

Brief Opinion

Thoracic Radiation Therapy During Coronavirus Disease 2019: Provisional Guidelines from a Comprehensive Cancer Center within a Pandemic Epicenter



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Received 3 April 2020; revised 8 April 2020; accepted 8 April 2020

Abstract

Coronavirus disease 2019 is an unprecedented pandemic with significant and evolving impact on the practice of radiation oncology. Radiation oncology departments must anticipate and account for coronavirus disease 2019 exposure risk for both patients and staff. The potential for severe radiation therapy resource constraints, particularly due to staff illness, must also be considered. Here we present provisional guidelines for thoracic radiation therapy adopted at our facility, a high-volume cancer center located in a United States pandemic epicenter. Generally, these guidelines reflect the principle that where evidence-supported hypofractionated schedules with comparable efficacy and toxicity exist, the shortest such schedules should be employed. In addition, we discuss potential adaptations in the prioritization and timing of radiation therapy for thoracic malignancies under these circumstances.

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Sources of support: This research was supported in part by NIH P30 CA008748.

Disclosures: Dr Wu has received research funding from CivaTech Oncology, Inc, personal fees from AstraZeneca, and travel grants from AlphaTau, Medical. Dr Rimner has received research funding from Varian Medical Systems, AstraZeneca, Boehringer Ingelheim, Pfizer, and Merck; personal fees from AstraZeneca, Merck, Research to Practice, Cybrea, and More Health; and nonfinancial support from Philips/Elekta. Dr Simone has received personal fees from Varian Medical Systems. Dr Gomez has received research funding from Boehringer Ingelheim, Varian Medical Systems, AstraZeneca, Merck, and Bristol-Myers Squibb and personal fees from Varian Medical Systems, AstraZeneca, Merck, Bristol-Myers Squibb, US Oncology, Reflexion, WebMD, Vindico, and Medscape and serves on an advisory board for AstraZeneca.

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<https://doi.org/10.1016/j.adro.2020.04.008>

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The global coronavirus disease 2019 (COVID-19) pandemic, still escalating at the time of this writing (April 6, 2020), has profound and difficult implications for the practice of radiation oncology. The New York metropolitan area has become an early pandemic epicenter in the United States, and indeed the whole world. The pandemic's scope in New York City in particular, and the probability that the city's experience will presage the impact of COVID-19 on the remainder of the country, has forced us to make rapid decisions about our indications and standards for thoracic radiation.

Pandemic conditions impose 2 new constraints not typically considered in radiation therapy decision-making

in the United States. First, travel to the radiation facility itself poses risk for exposure to SARS-CoV-2, which is especially true in New York City, with 72,000 patients infected and counting. This risk is proportional to the number of fractions prescribed and applies to both patients and staff. Second, pandemic conditions may cause a severe restriction in the availability of radiation therapy services owing to widespread staff illness (which has already affected our department), staff redeployment, or repurposing of other radiation therapy resources. This would require radiation oncology departments to ration care and make difficult but unavoidable decisions about which patients and indications are higher priority and which must be deferred or denied treatment altogether. Although our department has not yet been forced to ration radiation therapy, we have started deferring radiation in certain low-risk situations (eg, patients with prostate cancer already on hormonal therapy) in an effort to avoid this scenario.

Radiation therapy for primary lung cancer plays a crucial, potentially curative role in this common malignancy. Moreover, lung cancer generally has a poor prognosis and can progress rapidly, making blanket deferral or cancellation of radiation therapy an unacceptable policy. Yet patients with lung cancer are a particularly vulnerable population in this pandemic, as they often have baseline lung disease and other comorbidities predisposing them to severe complications from COVID-19. Therefore, proactive consideration and

prioritization of thoracic radiation therapy services, weighing COVID-19 exposure risk versus the aggressiveness of malignancy, is an urgent task for every radiation department in an environment where overall treatment capacity may diminish. These complex and difficult trade-offs are best addressed in a coordinated fashion, rather than in a reactive and subjective manner by individual physicians for individual patients.

As thoracic radiation specialists in a large cancer center in New York City, we present provisional consensus guidelines and considerations for lung radiation therapy under pandemic conditions (Table 1). Generally, these reflect the overarching principle that where evidence-supported hypofractionated schedules with comparable efficacy and toxicity exist, the shortest such course should be employed. We have adopted the maximal evidence-supported hypofractionation, and we recommend similar adoption nationally regardless of COVID-19's current impact on one's geographic area. The epidemiologic characteristics of a pandemic (ie, exponential growth) and the lengthy time horizon for radiation planning and delivery should compel us to change practice not on the basis of today's conditions but on the basis of worst-case projections several weeks or even months in the future.

