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Management of Lung Cancer during the COVID-19 Pandemic

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Management of Lung Cancer during the COVID-19 Pandemic

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Abstract

Coronavirus disease – 2019 (COVID-19) has had a devastating impact across the world. With high rates of transmission and no curative therapies or vaccine yet available, the current cornerstone of management focuses on prevention by social distancing. This includes decreased healthcare contact for patients. Patients with lung cancer are a particularly vulnerable population, where the risk of mortality from cancer must now be balanced by the potential risk of a life-threatening infection. In these unprecedented times, a collaborative and multidisciplinary approach is required to streamline, but not compromise care. We have developed guidelines at our academic cancer center to standardize management of patients with lung cancer across our healthcare system and to provide guidance to the larger oncology community. We recommend that general principles of lung cancer treatment continue to be followed for most cases where delays could result in rapid cancer progression. We recognize that our recommendations may change over time based on clinical resources and the evolving nature of the COVID-19 pandemic. In principle, however, treatment paradigms must continue to be individualized with careful consideration of risks and benefits of continuing or altering lung cancer-directed therapy.

Introduction

Coronavirus disease – 2019 (COVID-19), the disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic on March 11, 2020 after it was first reported in Wuhan, China, in December 2019.
As of April 15, 2020, there have been nearly 2 million confirmed cases of COVID-19 and over 123,000 attributable deaths worldwide\(^1\). Clinical presentation can range from minimal symptoms, fever, fatigue, anosmia and shortness of breath to multi-organ and respiratory failure requiring mechanical ventilation. Although several drugs are under active investigation, no established treatment exists for the disease other than supportive care and preventive strategies. Since SARS-CoV-2 spreads primarily via droplets, the most important preventative measures are physical distancing and limiting person-to-person contact. Given the rapid and high transmissibility\(^2\), this pandemic has overwhelmed the health-care systems of many countries including the United States\(^3\).

Early reports from China and Italy indicate that patients with cancer might be more susceptible to COVID-19 and have inferior outcomes compared to patients without cancer. In a study of 355 deaths attributable to COVID-19 in Italy, 20% had active cancer\(^4\). Of 1590 hospitalized patient cases of COVID-19 in a study from China, 18 patients (1%) had cancer, higher than the 0.29% incidence of cancer in the overall population\(^5\). Patients with cancer had much higher morbidity and mortality as defined by a composite end point of intensive care unit (ICU) admissions or ventilator requirement and death (39% vs. 8%, \(p=0.0003\))\(^5\). Patients with cancer who received anti-tumor therapy including surgery, radiation, chemotherapy, immunotherapy or targeted therapy in the 14 days prior to SARS-CoV-2 infection, seemed to have worse outcomes\(^6\).

Although the long-term impact of SARS-CoV-2 infection on cancer outcomes is unknown, there are certain populations that might be more susceptible than
others. Patients with lung cancer represent one such particularly vulnerable group due a relatively older age at presentation, presence of baseline compromise in pulmonary function and other co-morbidities. To make matters more challenging, patients with lung cancer often have symptoms that overlap with COVID-19 (e.g., cough and shortness of breath), potentially causing a delay in diagnosis. Finally, radiographic findings of COVID-19 may be indistinguishable from pneumonitis caused by lung cancer therapeutics including immunotherapy, radiation and oral tyrosine kinase inhibitors.7

