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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic is currently accelerating. Patients with locally advanced NSCLC (LA-NSCLC) may require treatment in locations where resources are limited, and the prevalence of infection is high. Patients with LA-NSCLC frequently present with comorbidities that increase the risk of severe morbidity and mortality from COVID-19. These risks may be further increased by treatments for LA-NSCLC. Although guiding data is scarce, we present an expert thoracic oncology multidisciplinary (radiation oncology, medical oncology, surgical oncology) consensus of alternative strategies for the treatment of LA-NSCLC during a pandemic. The overarching goals of these approaches are the following: (1) reduce the number of visits to a health care facility, (2) reduce the risk of exposure to severe acute respiratory syndrome-coronavirus-2, (3) attenuate the immunocompromising effects of lung cancer therapies, and (4) provide effective oncologic therapy. Patients with resectable disease can be treated with definitive nonoperative management if surgical resources are limited or the risks of perioperative care are high. Nonoperative options include chemotherapy, chemoinmunotherapy, and radiation therapy with sequential schedules that may or may not affect long-term outcomes in an era in which immunotherapy is available. The order of treatments may be on the basis of patient factors and clinical resources. Whenever radiation therapy
is delivered without concurrent chemotherapy, hypofractionated schedules are appropriate. For patients who are confirmed to have COVID-19, usually, cancer therapies may be withheld until symptoms have resolved with negative viral test results. The risk of severe treatment-related morbidity and mortality is increased for patients undergoing treatment for LA-NSCLC during the COVID-19 pandemic. Adapting alternative treatment strategies as quickly as possible may save lives and should be implemented through communication with the multidisciplinary cancer team.

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Keywords: Non–small cell lung cancer; Locally advanced; COVID; SARS–CoV-2

Introduction

The novel betacoronavirus severe acute respiratory syndrome–coronavirus-2 (SARS–CoV-2), which causes coronavirus disease 2019 (COVID-19), has led to a global pandemic. As of this writing, over 1.8 million cases have been diagnosed in the world and the incidence continues to rise. As a result, health care facilities in many areas are becoming or have already become resource-constrained. Nevertheless, locally advanced NSCLC (LA-NSCLC) continues to be diagnosed in many patients, many of whom are symptomatic at the time of diagnosis and may suffer from the progression of their disease if initiation of treatment is delayed. Patients must be made aware that LA-NSCLC is a life-threatening disease that requires treatment; however, both workup and treatment may increase their risk of exposure to COVID-19. Cancer therapies can lead to prolonged immunocompromised states that may affect the probability of severe infection-related morbidities and mortality. Patients require multiple visits to health care facilities, putting them at high risk of COVID-19. As such, an urgent need has emerged to consider alternative management options that may save lives.

Owing to the novel nature of the SARS–CoV-2 virus, there are limited data regarding the long-term benefits or costs of modifications to the standard of care, which are made because of the risks of infection or constrained resources. Thus, the consequences of modifications to the standard of care are unknown. However, most patients with LA-NSCLC cannot wait for until data become available, or until the risk of infection has completely passed, or till resources are plentiful before treatment is started. Clinical judgment will be necessary to decide whether a modification in the standard of care is warranted.

Several organizations including the American Society of Radiation Oncology (ASTRO) and American Society of Clinical Oncology have published recommendations for cancer care during the COVID-19 pandemic. A more radiotherapy-focused addition was a consensus statement that was recently published on April 1, 2020, by the European Society of Radiation Oncology and ASTRO, which covered various clinical scenarios for lung cancer radiotherapy. The European Society of Radiation Oncology–ASTRO consensus was developed through a modified Delphi process with 32 experts in radiation oncology. Adding to this consensus statement, the report submitted herein presents a focused set of recommendations for managing LA-NSCLC that was developed by a multidisciplinary panel of 11 experts in radiation, medical, and surgical oncology from a series of virtual meetings and discussions. A summary of these recommendations can be found in Table 1.

Why Consider Alternative Treatment Strategies?