Early-Stage Non-Small Cell Lung Carcinoma

Stereotactic body radiation therapy (SBRT), or stereotactic ablative radiation therapy, is inherently an extremely hypofractionated regimen and as such is already optimized for pandemic circumstances. However, single-fraction radiation therapy (34 Gy) for T1-2N0 peripheral lesions has now been validated in multiple randomized, multicenter trials and should be strongly considered over more common regimens such as 18 Gy \times 3, 12 Gy \times 4, or 10 Gy \times 5 fractions for small (\leq 5 cm) tumors outside the no-fly zone.^{1,2} It is important to respect established dose–volume constraints for single-fraction lung SBRT, such as limiting maximum cord dose to 14 Gy.¹

In other settings, such as larger or central lesions, the shortest fractionation that meets existing dose constraints should be selected. Our department uses 10 Gy \times 5 for central lesions. Although SBRT-induced toxicity has been reported with ultracentral lesions (those abutting the proximal bronchial tree or approaching the esophagus), these may also now be treated with risk-adapted hypofractionation, such as 7.5 Gy \times 8.³

Locally Advanced Non-Small Cell Lung Carcinoma

Concurrent, up-front chemoradiation therapy remains the optimal treatment for unresectable stage III non-small cell lung carcinoma (NSCLC), and referrals for definitive

Table 1 Recommendations for lung cancer radiation therapy under pandemic conditions

Indication	Recommendation
Peripheral T1-2N0 NSCLC	34 Gy/1 fraction
Central T1-2N0 NSCLC	50 Gy/5 fractions
Ultracentral T1-2N0 NSCLC	60 Gy/8 fractions
Locally advanced NSCLC (concurrent chemo)	55 Gy/20 fractions
Locally advanced NSCLC (no concurrent chemo)	45-60 Gy/15 fractions
Postoperative radiation for NSCLC	50 Gy/25 fractions
Limited-stage SCLC (thoracic RT)	45 Gy/30 twice-daily fractions (or 15 daily fractions)
Limited-stage SCLC (prophylactic cranial RT)	25 Gy/10 fractions versus MRI surveillance
Extensive-stage SCLC (thoracic RT)	30 Gy/10 fractions versus observation
Extensive-stage SCLC (prophylactic cranial RT)	MRI surveillance
Palliative lung RT	20 Gy/5, 17 Gy/2 or 10 Gy/1 fraction

Abbreviations: MRI = magnetic resonance imaging; NSCLC = non-small cell lung carcinoma; RT = radiation therapy; SCLC = small cell lung carcinoma.

These are guidelines only and may be adjusted based on patient-specific and facility-specific factors.

radiation may even increase for resectable disease given the potential impact of COVID-19 on thoracic surgical services. However, the standard 30- to 35-fraction schedule, in the context of concurrent chemotherapy toxicity and poor baseline pulmonary health of many patients with NSCLC, represents a significant exposure and complication risk from COVID-19 and heavy resource utilization. A schedule of 55 Gy in 20 fractions is already widely used in the United Kingdom, and prospective data suggest that concurrent chemotherapy with this regimen is not associated with excessive toxicity.^{4,5} Although individualized clinical judgment always applies, the benefit of curtailing treatment by 2+ weeks justifies considering 55 Gy in 20 fractions the default chemoradiation schedule under pandemic circumstances. Spinal cord dose should be limited to 44 Gy with this schedule; patients with particularly extensive nodal involvement requiring irradiation of ≥ 12 cm of the esophagus should receive standard fractionation.⁵

For patients not otherwise good candidates for concurrent chemoradiation owing to medical comorbidities or impaired functional status, induction chemotherapy followed by radiation therapy alone is a reasonable choice, particularly as it may allow the deferment of radiation therapy until the pandemic has passed. Although not a validated approach, patients with a targetable driver mutation (sensitizing epidermal growth factor receptor mutation, anaplastic lymphoma kinase rearrangement, etc) could also be considered for induction systemic therapy as a temporizing measure. In the meantime, hypofractionated schedules are strongly preferred for radiation therapy without concurrent chemotherapy, particularly a 15-fraction schedule. Retrospective data suggest that outcomes after 45 Gy in 15 fractions are equivalent to 60 Gy in 30 fractions, and this schedule has been endorsed in an American Society for Radiation Oncology (ASTRO) clinical practice guideline.^{6,7} Within the framework of this 15-fraction schedule, selective dose escalation to doses as high as 60 Gy may be considered; this dose is currently being investigated in patients with locally advanced NSCLC not receiving cytotoxic chemotherapy in NRG Oncology LU-004.⁸

Postoperative Radiation Therapy for NSCLC

The degree of survival benefit of routine postoperative radiation for resected N2 disease remains uncertain, and under severe resource restrictions, adjuvant treatments may receive lower prioritization than definitive radiation therapy. Nevertheless, significant evidence, and oncologic first principles (particularly in the case of positive margins), justify preserving the ability to deliver PORT.⁹⁻¹¹ ASTRO guidelines recommend doses of 54 to 60 Gy for margin-positive disease and 50 to 54 Gy for margin-negative disease, in 1.8- to 2.0-Gy fractions.¹² Choosing the lowest doses and shortest schedules consistent with

these guidelines (50 Gy in 2.0-Gy fractions) is recommended at this time. Patients in a postoperative state may be at heightened risk for morbidity or mortality from COVID-19, and as such, limiting target volumes to involved regions (positive nodal stations and staple line only) is also prudent. Hypofractionation in the postoperative setting has been associated with more toxicity and is thus not encouraged.¹³