The current challenge in treating patients with lung cancer is the need to balance the risk of a potentially life-threatening infection with COVID-19, against the dire consequences of delaying or not treating a life-threatening malignancy. Regional data on community spread, testing capabilities, resource availability (including personnel, personal protective equipment, operating room/infusion room space and critical care resources), and the ability to deliver treatments safely have to be factored into decision-making. While we have extensive treatment guidelines for the standard management of lung cancer from multiple sources, at this critical time we may need to deviate from this standard of care as we try to balance the risk of COVID-19 and mortality from lung cancer. A multi-disciplinary collaboration is essential to develop safe and effective guidelines. Working with our colleagues, we have developed a workflow to standardize the delivery of multidisciplinary care for patients with Non-Small Cell Lung Cancer (NSCLC), Small Cell Lung Cancer (SCLC) and Neuroendocrine Tumors (NETs) during this pandemic. These guidelines are based on the following principles: 1) continue to treat lung
cancer with modern techniques and principles aligned with the most up-to-date research; 2) maximize physical distancing; and 3) apply recent advances in radiation techniques such as shorter fractionation schedules, and personalized systemic therapeutic options without sacrificing oncologic endpoints. This consensus has been achieved through multiple discussions with our team of medical and radiation oncologists, thoracic surgeons, interventional pulmonologists and radiologists and is also based, in part, on peer-reviewed literature that applies to our population of patients. Our recommendations are intended as a guide – we must continue to individualize diagnostic and therapeutic approaches for each patient especially when exceptions are made to the established standards of care.

**Diagnosis and Staging**

We recommend pursuing image-guided transthoracic biopsies for initial diagnosis of lung cancer over transbronchial approaches to minimize generation of aerosols and limit SARS-CoV-2 transmission⁸. Non-invasive mediastinal staging with imaging (CT or PET) is preferred where possible and if invasive testing is felt to be essential, mediastinoscopy may, in certain circumstances, be preferred over bronchoscopy. Nodal staging via endobronchial ultrasound (EBUS) for the radiographically silent mediastinum, with no apparent involvement on CT or PET, may be omitted; and for stage III disease, where nodal disease is radiographically apparent, confirmation with EBUS may not be required ⁹. Although tissue diagnosis is still the ‘gold standard’ for diagnosis of lung cancer, if resources are extremely limited, consideration could be given to use plasma-based genotyping to direct
therapeutic care, especially if a driver mutation is detected for certain phenotypes (e.g., never-smoker, Asian, female) and the radiographic features of a lung cancer are thought to be unequivocal (e.g., spiculated lung mass), 10.

**Management of Early Stage NSCLC**

The mainstay of management of early stage (stage I or II) NSCLC remains surgical resection. The American College of Surgeons (ACS) has developed guidelines regarding thoracic surgery during COVID-1911. Recommendations are based on three phases of the pandemic. Phase I consists of few hospitalized COVID-19 patients with adequate hospital resources and ICU ventilator capacity. Phase II is many hospitalized COVID-19 patients coupled with limited ICU and ventilator capacity or when the local/regional case trajectory is on a steep upward trend. In Phase III, all hospital resources are already exhausted or being diverted to the care of COVID-19 patients. There are significant regional differences in these phases, and recommendations for management would naturally have some geographic variations.

For areas in phase I, the ACS recommends continuing surgery as planned for patients with solid or predominantly solid lung nodules > 2 cm in maximum dimension and in those with node positive disease. They also recommend continuing to perform staging mediastinoscopy and diagnostic VATS. Surgical management of predominantly ground glass nodules, solid nodules < 2 cm and indolent histology like carcinoids or slowly enlarging nodules should be deferred. Emerging evidence suggests that surgical mortality in patients with COVID-19
infection may be higher\textsuperscript{12}. Where possible, alternative therapies can be used such as stereotactic body radiation therapy (SBRT) for patients with stage I NSCLC\textsuperscript{13}. SBRT has typically been given in 45-54 Gray (Gy)/3 fractions or 48-50 Gy/4 or 5 fractions. Data from trials support the delivery 30-34 Gy/1 fraction in select patients, which has compared favorably to 3 and 4 fraction regimens and is an option to decrease exposure risks to patients, providers and support staff\textsuperscript{14} (Table 1).

For patients with NSCLC, where adjuvant chemotherapy is indicated, we recommend delaying adjuvant therapy by up to 4 months after resection based on retrospective data demonstrating similar efficacy and safety as the usual standard of care of 6-12 weeks post-surgery\textsuperscript{15}. Adjuvant therapy should be reconsidered altogether in patients who are older than 75 years (since many adjuvant chemotherapy trials explicitly excluded this sub-population and the benefits of cisplatin-based therapy in this age group may be minimal)\textsuperscript{16,17} and frail patients or those with node-negative disease where risks of chemotherapy might potentially outweigh benefits\textsuperscript{16}. Induction/neoadjuvant chemotherapy may be considered if surgery is not possible in the short term due to limited hospital or operating room (OR) capacity\textsuperscript{18} (Table 1).