Patients with LA-NSCLC are generally of advanced age and frequently present with high-risk comorbidities that may limit their ability to survive a COVID-19 infection. The evidence for factors that contribute to COVID-19–related mortality continues to emerge and may include baseline comorbidities that are common in patients with lung cancer, including poor pulmonary reserve owing to chronic lung disease, cardiac disease, diabetes, and other diseases. Patients may also have symptoms related to lung cancer that may mask any evidence of COVID-19 and could delay detection.

Unfortunately, treatments for LA-NSCLC require numerous visits and exposures to health care facilities that increase the patient’s and health care provider’s risk of acquiring COVID-19. Surgical care may entail multiple cycles of induction chemotherapy followed by perioperative care that requires hospitalization, all of which carry a high risk of exposure to the infection for both the patient and health care staff. The standard nonoperative management is concurrent chemoradiotherapy, generally administered over 6 weeks with daily radiation, and weekly or every 3 weeks of chemotherapy followed by 12 months of durvalumab, which is delivered every 2 weeks. According to preliminary data from the People’s Republic of China and Italy, cancer, along with other comorbidities, may increase the mortality from COVID-19. However, a lot of uncertainty remains, as the observations may be the result of malignancy, treatment effects, or both. These reports were about retrospectively evaluated small cohorts that had methodologic limitations, which are to be expected during a pandemic. Yet, they provide a reason for a pause in the way we manage patients with LA-NSCLC.
during this pandemic, given the potential consequences of viral pneumonia, acute respiratory distress, and sepsis that can occur in patients undergoing treatment for LA-NSCLC. More importantly, emerging data also reveals a mortality rate of around 10% for hospitalized patients with COVID-19 and 50% mortality for those requiring intensive care unit admission.12,13

Alternative treatment strategies for patients with LA-NSCLC offer opportunities to mitigate the risk of harm by reducing patient exposure to health care facilities and the immunocompromising effects of treatment. Though there are some early theories that immunomodulation may be beneficial for those with COVID-19,14-16 immunosuppression may increase the risk of secondary infections in addition to COVID-19. These changes will likely have minimal impact on overall survival and should be weighed against the risk of death and disability from developing COVID-19, even though they are not supported by clinical trial evidence.

Pathologic Diagnosis and Nodal Staging During a Pandemic

Inevitably, an increased number of visits to health care facilities and all diagnostic procedures increase the risk of exposure to COVID-19. At this time, a pathologic diagnosis of malignancy should be sufficient to initiate treatment for LA-NSCLC. There is no evidence at this time from any study that a repeat biopsy for further subtyping or determination of a specific oncogenic mutation affects management. The decision to stage the mediastinum with bronchoscopy or mediastinoscopy should be balanced against the risk of exposure of patients and staff to COVID-19, as these procedures may increase the risk owing to aerosolization.17,18 The availability of invasive staging procedures may ultimately be limited because pulmonologists and surgeons are increasingly needed for critical care services and operating room time may be unavailable; therefore,
initiation of treatment should not be delayed just because these procedures cannot be performed in a timely manner. Nodal staging by imaging has a relatively high accuracy and can be an appropriate substitute at this time.\(^{19-21}\) Positron emission tomography (PET) with 2-deoxy-2-[fluorine-18]fluoro-D-glucose, integrated with computed tomography (CT) scans, has a high sensitivity for detection of occult regional and distant disease and can also help define treatment targets for radiation therapy planning.\(^{22}\) Acquisition of PET-CT images requires considerably more time (h) in radiology departments than contrast-enhanced CT (min), and the limitations of each should be considered. If PET-CT staging is not available, staging can be performed by CT alone through the categorization of any mediastinal lymph node larger than 1 cm on the short-axis diameter as positive, which, therefore, should be targeted by radiation therapy.\(^{23,24}\) However, patients who are staged without a PET with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with CT should be informed that CT alone is not as sensitive or specific. Ultimately, all cases with LA-NSCLC should be carefully reviewed with a radiologist for input on the malignant appearance of lymph nodes and opinions on defining radiotherapy treatment targets if nonsurgical managements are pursued. In the lack of pathologic mediastinal staging, radiation oncologists should consider targeting all hypermetabolic (or enlarged on CT scan) lymph nodes with definitive doses.

