care delivery reviews

Management of Lung Cancer During the COVID-19 Pandemic

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abstract

Coronavirus disease 2019 (COVID-19) has had a devastating impact around 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 health care 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 health care system and provide guidance to the larger oncology community. We recommend that general principles of lung cancer treatment continue to be followed in 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.

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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,[1] 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 > 123,000 attributable deaths worldwide.[1] Clinical presentation can range from minimal symptoms, fever, fatigue, anosmia, and shortness of breath to multiorgan 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. Because SARS-CoV-2 spreads primarily via droplets, the most important preventative measures are physical distancing and limitation of 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 with patients without cancer. In a study of 355 deaths attributable to COVID-19 in Italy, 20% had active cancer.[4] Of 1,590 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% *v* 8%; $P = .0003$).[5] Patients with cancer who had received antitumor therapy, including surgery, radiotherapy, chemotherapy, immunotherapy, or targeted therapy, in the 14 days before 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 because of a relatively older age at presentation, presence of baseline compromise in pulmonary function, and other comorbidities. To make matters more challenging, patients with lung cancer often have symptoms that overlap with COVID-19 (eg, cough and shortness of

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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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, radiotherapy, and oral tyrosine kinase inhibitors (TKIs).[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 (OR)/infusion room space, and critical care resources), and ability to deliver treatment safely must be factored into decision making. Although 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. Multidisciplinary 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 lung neuroendocrine tumors (NETs) during this pandemic. These guidelines are based on the following principles: continue to treat lung cancer with modern techniques and principles aligned with the most up-to-date research; maximize physical distancing; and apply recent advances in radiotherapy techniques, such as shorter fractionation schedules, and personalized systemic therapeutic options without sacrificing oncologic end points. This consensus was achieved through multiple discussions with our team of medical and radiation oncologists, thoracic surgeons, interventional pulmonologists, and radiologists and 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 transmission.[8] Noninvasive mediastinal staging with imaging (computed tomography [CT] or positron emission tomography [PET]) is preferred where possible, and if invasive testing is felt to be essential, mediastinoscopy may be preferred over bronchoscopy in certain circumstances. 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, use of plasma-based genotyping to direct therapeutic care may be considered, especially if a driver mutation is detected for certain phenotypes (eg, never-smoker, Asian, female) and the radiographic features of lung cancer are thought to be unequivocal (eg, 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-19.[11] Recommendations are based on 3 phases of the pandemic. Phase 1 consists of few hospitalized patients with COVID-19 with adequate hospital resources and ICU ventilator capacity. Phase 2 involves many hospitalized patients with COVID-19 coupled with limited ICU and ventilator capacity or a steep upward trend in the locoregional case trajectory. In phase 3, all hospital resources are already exhausted or being diverted to the care of patients with COVID-19. There are significant regional differences in these phases, and recommendations for management would naturally have some geographic variations.

For areas in phase 1, 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. It also recommends continuing to perform staging mediastinoscopy and diagnostic video-assisted thoracoscopic surgery. 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.[12] Where possible, alternative therapies can be used, such as stereotactic body radiation therapy (SBRT) for patients with stage I NSCLC.[13] SBRT has typically been administered at 45 to 54 Gy in 3 fractions or 48 to 50 Gy in 4 or 5 fractions. Data from trials support the delivery of 30 to 34 Gy in 1 fraction in select patients, an approach that has compared favorably to 3- and 4-fraction regimens and is an option to decrease exposure risks to patients, providers, and support staff[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 efficacy and safety similar to those of the usual standard of care of 6 to 12 weeks postsurgery.[15] Adjuvant therapy should be reconsidered altogether in patients who are age > 75 years (because many adjuvant chemotherapy trials have explicitly excluded this subpopulation, and the benefits of cisplatin-based therapy in

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TABLE 1. Management Recommendations and Additional Considerations for Patients With NSCLC by Stage of Disease