**Management of Locally Advanced Non-Small Cell Lung Cancer**

Patients with locally advanced NSCLC require a multi-disciplinary approach and should be treated with curative intent. For patients where tri-modality therapy is an option (younger patients who may be a lobectomy candidate with no significant comorbidities and single station non-bulky mediastinal involvement), we
recommend induction chemotherapy alone followed by surgery and post-operative radiation therapy over concurrent chemo-radiation followed by surgery. Hospital resources, including access to OR, and ventilators must be taken into account during decision-making. For patients with more advanced unresectable disease, we recommend that they receive concurrent chemo-radiation followed by immunotherapy with durvalumab for up to one 1 year. For concurrent chemo-radiation, to minimize patient exposure we recommend the use of an every three-week platinum-based regimen over a weekly schedule. In frail patients or those with major co-morbidities, we prefer sequential chemotherapy with growth factor support followed by radiation instead of concurrent chemo-radiation. Typical radiation doses are 60-66 Gy/30-33 fractions when given concurrently with chemotherapy. Several studies over the past 5 years have investigated hypofractionation schemes, such as 60 Gy/24 fractions or 55 Gy/20 fractions with concurrent chemotherapy or up to 60 Gy in 15 fractions when delivered sequentially with chemotherapy; these schemes have shown both safety and comparable 2-year survival rates versus more standard radiotherapeutic approaches and should be incorporated where feasible. Consolidation chemotherapy should not be given after concurrent chemo-radiation, particularly since there is no documented survival benefit in the era of immunotherapy.

We also recommend delaying consolidation immunotherapy for up to 6 weeks after completion of chemo-radiation where deemed appropriate in relation to timing of the COVID-19 surge. If feasible, immunotherapy should be initiated as
early as possible for optimal outcomes although emerging data suggests that
delaying consolidation up to 8 weeks may be as efficacious\textsuperscript{26, 27}(Table 1).

**Management of Metastatic Non-Small Cell Lung Cancer**

During this unprecedented crisis, it is important to emphasize that
management of metastatic non-small cell lung cancer (mNSCLC) should still follow
the principles of providing the best possible care and palliative management of our
patients with an effort to improve overall survival and maintain quality of life.
Especially for patients with mNSCLC, there is a fine line between providing
incremental benefit in overall survival versus exposing patients to risks of infection
and worse outcomes if they were to become infected with SARS-CoV-2.

All patients with metastatic non-squamous NSCLC regardless of smoking
history and all never-smokers, light smokers (< 10 pack years) or remote former
smokers regardless of histology should be tested for molecular alterations upon
initial diagnosis. If biopsy samples are limited, use of plasma based next-generation
gene sequencing should be incorporated to increase the likelihood of detecting
actionable mutations\textsuperscript{28}. If an actionable mutation is detected, patients should be
treated with the appropriate targeted therapy\textsuperscript{29}. At this time, in the absence of
targetable mutations, we still recommend obtaining PD-L1 testing, and making
treatment decisions in the first-line setting based on PD-L1 testing. Patients should
receive induction chemo-immunotherapy or immunotherapy at the currently
recommended treatment intervals as the anticipated benefit outweighs the potential
risk\textsuperscript{30-32}. 
While immunotherapy infusions are generally dosed every 3-4 weeks, there are compelling data from pharmacokinetic modeling that shows that less frequent intervals of immunotherapy may be associated with similar efficacy, safety, and benefit-risk profile\textsuperscript{33,34}. Keeping these data in mind, consideration should be made to space out immunotherapy intervals as appropriate. This may be especially relevant for patients with mNSCLC who have been on therapy for > 6 – 12 months, and have ongoing sustained clinical benefit from therapy. For patients who have been on immunotherapy for greater than 2 years, further therapy should be stopped in line with currently available data\textsuperscript{31,35}. Home infusion options, including delivery of immunotherapy with home nursing services coupled with telemedicine visits, warrant further exploration.