**Surgical Management**

Surgical procedure plays a key role in the treatment of patients with single-station and low-volume stage IIIA NSCLC. Surgical decisions are typically guided by careful patient-centered risk-benefit assessments; but currently, health care resource allocation and risk to the treatment team must be included in that challenging decision. The Centers for Disease Control, American College of Surgeons, and numerous other government agencies have recommended cancellation of elective surgical procedures during the global pandemic and creation of a tiered system for prioritization of other surgical procedures.\(^{25,26}\) Lung cancer resections fall into the scope of medically necessary time-sensitive procedures.\(^{27}\) For patients with LA-NSCLC who have completed induction therapy, time sensitivity is particularly crucial as the window for meaningful and safe surgical intervention typically spans over a 4- to 12-week period. Unfortunately, exposure to various risks and resource utilization for lung resections are high; they require general anesthesia, manipulation of the aerodigestive tract, and hospital stay. The decision to proceed with surgical intervention is highly dependent on the current phase of the pandemic at the treating institution. Those in the early phase in which there are still adequate health care resources (such as operating rooms, ventilators, hospital beds, surgeons, and anesthesiologists) may choose to proceed, whereas those in the later stages will have little choice but to defer planned resections. Although there is an argument that a brief operative intervention for stage I disease might only require a one- to two-night hospital stay and may have less risk of exposure and resource utilization than radiation therapy, the same does not apply for LA-NSCLC, in which the potential postinduction hilar and mediastinal fibrosis increases the risk for an open procedure (if delayed beyond the “window of opportunity”), prolonged hospital stay, and perioperative complications. Early reports regarding patients who were initially asymptomatic but manifested severe COVID-19–related complications with resultant high postoperative mortality after undergoing elective operations are sobering, and resources in most communities do not allow for preoperative screening of patients who are asymptomatic.\(^{28}\) If a surgical procedure is still to be performed, some centers recommend rapid COVID-19 testing and an immediate CT scan before the operation to look for early bilateral pulmonary infiltrates; but uniform recommendations do not currently exist. Unfortunately, the accessibility of surgical procedures for patients with lung cancer will become more limited over the coming weeks and we need to consider alternative treatment strategies. Most of these patients who would normally have surgical management of their locally advanced lung cancer may instead receive nonsurgical management owing to constrained resources and risks associated with perioperative management.\(^{29,30}\) Therefore, nonoperative management of patients with surgically resectable LA-NSCLC should be considered at this time during a pandemic.

**Nonoperative Management**

There are two key dilemmas for the nonoperative management of LA-NSCLC. The first relates to the general approach of treatment with 6 weeks of concurrent chemoradiation therapy followed by durvalumab consolidation, given every 2 weeks for an additional 12 consecutive months. The frequency and duration of these treatments could subject patients, health care providers, and other potentially immunocompromised patients with cancer to a high risk of acquiring COVID-19. The second dilemma relates to the immunocompromising effects of chemotherapy and radiation therapy, which may be increased when given concurrently 5 days a week for 6 consecutive weeks. This may increase the chance of infections, including COVID-19. Each of these dilemmas creates a high-risk
environment for a concurrent COVID-19 that will generally lead to a treatment interruption, which is known to increase mortality.\textsuperscript{31} Strategies to mitigate these risks are described below.

