

Short-Term Recommendations for Non-Small Cell Lung Cancer Management During the COVID-19 Pandemic

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had an immense effect on society in 2020, and, in particular, it affects vulnerable populations, which include patients with non-small cell lung cancer (NSCLC). Given the effect of coronavirus disease 2019 (COVID-19) on the lungs, an organ already affected in NSCLC, these patients are at heightened risk of complications from COVID-19 either directly or indirectly. This advisory document should be interpreted within the context of the practitioner's local situation (ie, country, state, county, city, institution) and by no means should supersede local authority, but rather should provide potential guidance in the care of patients with NSCLC during the COVID-19 pandemic.

General Principles

- COVID-19 is a global pandemic of a novel virus for which pre-existing immunity and a vaccine are not available, leading to a unique scenario in which initial exposure to the virus can be lethal and overwhelm health care systems.
- There may be additional peaks of infection after the initial wave, which is currently ongoing.
- This virus is thought to predominantly spread through droplets from infected individuals who cough or sneeze, so a combination of social distancing, appropriate face mask utilization, and hand washing hygiene can help mitigate risk.
- There is no current proven therapy to treat COVID-19 aside from supportive care. Medications currently reported to be potential treatments for COVID-19 are unproven, have potentially lethal side effects, and should not be administered outside of a clinical trial or a physician's direction.
- Prevention is the best treatment for COVID-19, because it represents one of the few effective interventions to date. Therefore, health care systems should implement screening, cohorting/isolation, personal protective equipment (PPE), and other related policies.
- Robust testing for COVID-19 is essential to any workflow to minimize spread. NSCLC represents an aggressive and potentially lethal malignancy, and similar

to other cancers, very few treatments are truly elective over a prolonged period. Balancing the risk of COVID-19 against the risk of cancer requires shared decision-making between the patient and treating provider.

- This risk of COVID-19 must be balanced against the risk to the patient of lung cancer progression, which in most cases still represents the highest risk of mortality in these patients.
- Individual clinical judgment is necessary; these recommendations cannot provide absolutes for alternate strategies during the COVID-19 outbreak. Some of the following suggestions represent extrapolations from the available literature. Furthermore, some of these recommendations would not normally be considered standard of care or optimal but are reasonable under these unusual circumstances in which minimizing visits and potential exposure has become a priority.

Systems-Based Interventions

- Entry points to the health care system should feature screening of patients and providers (ie, questionnaire, temperature-based screening, standard and rapid COVID-19 testing). If resources are sufficient, screening of visitors who can accompany patients is reasonable, although many institutions have visitation restrictions to facilitate social distancing.
- Use of appropriate face masks and PPE procedures should be implemented and in accordance with local guidelines and with respect to available resources.
- Spacing of chairs in the clinic area and infusion center, and sterilization of equipment between use can help minimize transmission risk.
- Video telemedicine should be utilized as much as possible, and if feasible. Many patients may lack equipment for telemedicine, and phone calls may be a substitute for in-person visits.
- Certain medical and demographic populations (in recent weeks, African Americans in the United States seem to have elevated risk) appear to be at heightened risk for severe COVID-19 infections. Many of the most at-risk groups may lack resources for transitions to telemedicine, and efforts to bridge the digital divide are key. Efforts to integrate community and advocacy leaders into systems-based interventions and research into COVID-19 is critical.
- Similarly, meetings between health care providers (eg, tumor boards) should be done via teleconference to minimize iatrogenic spread between providers.
- Therapeutic clinical trials should continue to be made available to patients, when possible, especially for those who lack reasonable standard-of-care alternatives. Sponsors (including NCI/CTEP) have provided interim guidance on the conduct of clinical trials during the pandemic (https://ctep.cancer.gov/investigatorResources/corona_virus_guidance.htm).
- Vaccinations for influenza, pneumococcal pneumonia, and others should continue to mitigate superinfection risk.

Diagnostic Setting

- If resources are available, pre-procedure COVID-19 testing of the patient can help conserve PPE and facilitate cohorting of patients.
- For patients with positive or unknown COVID-19 status undergoing aerosol-generating procedures, health care providers should utilize both respiratory and contact precautions as designated in their health care system. For percutaneous biopsy of the lung, moderate sedation or local anesthesia should be the preferred options for sedation.
- For asymptomatic patients with negative COVID-19 status or documented COVID-19 humoral immunity, routine practices may be reasonable.
- Minimize the number of staff in the procedure suite. For reusable instrumentation, PPE must be worn until disinfection of instrumentation and room are complete.

