment with a high (>50%) chance to extend the life of >1 year |
| 4 | Curative therapy with a low (0%-15%) chance of success or noncurative therapy with an intermediate (15%-50%) chance to extend the life of >1 year |
| 5 | Noncurative therapy with a high (>50%) chance of palliation or temporary tumor control and <1 year expected extension to life |
| 6 | Noncurative therapy with an intermediate (15%-50%) chance of palliation or transient tumor control and an expected life extension in <1 year |

Cancer patients receiving treatment with anti-programmed cell death protein 1 (PD-1) / anti- programmed death-ligand-1 (PD-L1), anti- cytotoxic t lymphocyte-associtaed antigen 4 (CTLA-4) and immune checkpoint inhibitors (ICI) form a growing oncological population.[26] However, their specific susceptibility to bacterial or viral infections has not been researched, considering that immunotherapy with ICI is able to repair the cellular immunocompetence. The patient undergoing immune checkpoint blockade could be more immunocompetent than cancer patients undergoing chemotherapy.[27,28] There are negative considerable effects of ICI on infected patients with COVID-19. First, pneumonitis which is a rare side effect of ICI may be underdiagnosed due to similar radiological pattern with coronavirus-related interstitial pneumonia, and the follow-up for the development of pneumonitis can be difficult. Second, possible negative interference of ICI and cytokine release syndrome (CRS) which is a phenomenon of immune hyperactivation and can result in severe organ dysfunction and death. ICIs have prolonged response in lung cancer patients.[29] Hence, prolonged treatment interval is not expected to have a role for the development of disease progression. In view of the epidemic, physicians must consider appropriately extending the interval between immunotherapies.[22]

## Radiotherapy during Pandemic

Unlike other therapies, radiotherapy requires regular hospital visits. Patients currently on treatment must continue with taking protective measures. Patients with suspected contact or high risk should be treated in a separate room.[30] According to the American Society for Radiation Oncology recently published recommendations, radiation oncologist can make low fractioned treatment plan adhering to evidence-based guidelines. Except of function-or life-threatening situations, radiotherapy for palliative purposes can be postponed. Scheduling of follow-up patients after completing their course must be planned case by case. New patients and their visitors should be screened for COVID-19 symptoms, suspected contact with COVID-19 patient person or travel.[31]

If the capacity of pandemic hospitals for COVID-19 is restricted, prioritization of patients with COVID-19 for radiotherapy during this pandemic is very crucial. For radiotherapy, the classification of patients of priority is shown in Table 2.

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**Table 2: Priority radiotherapy treatments**

| Order of priority | Treatment |
|---|---|
| Level 1 | Radical radiotherapy or chemoradiotherapy for therapeutic purposes in patients with a rapidly growing tumor, where treatment has already begun and interrupting treatment cannot be compensated |
| | Brachytherapy following external beam radiotherapy in patients with a rapidly proliferating tumor and external beam therapy previously initiated |
| | Radiotherapy in patients with a rapidly growing tumor and planned to start radiotherapy under normal conditions according to the clinical situation |
| Level 2 | Emergency palliative radiotherapy for patients with malignant spinal cord compression with recoverable neurological function |
| Level 3 | Radical radiotherapy for less aggressive tumors, if radiotherapy is the first treatment for curative purposes |
| | Postoperative radiotherapy in the presence of aggressive tumor or postoperative residual disease |
| Level 4 | Palliative radiotherapy, where improving symptoms would reduce the need for other interventions |
| Level 5 | Adjuvant radiotherapy in patients with complete resection and local recurrence risk <20% within 10 years |

European Society of Medical Oncology (ESMO) guideline gives recommendation about how to treat small-cell lung cancer during this pandemic. First-line treatment for extensive-stage disease and concurrent chemotherapy/radiotherapy for limited stage disease, palliative or ablative radiotherapy Stereotactic body radiation therapy (SBRT) outside the lung should be started when possible. Prophylactic cranial irradiation, thoracic consolidation radiotherapy for the extensive stage, and third and beyond lines of chemotherapy in patients at significant COVID-19-related risk should not be started without justification.[32]

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## Conflicts of interest
There are no conflicts of interest.

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