The use of sequential radiation and chemotherapy offers an opportunity to reduce the combined immunosuppressive effects of concurrent chemoradiotherapy, and deliver a treatment that is better tolerated but comes at a cost of longer total treatment time.\textsuperscript{32,33} Such a modification requires careful coordination between medical and radiation oncologists as this approach represents a departure from accepted standards. Although the overall survival benefits of concurrent chemoradiation versus sequential therapy have been established using randomized phase III data, the absolute benefit is modest and may be outweighed by the acute toxicities that could emerge and be more difficult to manage during the pandemic.\textsuperscript{32,34}

Whenever considering sequential therapy, the order of therapy initiation should be on the basis of clinical and situational factors, such as patient symptoms, rate of progression of the disease, overall disease burden, and available resources, among other factors. Upfront radiation therapy should be considered whenever tumors are either causing or likely to cause symptoms owing to the presence of hilar disease, bronchial or vascular compression, atelectasis, pulmonary symptoms, and pneumonia.\textsuperscript{35} Patients without these features may be best treated with upfront systemic therapy, followed by radiotherapy alone or chemoradiotherapy. Upfront systemic therapy decreases patient exposure to one visit every several weeks and postpones the initiation of daily radiation therapy treatment.

Durvalumab 10 mg/kg every 2 weeks is now routinely given after chemoradiotherapy on the basis of results of the phase III A Global Study to Assess the Effects of MEDI4736 Following Concurrent Chemoradiation in Patients With Stage III Unresectable Non-Small Cell Lung Cancer (PACIFIC) trial, which reported substantial improvement in overall survival (HR = 0.68). In that study, 25.3% of patients received induction chemotherapy followed by chemoradiation therapy before receiving durvalumab.\textsuperscript{36} Patients in the PACIFIC trial received concurrent chemoradiation, and the use of sequential chemotherapy and radiation followed by durvalumab is currently being investigated in the PACIFIC 6 trial.\textsuperscript{37} After radiotherapy and chemotherapy, durvalumab may be administered at a dose of 1500 mg every 4 weeks as this schedule has been used in other trials.\textsuperscript{38-40} Per the PACIFIC trial, durvalumab can be administered up to 6 weeks after chemoradiation.

The course of the COVID-19 pandemic is projected to peak at a certain point (i.e., days when the highest number of new cases is achieved) and then decelerate. The goal is to minimize exposure during this peak while treating patients, with daily radiation only given when there is less risk of exposure. Sequential therapy with systemic therapy followed by hypofractionated radiation may accomplish this. Patients treated with sequential therapy could be treated with a hypofractionated schedule with treatment courses as short as 3 weeks. Multiple studies have revealed such an approach to be safe and effective.\textsuperscript{41-45} Shorter courses have been associated with decreased immunosuppression in other cancers, such as leukemia and pancreatic cancer.\textsuperscript{44-46} This may offer advantages for LA-NSCLC, although the primary benefit during a pandemic is to minimize the number of encounters. Approaches employing 15- and 20-fraction schedules preceded the current pandemic and have already been reported to be safe and effective. For those who have access to a proton facility, protons can be used for hypofractionated lung radiation.\textsuperscript{47} Hypofractionated courses can be delivered with either induction or adjuvant chemotherapy or chemo-immunotherapy. Some centers are comfortable with treatment using concurrent chemotherapy and hypofractionated therapy; though other centers have concerns of increase in late toxicity. Standard chemotherapy schedules can be referenced in evidence-based guidelines, such as those found in the National Cancer Network Guidelines, with consideration of schedules that minimize the frequency of visits to a health care institution.\textsuperscript{48} Table 2 summarizes the frequently used hypofractionated schedules for locally advanced lung cancer.\textsuperscript{49-56} The use of intensity-modulated radiation therapy techniques is encouraged for hypofractionation as it can minimize the volume of normal tissues exposed to the prescription dose. Whenever normal organ dose constraints cannot be met during hypofractionated radiotherapy treatment planning, radiation oncologists should consider delivering the full prescription dose to the gross tumor volume and planning treatment volume margin while reducing the dose prescribed for the clinical treatment volume and planning treatment volume margin. This can be often achieved with intensity-modulated radiation therapy using a simultaneous integrated boost technique.\textsuperscript{57}