The use of oral tyrosine kinase inhibitors (TKIs) as the preferred agents managing mNSCLC bearing oncogenic driver mutations should continue, as the risks of adverse events due to these drugs in the setting of the COVID19 pandemic are either yet unknown or minimal (Table 1).

For patients with respiratory symptoms and imaging concerning for immunotherapy/TKI or radiation pneumonitis, COVID-19 should be strongly considered in the differential diagnosis. This could pose a diagnostic challenge; although typical CT findings in COVID-19 are bilateral, multifocal rounded and peripheral ground glass opacities (GGOs), atypical findings of patchy GGOs in a non-specific pattern may be difficult to distinguish from TKI or immunotherapy related drug toxicity\textsuperscript{36,37}. This situation can also pose a therapeutic dilemma; whereas the mainstay of treatment for immunotherapy/radiation/TKI pneumonitis is high dose
corticosteroids, steroids are not recommended in COVID-19 infections due to concern regarding delayed viral clearance. In addition to a careful history of symptoms such as fever and possible sick contacts, rapid COVID-19 testing in this situation is essential and may prove invaluable.

Patients with an established clinical response to cancer therapy that are not exhibiting any signs or symptoms of tumor progression may defer routine restaging scans. When the likely benefit of additional palliative systemic therapy is very small, particularly in the third line setting, patients and providers may conclude that the risks of treatment outweigh the possible gains in outcome. A goals of care discussion and shared decision-making at that point is imperative.

**Management of Small Cell Lung Cancer**

Small-cell lung cancer (SCLC) is an aggressive malignancy, which needs to be treated expeditiously for the best outcomes. Treatment of SCLC can be extremely challenging due to the often-significant myelosuppression associated with chemotherapy and the need for concurrent radiation therapy in limited stage patients.

For limited stage SCLC, we recommend prompt initiation of concurrent chemo-radiation as standard of care, whenever feasible. Starting radiation with cycle 2 is standard of care and could delay frequent hospital visits and myelosuppression by a few weeks. Even though twice a day radiotherapy is infrequently used in current practice, it should be used wherever feasible to minimize the duration of radiation therapy. Prophylactic Cranial Irradiation (PCI)
should still be the standard in patients with limited stage SCLC under the age of 75 years who have completed chemo-radiation without disease progression.

For extensive stage SCLC, chemo-immunotherapy should be administered as the current standard of care\textsuperscript{35,40} in eligible patients. Oral etoposide can be used on days 2 and day 3 of the chemotherapy cycles to minimize exposure, as well as contact with healthcare workers and facilities. After the completion of the first four cycles of induction chemo-immunotherapy, a q4-week regimen of immunotherapy should be used, with durvalumab at 1500 mg IV, which has recently been approved by the FDA\textsuperscript{35}, or atezolizumab, at the 1680 mg IV dose every 4 weeks\textsuperscript{33}.

Since there are limited data supporting efficacy of PCI in patients with extensive stage SCLC\textsuperscript{41,42}, PCI should be deferred and surveillance imaging used instead. Discussions regarding consolidative radiation therapy to the mediastinum\textsuperscript{43} should continue on a case-by-case basis in the multidisciplinary setting based on responsiveness to chemo-immunotherapy and both initial and current extent of disease (Table 2).

Management of well-differentiated lung neuroendocrine tumors (NETs)

For early stage well-differentiated lung NETs, surgery may be deferred by several weeks\textsuperscript{11}. For patients that have undergone resection, adjuvant therapy should be avoided, particularly in patients without adverse histological features (e.g., positive margins, gross residual disease, extensive necrosis or high Ki67) given lack of data supporting its utility in this disease\textsuperscript{44,45}. For patients with advanced or metastatic disease on maintenance somatostatin analogs (SSAs), with no history of
carcinoid syndrome, this treatment can be delayed by a few weeks if minimally symptomatic. For patients on SSAs, home injections are ideal, if available.