Curative Intent Setting

- If institutional resources (ie, ventilators, staff, rooms) are available, curative-intent procedures should continue as planned.
- Preoperative testing of patients for COVID-19 should be performed if available.

Thoracic Surgery

Stage I – Stage II

- Patients with a pure ground-glass opacity (no solid component) can usually be deferred for 6 months or more.
- Patients with a clinical stage I lepidic adenocarcinoma (ground-glass opacity with small solid component) can usually be deferred for 3–6 months.
- Patients with clinical stage IA1 solid tumors can usually be deferred for 2–3 months.
- Patients with clinical stage IA2 to stage IIB should be considered urgent for purposes of surgical planning, proceed with surgical evaluation and planning, and proceed to surgery within 1 month if feasible with local hospital resources.
- For patients with surgery recommended as guideline-concordant care, surgery continues to be preferred over non-surgical therapy unless resource restrictions are severe and of indeterminate duration.
- In the context of minimizing procedures and potential viral exposure in patients with no evidence of nodal involvement on recent PET and CT, it is acceptable to omit invasive mediastinal staging. Mediastinoscopy can be considered as an alternative to endobronchial ultrasound (EBUS).
- Patients with strong clinical evidence or biopsy-proven N1 disease can have consideration of primary surgery (invasive mediastinal staging recommended) followed by adjuvant chemotherapy versus induction chemotherapy followed by surgery as dictated by local resources, multidisciplinary planning, and patient preference.

Stage IIIA (Non-N2)

- Patients with clinical stage IIIA (T3,N1 or T4,N0) should be considered urgent for purposes of surgical planning, proceed with surgical evaluation and planning, and proceed to surgery within 1 month if feasible with local hospital resources (invasive mediastinal staging recommended).
- For patients with surgery recommended as guideline-concordant care, surgery continues to be preferred over non-surgical therapy unless resource restrictions are severe and of indeterminate duration.
- Patients with strong clinical evidence or biopsy-proven N1 disease can have consideration of primary surgery (invasive mediastinal staging recommended) followed by adjuvant chemotherapy versus induction chemotherapy followed by surgery as dictated by local resources, multidisciplinary planning, and patient preference.

Stage IIIA (T1–2,N2)

- Patients with clinical stage IIIA (N2) with single-station, non-bulky mediastinal nodal disease can be considered for induction chemotherapy or chemoradiotherapy followed by restaging and surgical resection or definitive chemoradiation alone.
- Patients with multi-station and/or bulky mediastinal nodal disease should undergo definitive chemoradiation without surgery.

Radiation Oncology

Stage I or Stage II (N0)

- Patients with a pure ground-glass opacity (no solid component) referred for stereotactic body radiation therapy (SBRT)/stereotactic ablative radiotherapy (SABR) can usually be deferred for 6 months or more.
- Patients with a stage I lepidic adenocarcinoma (ground-glass opacity with small solid component) referred for SBRT/SABR can usually be deferred for 3–6 months.
- For peripheral lesions <3 cm, consider single-fraction SABR (other regimens include 54 Gy/3 fractions or 48 Gy/4 fractions that are also short and have more literature supporting their efficacy).
- For patients referred for SBRT/SABR for tumors demonstrating more aggressive features, including large size (≥ 3 cm), solid and/or central location, high FDG uptake on PET, or significant growth on serial imaging, it is not appropriate to defer treatment, as these lesions are at higher risk of nodal and/or distant metastases. (However, the patient's medical frailty must also be considered.)
- In the context of minimizing procedures and potential viral exposure, in patients with no evidence of nodal involvement on recent PET and CT, it is acceptable to omit invasive mediastinal staging before SABR.

- Similarly, SABR may be considered for patients who are otherwise surgical candidates to minimize exposures in an inpatient environment.