Regarding the definition of radiation treatment volumes, we urge our colleagues to avoid elective lymph node irradiation, which is an outdated approach to the radiotherapeutic management of LA-NSCLC.\textsuperscript{58-60} The extension of target volumes to include even one nodal stage superiorly or inferiorly increases the risk of treatment-related immunosuppression and pneumonitis that may mask early symptoms of COVID-19. If contouring nodal stations with CT alone, radiation oncologists should consider including any lymph nodes larger than 1 cm in the short axis (not greatest dimension). In
addition, daily image guidance using cone-beam CT may help assess the development of infiltrates in patients who are asymptomatic.61

If there is a preference to deliver concurrent chemoradiation, then induction chemotherapy may be considered to delay the time when patients need to come in for daily chemoradiotherapy treatments. Results from randomized phase II and III trials support such an approach after having compared chemoradiotherapy with and without induction chemotherapy, which revealed similar survival rates.62–64 Although the use of induction chemotherapy prolongs the total length of treatment, it offers an opportunity at this time to delay initiation of chemoradiotherapy, which requires daily visits at facilities that may soon be resource-constrained.

Patients Infected With COVID-19

Once a patient with LA-NSCLC contracts COVID-19, specific patient and treatment factors should be considered before the difficult decision of whether to hold or continue therapy is made. These factors include patient symptoms, status, the growth rate of NSCLC, and available resources within the health care facility, among other factors. There are currently no data that support either proceeding with or withholding treatment on the basis of COVID-19 status, presence of symptoms, or severity of symptoms. If a patient has a obstruction, hemoptysis, or other symptoms that may be alleviated by oncologic treatment, it may be necessary to treat regardless of the status of COVID-19 symptoms. This may be radiotherapy alone. The use of concurrent chemotherapy is unlikely to be of benefit given the potential for myelosuppression, esophagitis, and pneumonitis and should only be considered if reduction of a large mass is necessary to alleviate acute pulmonary compromise. However, patients with severe symptoms should not receive any cancer therapies until they recover. For patients with mild to no symptoms of COVID-19, treatment strategies such as strict personal protective equipment use for patients and staff, physical separation of infected and uninfected patients, and frequent and robust sanitation of equipment should be implemented. For all patients receiving radiotherapy, it may be ideal to provide separate waiting rooms, changing facilities, and different machines, if possible.

Treating patients with COVID-19 at the end of the day and thorough cleaning of all facilities may also limit the spread of the virus. These strategies have been described in-depth in reports from the People’s Republic of China, Italy, and the United States.65–68

Management of a patient who tests positive for COVID-19 but is asymptomatic is more difficult. They may be considered physiologically unfit to tolerate any further lung cancer therapies as many patients develop worsening symptoms in the second week of infection.69

The influence of active treatment for lung cancer on COVID-19 is unknown at this time. As such, a 1- to 2-week waiting period can help confirm whether the patient manifests any viral symptoms. Early studies have revealed that COVID-19 can lead to acute respiratory distress syndrome with pathologic changes, such as the destruction of the alveoli and cellular fibromyxoid exudates.70,71 These pathologic changes may lead to prolonged injury of lung tissue, even after clearing the viral infection. COVID-19 can also lead to an increase in inflammatory biomarkers, which have been correlated with the severity of morbidity.72 Similarly, serum inflammatory cytokines have been shown to be predictive of both thoracic toxicity and survival after thoracic radiotherapy.73–77 Although these data raise concerns, we are not entirely sure how they can manifest in patients with COVID-19 as data on this pandemic are still emerging, and the degree of morbidity seen has been variable. For some patients, the effects of the virus and lung cancer therapies may simultaneously damage pulmonary tissue and increase the chance of pneumonitis. At the same time, these risks should be carefully weighed to avoid treatment delays or interruptions whenever possible, given that improperly treated lung cancer can lead to worse oncologic outcomes.31 Given the lack of actual clinical data, a reasonable approach would be to retest patients with asymptomatic or minimally symptomatic COVID-19 in 14 days and initiate therapy if they are both asymptomatic and have negative results. If a patient becomes symptomatic and tests positive during concurrent or sequential chemoradiotherapy, it is probably appropriate to temporarily halt treatment and wait until the resolution of symptoms owing to COVID-19. In the event of hospitalization, the treating oncologic team must be in communication with