**Other general principles**

Growth factor support for regimens with concern for neutropenia should continue. The National Comprehensive Cancer Network (NCCN) guidelines were expanded recently to include support for regimens with intermediate risk of myelosuppression. These guidelines caution regarding use in cases of suspected or confirmed COVID-19 disease due to the potential of an increased risk of pulmonary inflammation or hypothetical risk of increasing inflammatory cytokines associated with adverse outcome\textsuperscript{46}. Telemedicine should be utilized (with phone and or video capability) to reduce the risk of transmission of SARS-CoV-2 to patients and providers\textsuperscript{47,48}. Routine follow-up surveillance imaging can be deferred/delayed by 3-6 months; patient reported outcomes coupled with symptom assessment can be used to dictate scan frequency \textsuperscript{49}. Interventions that alleviate severe symptoms should remain a high priority. When using palliative radiation therapy, hypofractionation should be the considered with single fraction regimens for bone metastases (8-24 Gy/1 fraction), and spinal cord compression or 2 fraction regimens for airway obstruction (17 Gy/ 2 fractions)\textsuperscript{50}. Bone modifying treatments (intravenous bisphosphonates or denosumab) can be deferred in patients without hypercalcemia or active, symptomatic bone invasion.

Ensuring that patients receive care that is consistent with their goals and values must remain a critical component of our practice. Priority should be given to
patients’ wishes about resuscitation, ventilator support and overall goals of care. This issue is all the more acute in the current setting, where patients are at risk for pulmonary compromise not only from their cancer but also from potential of COVID-19 and the interaction between these factors likely places patients with lung cancer at exceptional risk for poor outcomes even with maximal supportive measures such as intensive care and mechanical ventilation. Guides such as those developed by the Ariadne Labs can be used to aid these crucial conversations\textsuperscript{51}.

It is also important to note that clinical trial enrollment has been adversely affected during this pandemic; many clinical trials have been halted or suspended for accrual at several institutions. Enrollment on clinical trials should still continue, if feasible, especially in the absence of standard of care therapeutic options. Institutional efforts must be directed to create databases for lung cancer patients with and without COVID-19, so that their outcomes can be analyzed in a longitudinal manner.

Now that we are fully in the midst of the COVID-19 pandemic, the question often arises how to proceed with patients that may present with symptoms, or may have been in contact with a person who has tested positive for COVID-19. At our center, all patients with lung cancer are screened with a simple questionnaire (Supplementary Table 1), which includes travel history and an inventory of current relevant symptoms (Figure 1). For patients who screen positive, or those with concerning symptoms, we recommend testing for COVID-19 either at a drive-through facility (if stable) or management in the emergency room for patients with more severe clinical symptoms. Management decisions regarding systemic therapy
for their lung cancer are then based on COVID-19 test results. Individual patients do not necessarily need testing prior to initiation of systemic therapy although the availability of rapid point of care testing may change our approach. Whether to defer oral targeted agents in patients with either suspected COVID19 symptoms or are under COVID19 investigation is an area of medical uncertainty, and clinical judgment must be exercised to make those nuanced therapeutic decisions.

**Conclusion**

The COVID-19 pandemic has created a generational crisis, and an unprecedented strain on healthcare resources and our ability to deliver high quality seamless care for patients with lung cancer. Management of patients with lung cancer has always required a highly integrated and multidisciplinary approach. In this article, we present guidance and offer insight on suggested best practices for lung cancer management from a large tertiary academic medical center. It is critical for physicians to understand the rapidly changing local conditions and available resources as well as risks/benefits of various treatments and their implications for patients, staff and hospital systems. The basic tenets of cancer care delivery and coordination should be followed as much as possible during the COVID-19 pandemic.
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### Table 1. Management recommendations and additional considerations for patients with NSCLC by stage of disease