Stage II (N1) to Stage IIIA (postoperative radiotherapy)

- If patients have recently completed adjuvant chemotherapy, one might consider a hypofractionated approach (eg, 15–20 fractions) that provides an EQD2 (equivalent dose in 2 Gy fractions) of 50 Gy (R0/R1 resection) to 60 Gy (R2 resection). However, we are not aware of published data on this approach.

Stage II (N1) to Stage IIIB (definitive chemoradiotherapy)

- Consider accelerated regimens. These should be delivered with intensity-modulated RT (IMRT) and image-guided RT (IGRT)/motion management techniques to minimize the target volume and associated toxicity. Examples include:
 - 66 Gy in 24 fractions; this has been demonstrated to be safe and effective concurrent with low-dose daily cisplatin (but not other chemotherapy regimens); it is likely safe with conventional concurrent chemotherapy regimens when normal tissue doses can be kept well below the typical constraints for 30-fraction courses (eg, when target volumes are relatively small).
 - Sequential chemotherapy followed by hypofractionated radiotherapy (eg, 60 Gy in 15 fractions).
- With such regimens it is important to minimize the esophageal volume (and cross-section) receiving doses >56 (or so) Gy to minimize esophageal toxicity. Consider a simultaneous integrated boost (SIB) approach. Alternatively, consider relaxing the planning target volume (PTV) (and/or clinical target volume [CTV]/cumulative index of target volume [CITV]) coverage in regions of overlap with the esophagus to appropriately spare the esophagus. Similarly, one should be very careful not to create hot spots on other critical targets (eg, spinal cord, heart, trachea, central airways).

Interventional Radiology

Stage I or Stage II (N0)

- Patients with a pure ground-glass opacity (no solid component) referred for image-guided percutaneous tumor ablation can usually be deferred for >6 months.
- Patients with a stage I lepidic adenocarcinoma (ground-glass opacity with small solid component) referred for image-guided percutaneous tumor ablation can usually be deferred for 3–6 months.
- For appropriate lesions <3 cm, consider image-guided percutaneous tumor ablation as a single encounter treatment option.
- In the context of minimizing procedures and potential viral exposure, in patients with no evidence of nodal involvement on recent PET/CT or CT, it is acceptable

to omit invasive mediastinal staging before image-guided percutaneous tumor ablation.

- For patients with stage II (N0) and chest wall involvement, consider image-guided percutaneous tumor ablation as a single encounter treatment option for both local tumor control and palliation of chest wall pain.

Medical Oncology

- Curative-intent systemic therapy (ie, adjuvant, concurrent) should continue uninterrupted as local resources permit. In a resource-limited setting or if patient preference, it may be reasonable to delay adjuvant chemotherapy for up to 4 months postoperatively (Salazar MC, et al. JAMA Oncol 2017;3(5):610-619).
- Consideration of neoadjuvant chemotherapy in lieu of adjuvant therapy, if there are COVID-19–related delays in local therapy (ie, lack of ventilators for operating room), is reasonable with similar outcomes based on limited historical data.
- Appropriate use of neutrophil growth factor support in high-risk patients should continue and might be liberalized to include those with intermediate risk, especially with 1 or more risk factors per the NCCN Guidelines. In addition, the use of delayed-delivery devices is recommended to reduce the need for an additional infusion center visit.
- Use of extended interval immunotherapy, if available and approved by the payer, given the visit frequency and duration, can be considered. This should carefully be discussed with the patient. Payer reimbursement may be problematic for modifications to dose and interval not approved by regulatory bodies. A consent process detailing both potential medical and financial risks related to non-approved dosing should be considered. Use of an alternative agent outside of its approved indication is discouraged outside of clinical trials.
- For unresectable stage III patients treated with concurrent definitive chemo/RT, consider delaying consolidation immunotherapy with durvalumab for up to 6 weeks following completion of chemoradiation.

Surveillance Imaging

- Consider lengthening the interval of surveillance imaging; many clinical scenarios have ranges of imaging surveillance in the NCCN Guidelines and consideration of scheduling scans towards the less frequent portion of the range may be prudent to mitigate COVID-19 risk.

Metastatic Setting

Radiation Oncology

Stage IVA (oligometastatic)

- Refer for chemotherapy/immunotherapy/targeted therapy first, if not already completed.

