

Advances in Radiation Oncology

Thoracic radiation therapy during COVID-19: provisional guidelines from a comprehensive cancer center within a pandemic epicenter

--Manuscript Draft--

Manuscript Number:	ADVANCESRADONC-D-20-00098R3
Article Type:	Brief Opinion
Section/Category:	COVID-19
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Abstract:	

Thoracic radiation therapy during COVID-19: provisional guidelines from a comprehensive cancer center within a pandemic epicenter

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Running title: Thoracic RT during COVID-19

Disclosures: AJW has received research funding from CivaTech Oncology, Inc., personal fees from AstraZeneca, and travel grants from AlphaTau, Medical. AR has received research funding from Varian Medical Systems, AstraZeneca, Boehringer Ingelheim, Pfizer, and Merck and personal fees from AstraZeneca, Merck, Research to Practice, Cybrexa, and More Health; and non-financial support from Philips/Elekta. CBS has received personal fees from Varian Medical Systems. DRG has received research funding from Boehringer-Ingelheim, Varian Medical Systems, AstraZeneca, Merck, and Bristol-Myers Squibb; 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.

The global 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 its 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 two new constraints not typically considered in radiotherapy decision-making in the United States. First, travel to the radiation facility itself poses risk for exposure to SARS-CoV2, 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 radiotherapy services due to widespread staff illness (which has already affected our department), staff redeployment, and/or repurposing of other radiotherapy 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. Though our department has not yet been forced to ration radiotherapy, we have started deferring radiation in certain low-risk situations (for example, prostate cancer patients 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 lung cancer patients are a particularly vulnerable population in this pandemic, as they often have baseline lung disease and other comorbidities predisposing to severe complications from COVID-19. Therefore, proactive consideration and prioritization of thoracic radiotherapy services is an urgent task for every radiation department, weighing COVID-19 exposure risk vs. the aggressiveness of malignancy, 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 (i.e. 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 NSCLC

Stereotactic body radiation therapy (SBRT, or SABR) is inherently an extremely hypofractionated regimen and as such, is already optimized for pandemic circumstances. However, single-fraction radiation therapy (34Gy) for T1-2N0 peripheral lesions has now been validated in multiple randomized, multicenter trials and should strongly be considered over more common regimens such as 18Gy x 3, 12 Gy x 4 or 10Gy x 5 fractions for small (≤ 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 14Gy.(1)

In other settings, such as larger or central lesions, the shortest fractionation that meets existing dose constraints should be selected. Our department uses 10Gy x 5 for central lesions. Though SBRT-induced toxicity has been reported with ultra-central lesions (those abutting the proximal bronchial tree or approaching the esophagus), these should also now be treated with risk-adapted hypofractionation, such as 7.5Gy x 8.(3)

Locally advanced NSCLC

Concurrent, upfront chemoradiation therapy remains the optimal treatment for unresectable Stage III NSCLC, and referrals for definitive radiation may even increase for resectable disease, given the potential impact of COVID-19 on thoracic surgical services.

However, the standard 30-35-fraction schedule, in the context of concurrent chemotherapy toxicity and poor baseline pulmonary health of many NSCLC patients, represents a significant exposure and complication risk from COVID-19, as well as heavy resource utilization. A schedule of 55Gy 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) Though individualized clinical judgment always applies, , the benefit of curtailing treatment by two-plus weeks justifies considering 55Gy in 20 fractions the default chemoradiation schedule under pandemic circumstances. Spinal cord dose should be limited to 44Gy 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 due to medical comorbidities or impaired functional status, induction chemotherapy followed by radiotherapy alone is a reasonable choice, particularly as it may allow the deferment of radiotherapy until the pandemic has passed. Though not a validated approach, patients with a targetable driver mutation (sensitizing EGFR mutation, ALK rearrangement, etc.) could also be considered for induction systemic therapy as a temporizing measure. In the meantime, hypofractionated schedules are strongly preferred for radiotherapy without concurrent chemotherapy, particularly a 15-fraction schedule. Retrospective data suggest that outcomes after 45Gy in 15 fractions are equivalent to 60Gy in 30 fractions, and this schedule has been endorsed in an ASTRO clinical practice guideline.(6,7) Within the framework of this 15-fraction schedule, selective dose-escalation to doses as high as 60Gy may be considered; this dose is currently being investigated in locally advanced NSCLC patients not receiving cytotoxic chemotherapy in NRG Oncology LU-004.(8)

Postoperative radiotherapy 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 radiotherapy. Nevertheless, significant evidence, as well as oncologic first principles (particularly in the case of positive margins), justify preserving the

ability to deliver PORT(9-11). ASTRO guidelines recommend doses of 54-60Gy for margin-positive disease and 50-54Gy for margin-negative disease, in 1.8Gy-2.0Gy fractions.(12) Choosing the lowest doses and shortest schedules consistent with these guidelines (50Gy in 2.0Gy 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 SCLC (T1-2N0) may be treated with surgery or SBRT, avoiding the need for more fractionated radiotherapy.(14,15) Otherwise, the standard regimen for limited-stage SCLC is 45Gy in twice-daily 1.5Gy regimens. Though this remains the standard, daily treatment such as 66-70Gy in 33-35 fractions appears substantially equivalent.(16) Hyperfractionation vs. 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 two daily fractions at least six hours apart. Overall, we believe that minimizing overall treatment length is more important and recommend standard twice-daily treatment to 45Gy. One potential adaptation, albeit one without as direct supporting evidence, is the conversion of this regimen to once-daily fractionation (45 Gy in 15 daily fractions), which, as noted above, is well-established for NSCLC. However, as the NSCLC data applies 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 radiotherapy ("early," i.e. with the first or second cycle of chemotherapy) also may be adjusted under these circumstances. The benefit of early vs. late radiotherapy is modest, and one more recent randomized trial suggests equivalence

when delivering RT with the third cycle vs. the first cycle of chemotherapy.(17,18) Therefore, delaying concurrent radiotherapy 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.

Small cell lung cancer—prophylactic cranial irradiation (PCI) and extensive-stage disease

Particularly for limited-stage disease, PCI remains a survival-enhancing intervention for a potentially curable malignancy. As such, PCI should remain a standard recommendation for limited-stage SCLC patients with response to initial chemoradiotherapy, consistent with the recently published ASTRO guidelines(14,15). The standard dose of PCI remains 25Gy in 10 fractions. However, prospective data from extensive-stage patients suggest that deferring PCI in favor of close MRI 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 SCLC patients including limited-stage, and that strong consideration during pandemic conditions be given to MRI 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 20Gy 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, 30Gy schedule. Since 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, 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 20Gy in 5 fractions, 17Gy in 2 fractions, or 10Gy 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. Radiotherapy 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 radiotherapy 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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Table 1: Recommendations for lung cancer radiotherapy under pandemic conditions. These are guidelines only and may be adjusted based on patient-specific and facility-specific factors.

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