Stage	Recommendation	Additional Consideration
I	Defer surgery for lung nodules < 2 cm, GGOs, carcinoid tumors	Consider SBRT/ablation
	Follow ACS guidelines; decisions must be based on institutional resources	
II/III	Delay adjuvant chemotherapy 3-4 months postoperatively	Consider withholding adjuvant chemotherapy for patients age > 75 years or with significant comorbidities
		Consider neoadjuvant/induction therapy if surgery not immediately feasible
III	Delay start of consolidation durvalumab up to 6 weeks from completion of concurrent chemoradiotherapy	Consider delaying start of concurrent chemoradiotherapy on case-by-case basis; discuss with radiation oncology the possibility of sequential chemotherapy followed by concurrent chemoradiotherapy
	Hypofractionated radiotherapy schedules should be used with concurrent chemotherapy, when feasible	Consider using once-every-3-week chemotherapy regimens, instead of weekly chemotherapy, to minimize exposure
	No consolidation chemotherapy should be administered after completion of concurrent chemoradiotherapy	
IV	After initial induction chemoimmunotherapy, consideration should be made to space intervals between maintenance infusions, especially for those who have been receiving therapy for > 6 months and those with excellent clinical/radiographic response	In patients receiving TKIs, do not routinely hold TKIs for COVID-19–positive patients unless symptomatic
	Stop immunotherapy for patients who have completed 2 years of treatment	If patients are symptomatic and there is concern for pneumonitis, advise testing for COVID-19 before making decision about stopping therapy

Abbreviations: ACS, American College of Surgeons; GGO, ground-glass opacity; NSCLC, non–small-cell lung cancer; SBRT, stereotactic body radiotherapy; TKI, tyrosine kinase inhibitor.

this age group may be minimal),[16,17] frail patients, or those with node-negative disease, in whom risks of chemotherapy might potentially outweigh benefits.[16] Induction/neoadjuvant chemotherapy may be considered if surgery is not possible in the short term because of limited hospital or OR capacity[18] (Table 1).

MANAGEMENT OF LOCALLY ADVANCED NSCLC

Patients with locally advanced NSCLC require a multidisciplinary approach and should be treated with curative intent. For patients in whom trimodality therapy is an option (eg, younger patients who may be lobectomy candidates with no significant comorbidities and single-station non-bulky mediastinal involvement), we recommend induction chemotherapy alone followed by surgery and postoperative radiotherapy over concurrent chemoradiotherapy followed by surgery. Hospital resources, including access to the OR and ventilators, must be taken into account during decision making. For patients with more advanced unresectable disease, we recommend concurrent chemoradiotherapy followed by immunotherapy with durvalumab for up to 1 year.[19] For concurrent chemoradiotherapy, to minimize patient exposure, we recommend the use of a platinum-based regimen administered once every 3 weeks over a weekly schedule.[20] In frail patients or those with major comorbidities, we prefer sequential chemotherapy with growth factor support followed by radiotherapy instead of concurrent chemoradiotherapy. Typical radiation doses are 60 to 66 Gy in 30 to 33 fractions when administered concurrently with chemotherapy. Several studies over the past 5 years have investigated hypofractionation schemes, such as 60 Gy in 24 fractions or 55 Gy in 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.[21-23] Consolidation chemotherapy should not be administered after concurrent chemoradiotherapy, particularly because there is no documented survival benefit in the era of immunotherapy.[24]

We also recommend delaying consolidation immunotherapy for up to 6 weeks after completion of chemoradiotherapy where deemed appropriate in relation to timing of the COVID-19 surge.[19,25] If feasible, immunotherapy should be initiated as early as possible for optimal outcomes, although emerging data suggest that delaying consolidation up to 8 weeks may be as efficacious[26,27] (Table 1).

MANAGEMENT OF METASTATIC NSCLC

During this unprecedented crisis, it is important to emphasize that management of metastatic NSCLC (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

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exposing patients to risks of infection or worse outcomes if they were to become infected with SARS-CoV-2.

All patients with nonsquamous mNSCLC 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.[28] If an actionable mutation is detected, patients should be treated with the appropriate targeted therapy.[29] At this time, in the absence of targetable mutations, we still recommend obtaining programmed death-1 ligand (PD-L1) testing and making treatment decisions in the first-line setting based on PD-L1 testing. Patients should receive induction chemoimmunotherapy or immunotherapy at the currently recommended treatment intervals, because the anticipated benefit outweighs the potential risk.[30-32]

Although immunotherapy infusions are generally dosed every 3 to 4 weeks, there are compelling data from pharmacokinetic modeling that show that less frequent intervals of immunotherapy may be associated with similar efficacy, safety, and benefit-risk profile.[33,34] Keeping these data in mind, consideration should be made to space immunotherapy intervals as appropriate. This may be especially relevant for patients with mNSCLC who have been receiving therapy for > 6 to 12 months and have ongoing sustained clinical benefit from therapy. For patients who have been receiving immunotherapy for > 2 years, further therapy should be stopped in line with currently available data.[31,35] Home infusion options, including delivery of immunotherapy with home nursing services coupled with telemedicine visits, warrant further exploration.