Small Cell Lung Cancer—Limited Stage

Early-stage small cell lung carcinoma (SCLC; T1-2N0) may be treated with surgery or SBRT, avoiding the need for more fractionated radiation therapy.^{14,15} Otherwise, the standard regimen for limited-stage SCLC is 45 Gy in twice-daily, 1.5-Gy fraction regimens. Although this remains the standard, daily treatment such as 66 to 70 Gy in 33 to 35 fractions appears substantially equivalent.¹⁶ Hyperfractionation versus daily fractionation under pandemic conditions raises the question of whether minimizing overall treatment length, or length of a given treatment day, is preferred. This choice, in turn, may depend on facility-specific factors such as the effectiveness of the facility's COVID-19 precautions and its logistical ability to deliver 2 daily fractions at least 6 hours apart. Overall, we believe that minimizing overall treatment length is more important and recommend standard twice-daily treatment to 45 Gy. One potential adaptation, albeit one without much direct supporting evidence, is the conversion of this regimen to once-daily fractionation (45 Gy in 15 daily fractions), which, as noted earlier, is well established for NSCLC. However, as the NSCLC data apply to patients not receiving concurrent chemotherapy, and SCLC disease is often bulky and central, we would consider this a measure of last resort for carefully selected patients under conditions of imminent resource restriction, and we have not moved to this fractionation at our facility at this time.

The standard recommended timing of radiation therapy ("early," ie, with the first or second cycle of chemotherapy) may also be adjusted under these circumstances. The benefit of early versus late radiation therapy is modest, and one more recent randomized trial suggests equivalence when delivering radiation therapy (RT) with the third cycle versus the first cycle of chemotherapy.^{17,18} Therefore, delaying concurrent radiation therapy until the third cycle of chemotherapy may be preferred if it allows radiation therapy to be deferred until after the projected peak of COVID-19 pandemic conditions.

SCLC—Prophylactic Cranial Irradiation and Extensive-Stage Disease

Particularly for limited-stage disease, prophylactic cranial irradiation (PCI) remains a survival-enhancing

intervention for a potentially curable malignancy. As such, PCI should remain a standard recommendation for patients with limited-stage SCLC with response to initial chemoradiotherapy, consistent with the recently published ASTRO guidelines.^{14,15} The standard dose of PCI remains 25 Gy in 10 fractions. However, prospective data from extensive-stage patients suggest that deferring PCI in favor of close magnetic resonance imaging surveillance can achieve equivalent outcomes without the neurocognitive risks of brain radiation—and in these circumstances, without exposure risk to COVID-19.¹⁹ Therefore, we suggest that risks and benefits of PCI be carefully discussed with all eligible patients with SCLC, including those with limited-stage disease, and that strong consideration during pandemic conditions be given to magnetic resonance imaging surveillance as an alternative. This is particularly true for extensive-stage disease, where the benefits of PCI are more questionable and which represents an incurable condition regardless. For extensive-stage patients receiving PCI, a shorter regimen of 20 Gy in 5 fractions could be considered.²⁰

Consolidative thoracic radiation after induction chemotherapy for extensive-stage SCLC has been associated with a survival benefit that led to its incorporation into guidelines as a standard recommendation.²¹ However, the magnitude of its benefit is debated, especially with the increasing role of immunotherapy in this setting.²² As such, individualized discussion of risks and benefits of consolidative thoracic RT is also indicated, and if delivered, should be limited to no more than the established 10-fraction, 30-Gy schedule. Because patients recommended consolidative thoracic RT are likely also candidates for PCI, concurrent delivery of thoracic and brain RT is logical under these circumstances.

Palliation

Under pandemic conditions, palliative lung radiation should be deferred when possible and otherwise reserved for patients with life-threatening complications such as high-volume hemoptysis or superior vena cava syndrome. Very short courses of palliative lung radiation have been validated in prospective, randomized trials.²³ Schedules such as 20 Gy in 5 fractions, 17 Gy in 2 fractions, or 10 Gy in a single fraction should be favored at this time.²⁴

Conclusion

The COVID-19 pandemic is an unprecedented and unpredictable global health crisis whose impact on thoracic radiation therapy is already significant and certain to grow. Radiation therapy departments will be confronted with excruciating decisions about how to alter treatment recommendations and even withhold treatment

entirely, given the additional risks of delivering radiation under these circumstances and the potential that radiation therapy resources will be sharply curtailed. Urgently considering and adopting guidelines such as these is imperative for our field so that we can not only maintain our commitment to treat life-threatening malignancies but protect the health of all patient-facing radiation staff and help preserve the availability and integrity of health services for society as a whole.

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