<table>
<thead>
<tr>
<th>STAGE</th>
<th>RECOMMENDATIONS</th>
<th>ADDITIONAL CONSIDERATIONS</th>
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<tbody>
<tr>
<td>STAGE I</td>
<td>Defer surgery for lung nodules &lt; 2cm, GGO, carcinoid tumors</td>
<td>Consider SBRT/ Ablation</td>
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<td></td>
<td>Follow ACS guidelines, and decisions must be based on institutional resources</td>
<td></td>
</tr>
<tr>
<td>STAGE II/III</td>
<td>Delay adjuvant chemotherapy to 3-4 months post-operatively</td>
<td>Consider withholding adjuvant chemotherapy for patients &gt; 75 years of age or with significant comorbidity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider Neo-adjuvant/ Induction if surgery not immediately feasible.</td>
</tr>
<tr>
<td>STAGE III</td>
<td>Delay start of consolidation durvalumab up to 6 weeks from completion of concurrent Chemo Radiation</td>
<td>Consider delaying start of concurrent Chemo Radiation on case-by-case basis, discuss with Radiation Oncology about sequential chemotherapy followed by Concurrent Chemo Radiation</td>
</tr>
<tr>
<td></td>
<td>Hypo-fractionated RT schedules should be used with concurrent chemotherapy, when feasible</td>
<td>Consider using Q3W chemotherapy regimens, instead of QW chemotherapy to minimize exposure</td>
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<tr>
<td></td>
<td>No consolidation chemotherapy should be administered after completion of concurrent Chemo Radiation</td>
<td></td>
</tr>
<tr>
<td>STAGE IV</td>
<td>After initial induction chemo-immunotherapy, consideration should be made to space out interval between maintenance infusions, especially for those who have been on therapy for &gt; 6 months and those with an excellent clinical/ radiographic response</td>
<td>For patients on TKI: Do not routinely hold TKI for Covid-19 positive patients unless symptomatic</td>
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<td></td>
<td>Stop immunotherapy for patients who have completed 2 years of treatment</td>
<td>If symptomatic and concern for pneumonitis, advise testing for Covid-19 before making a decision about stopping therapy</td>
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Abbreviations: GGO: ground glass nodules, ACS: American College of Surgeons, SBRT: Stereotactic Body Radiation Therapy, TKI: Tyrosine Kinase Inhibitor
Table 2. Management recommendations and additional considerations for patients with SCLC by stage of disease

<table>
<thead>
<tr>
<th>STAGE</th>
<th>RECOMMENDATIONS</th>
<th>ADDITIONAL CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS-SCLC</td>
<td>Continue with therapy as planned</td>
<td>Consider BID Radiation Therapy to minimize duration and exposure. Start Radiation Therapy with cycle 2 of chemotherapy. PCI should be recommended for patients &lt; 75 years of age.</td>
</tr>
<tr>
<td>ES-SCLC</td>
<td>Use oral instead of intravenous etoposide on days 1-3 of chemotherapy. After induction chemo-immunotherapy, maintenance immunotherapy should be dosed Q4W (atezolizumab 1680 mg or durvalumab 1500 mg IV).</td>
<td>Consider oral therapies such as PO temozolomide or PO topotecan for second line platinum resistant, refractory SCLC. Refrain from PCI in consultation with radiation oncology.</td>
</tr>
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Abbreviations: BID: Twice Daily, PO: Oral, IV: Intravenous, PCI: Prophylactic Cranial Irradiation

Supplementary Table 1. Screening Questionnaire used at UPHS

<table>
<thead>
<tr>
<th>TRAVEL HISTORY OR CONTACT</th>
<th>Travel Outside the US or to the NYC Metro Area in the past 2 weeks. Contact with a Person Under Investigation. COVID-19 Testing Pending.</th>
</tr>
</thead>
</table>

Abbreviations: UPHS: University of Pennsylvania Health System
Figure 1. Algorithm for treating patients with Lung Cancer during the COVID-19 pandemic. *Screening Questionnaire detailed in Supplemental Table 1, ** Drive through testing preferred (if available) for stable patients, in-hospital evaluation for patients with severe symptoms or hypoxia.