- In the absence of progression, consider consolidative RT, particularly hypofractionated approaches including SABR, to the known areas of disease.

Stage IV (palliative)

- Maximize use of hypofractionated approaches with 10 or fewer (preferably 5 or fewer) fractions (eg, 8–12 Gy in 1 fraction, 20–30 Gy in 5 fractions, 30–40 Gy in 10 fractions).
- Doses at the higher end of these ranges should be delivered using conformal techniques to reduce the risk of toxicity.

Interventional Radiology

Stage IVA (oligometastatic)

- Refer for chemotherapy/immunotherapy/targeted therapy first, if not already completed.
- In the absence of progression, consider image-guided percutaneous tumor ablation to known areas of intra- or extrathoracic disease.

Stage IV (palliative)

- Consider image-guided percutaneous tumor ablation for disease control for tumors that have failed other local treatment options and for pain palliation.

Medical Oncology

- Treatment interval prolongation or deferring doses may be more reasonable in the metastatic setting, although efforts should be made to continue treatment on schedule.
- Oral therapies should be prioritized over intravenous chemotherapy where appropriate; they are often the standard of care in many targetable driver mutations. In the absence of symptomatic issues, follow-up via telehealth options is appropriate.
 - Potential regimen alterations include:
 - Use of oral etoposide instead of IV
 - Use of oral topotecan instead of IV
 - Use of temozolomide instead of IV options for relapsed/refractory small cell lung cancer (SCLC)
- Upon progression from oral therapy, circulating tumor DNA (ctDNA) testing for resistance mechanisms may be a reasonable option (rather than tissue testing) if this information is needed.
- Prophylactic use of granulocyte colony-stimulating factor (G-CSF) is recommended to minimize risk of febrile neutropenia, with the goal of reducing cases flowing into emergency rooms (ERs) and hospitals (see [Hematopoietic Growth Factor \[HGF\] guidance](#)). In addition, the use of delayed-delivery devices is recommended to reduce the need for an additional infusion center visit.
- As immunotherapy represents a high intensity of infusion visits, adjustments in schedule based on existing data may have meaningful impacts on minimizing COVID-19 risk while continuing effective therapy. Use of extended interval immunotherapy, given the visit frequency and duration, can be considered. This

should carefully be discussed with the patient. Payer reimbursement may be problematic for modifications to dose and interval not approved by regulatory bodies. A consent process detailing both potential medical and financial risks related to non-approved dosing should be considered. Use of an alternative agent outside of its approved indication is discouraged outside of clinical trials. The extended intervals presented below have clinical data in other settings or reasonable pharmacokinetic data to suggest their use during the COVID-19 pandemic.

- Potential interval alterations include:
 - Extended-interval zoledronic acid 4 mg IV every 12 weeks based on robust breast and prostate cancer data is reasonable, in particular for patients on oral therapy, and especially after long-term use beyond a year. There exist limited data for denosumab every 12 weeks based on reports that de-escalation of denosumab might be equally effective.
 - Atezolizumab 1680 mg IV every 4 weeks (approved in SCLC)
 - Durvalumab 10 mg/kg IV every 2 weeks is utilized as consolidation immunotherapy after chemoradiation in stage III NSCLC; in SCLC there is approval for durvalumab 1500 mg IV every 4 weeks
 - Nivolumab 480 mg IV every 4 weeks (approved for second-line therapy in metastatic NSCLC; if utilized with ipilimumab 1 mg/kg IV every 6 weeks for first-line therapy in metastatic NSCLC, alternating with every-2-week dosing is a consideration)
 - Pembrolizumab 400 mg IV every 6 weeks (approved by the U.S. FDA and European Medicines Agency [EMA])
 - Holding immunotherapy for responders after 2 years in frontline metastatic NSCLC, as per the frontline clinical trial protocols
- Consider lengthening the time between restaging imaging (eg, in patients with stable symptoms and/or who have had durable responses already).
- Discussions of goals of care and code status are especially important at this time, particularly for metastatic patients. Physician Orders for Life-Sustaining Treatment (POLST) forms and advance directives in particular are tools for clarifying patient preferences about intubation in the setting of respiratory decline and can be signed remotely. When available, supportive care and psycho-oncology resources can be helpful for addressing the additional stressors at play.