The use of oral TKIs as the preferred agents in managing mNSCLC bearing oncogenic driver mutations should continue, because the risk of adverse events resulting from these drugs in the setting of the COVID-19 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) and atypical findings of patchy GGOs in a nonspecific pattern may be difficult to distinguish from TKI- or immunotherapy-related drug toxicity.[36,37] This situation can also pose a therapeutic dilemma; whereas the mainstay of treatment for immunotherapy/radiotherapy/TKI pneumonitis is high-dose corticosteroids, steroids are not recommended in COVID-19 infections because of a concern regarding delayed viral clearance.[38] 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 who 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 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 are imperative.

MANAGEMENT OF SCLC

SCLC is an aggressive malignancy, which needs to be treated expeditiously for the best outcomes. Treatment of SCLC can be extremely challenging because of the often-significant myelosuppression associated with chemotherapy and the need for concurrent radiotherapy in patients with limited-stage disease.

For limited-stage SCLC, we recommend prompt initiation of concurrent chemoradiotherapy as standard of care, whenever feasible. Starting radiotherapy with cycle 2 is standard of care and could delay frequent hospital visits and myelosuppression by a few weeks. Even though twice-per-day radiotherapy is infrequently used in current practice,[39] it should be used wherever feasible to minimize the duration of radiotherapy. Prophylactic cranial irradiation (PCI) should remain the standard in patients with limited-stage SCLC age < 75 years who have completed chemoradiotherapy without disease progression.

For extensive-stage SCLC, chemoimmunotherapy should be administered as the current standard of care[35,40] in eligible patients. Oral etoposide can be used on days 2 and 3 of the chemotherapy cycles to minimize exposure, as well as contact with health care workers and facilities. After the completion of the first 4 cycles of induction chemoimmunotherapy, a regimen of immunotherapy administered once every 4 weeks should be used, with 1,500 mg of intravenous (IV) durvalumab, which has recently been approved by the US Food and Drug Administration,[35] or 1,680 mg of IV atezolizumab every 4 weeks.[33]

Because there are limited data supporting the efficacy of PCI in patients with extensive-stage SCLC,[41,42] PCI should be deferred and surveillance imaging used instead. Discussions regarding consolidative radiotherapy to the mediastinum[43] should continue on a case-by-case basis in the multidisciplinary setting based on responsiveness to chemoimmunotherapy and both initial and current extents of disease (Table 2).

MANAGEMENT OF WELL-DIFFERENTIATED LUNG NETS

For early-stage well-differentiated lung NETs, surgery may be deferred for several weeks.[11] For patients who have undergone resection, adjuvant therapy should be avoided, particularly in patients without adverse histologic features (eg, positive margins, gross residual disease, extensive

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TABLE 2. Management Recommendations and Additional Considerations for Patients With SCLC by Stage of Disease

Stage	Recommendation	Additional Consideration
Limited	Continue with therapy as planned	Consider twice-per-day radiotherapy to minimize duration and exposure
		Start radiotherapy with cycle 2 of chemotherapy
		PCI should be recommended for patients age < 75 years
Extensive	Use oral versus IV etoposide on days 2-3 of chemotherapy after induction chemoimmunotherapy; maintenance immunotherapy should be dosed once every 4 weeks (atezolizumab 1,680 mg or durvalumab 1,500 mg IV)	Consider oral therapies such as temozolomide or topotecan for second-line treatment of platinum-resistant/refractory SCLC
		Refrain from PCI in consultation with radiation oncology

Abbreviations: IV, intravenous; PCI, prophylactic cranial irradiation; SCLC, small-cell lung cancer.

necrosis, or high Ki67), given the lack of data supporting its utility in this disease.[44,45] For patients with advanced or metastatic disease receiving maintenance somatostatin analogs (SSAs), with no history of carcinoid syndrome, this treatment can be delayed by a few weeks if minimally symptomatic. For patients receiving SSAs, home injections are ideal, if available.