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**Table 2. Frequently Used Hypofractionated Radiation Therapy Schedules for LA-NSCLC**

| Total Dose, Gy | Number of Fractions | Dose Per Fraction, Gy | Biologically Effective Dose, Gy, (α/β Ratio = 10) | References |
|---------------|---------------------|----------------------|-----------------------------------------------|------------|
| 60            | 15                  | 4                    | 84                                            | 49-51      |
| 60            | 20                  | 3                    | 78                                            | 52,53      |
| 55            | 20                  | 2.75                 | 70                                            | 54-56      |

LA-NSCLC, locally advanced NSCLC.
the inpatient team regarding the possibility of confusing radiologic findings of radiation pneumonitis, immunotherapy pneumonitis, and COVID-19. Resumption of treatment after recovery from symptomatic COVID-19 is likely to be very difficult given the severe impairment experienced by many patients.

For patients with COVID-19, the clinical focus should include aggressive and supportive care with the consultation of infectious disease and critical care specialists and possible enrollment into clinical trials directed at COVID-19. These efforts can help restart cancer therapy as soon as possible. It is important to emphasize that the challenges of managing patients with COVID-19 are best avoided by the previously recommended strategies to prevent an infection in the first place.

Preserving Effective Communication and a Multidisciplinary Approach

Communication must be frequent with all health care providers who may be unfamiliar with any of the recommended alternative treatment approaches. Clinicians should have heightened awareness about the importance of careful and thorough documentation, especially if cross-coverage is needed in case of an unexpected event. Multidisciplinary tumor board reviews should continue to be held for all patients (remotely if necessary) at this time. This ensures thoughtful reviews for each case with input from radiologists, as mentioned above. It also affords an opportunity for medical oncologists to discuss the risks and benefits of different systematic treatment approaches in the context of COVID-19 and allows radiation oncologists to describe the rationale for alternative treatment schedules. Clinicians also need to have careful and informative conversations with each patient regarding any deviations from the standard of care. Topics such as risks, benefits, and reasoning for these deviations must be explained to the patients so that they can have a proper understanding of the trajectory of their care. Patient preference must also be factored into management. Patients should also be advised to self-isolate during treatment to reduce the risk of acquiring the infection and spreading it to other patients with cancer.

Final Considerations Regarding Lung Cancer Stigma and Nihilism

Recent reports in the media indicate that health care systems are taking measures during the global pandemic to ration resources that may limit access to care for patients living with lung cancer. This includes restricting access to a ventilator if they develop respiratory distress for any reason whether or not related to COVID-19. Educating our colleagues and citing evidence may be helpful, such as the recent results of the PACIFIC trial, which revealed a 3-year overall survival of 66% among patients with LA-NSCLC treated with chemoradiotherapy and consolidation durvalumab. Health care administrators and colleagues taking care of these acutely ill patients on the front line may be largely unaware of recent advances in lung cancer care and the opportunity for long-term survival in all patients with lung cancer regardless of stage. Therefore, efforts to protect against nihilism may be needed now more than ever.

Conclusions

Patients with newly diagnosed LA-NSCLC are a vulnerable population during the COVID-19 global pandemic. Standard of care strategies, including surgical procedure, radiation therapy, and systemic therapies, can take a long time to deliver and expose patients to multiple visits to health care facilities. For patients who are confirmed to have COVID-19, consideration should be given to withholding their cancer therapies until they are fully recovered. However, the initiation of treatment for patients without an infection should not be delayed. The alternative treatment strategies presented in this report can reduce the risk of contracting and transmitting the infection and should be considered for each patient while the global pandemic persists. There are little data, and the consequences of modifications to the standard of care are not fully known. Some surgical, radiation, and medical oncology practices may still currently be operating in geographic locations that have not yet been hit by this pandemic; however, with this pandemic having reached across the globe, the authors urge all oncologists to consider these measures to optimize patient outcomes until this current crisis is over.

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