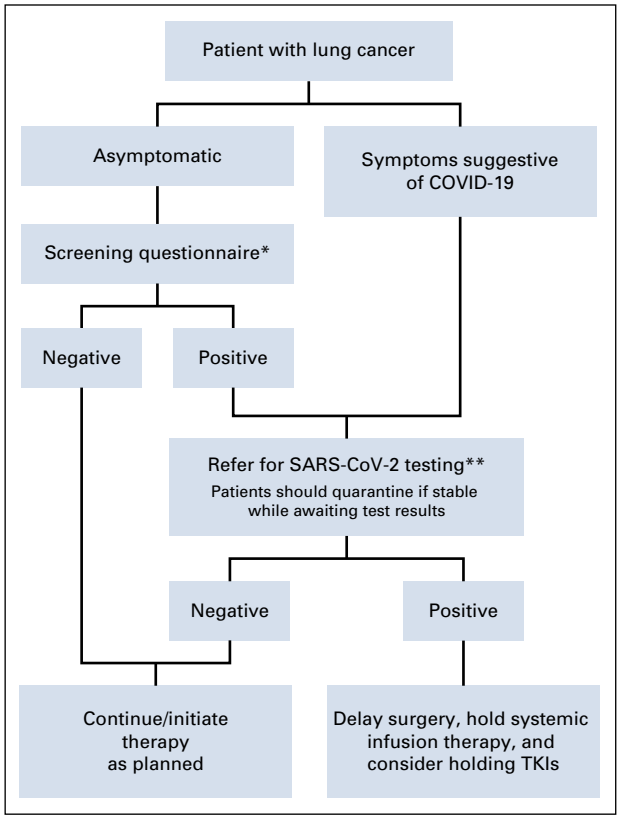

FIG 1. Algorithm for treating patients with lung cancer during the COVID-19 pandemic. TKI, tyrosine kinase inhibitor. (*) Screening questionnaire detailed in Appendix Table 1 (online only). (**) Drive-through testing preferred (if available) for stable patients; in-hospital evaluation should be performed for patients with severe symptoms or hypoxia.

OTHER GENERAL PRINCIPLES

Growth factor support for regimens with concern for neutropenia should continue. The National Comprehensive Cancer Network guidelines were expanded recently to include support for regimens with intermediate risk of myelosuppression. These guidelines caution against use in cases of suspected or confirmed COVID-19 disease because of a potential increased risk of pulmonary inflammation or hypothetic risk of increasing inflammatory cytokines associated with adverse outcomes.[46] Telemedicine should be used (with telephone and or video capability) to reduce the risk of transmission of SARS-CoV-2 to patients and providers.[47,48] Routine follow-up surveillance imaging can be deferred/delayed by 3 to 6 months; patient-reported outcomes coupled with symptom assessment can be used to dictate scan frequency.[49] Interventions that alleviate severe symptoms should remain a high priority. When using palliative radiotherapy, hypofractionation should be the considered with single-fraction regimens for bone metastases (8-24 Gy in 1 fraction) and spinal cord compression or 2-fraction regimens for airway obstruction (17 Gy in 2 fractions).[50] Bone-modifying treatments (IV 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 infection, 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 Ariadne Laboratories can be used to aid in these crucial conversations.[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

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several institutions. Enrollment in 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 patients with lung cancer with and without COVID-19, so 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 of how to proceed with patients who 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 (Appendix Table A1, online only), which includes travel history and an inventory of current relevant symptoms (Fig 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 via 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 before 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 suspected COVID-19 symptoms or those who are under COVID-19 investigation is an area of medical uncertainty, and clinical judgment must be exercised to make such nuanced therapeutic decisions.

In conclusion, the COVID-19 pandemic has created a generational crisis and placed an unprecedented strain on health care 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 regarding 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 and 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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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Management of Lung Cancer During the COVID-19 Pandemic

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APPENDIX

TABLE A1. Screening Questionnaire Used at UPHS

Question	Response Choice
Travel history or contact	Travel outside United States or to New York City metro area in past 2 weeks
	Contact with person under investigation
	COVID-19 testing pending
Infectious disease screening	Fever
	Headache
	Arthralgia
	Myalgia
	Cough
	Difficulty breathing
	Shortness of breath
	Abdominal pain
	Vomiting
	Hemorrhage

Abbreviation: UPHS, University of Pennsylvania Health System.

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