

Teaching Case

Technical Considerations in Stereotactic Ablative Radiotherapy for Localized Neuroendocrine Cancer of the Lung: Case Report and Review of the Literature

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Introduction

Small cell lung cancer (SCLC) is a rapidly progressive disease that presents in the limited stage only 30% of the time.¹ Limited-stage SCLC is typically treated with concurrent chemoradiation therapy²; however, uncommonly, this disease can present as a small, solitary pulmonary nodule without nodal involvement.³ In this early stage scenario, lobectomy with mediastinal lymph node dissection is often considered. Patients with lung cancer frequently have comorbidities that increase surgical risks; thus, surgery may not always be a viable option. In patients with analogous non-small cell lung cancer (NSCLC), stereotactic ablative radiotherapy (SABR) is broadly recognized as the standard of care.⁴ A growing body of retrospective literature has emerged on clinical outcomes of SABR for stage I SCLC, but a description of technical considerations is lacking.

SCLC exists on a spectrum of pulmonary neuroendocrine tumors that also includes large cell neuroendocrine carcinoma and carcinoid tumors. High-grade neuroendocrine tumors are known to be highly radioresponsive and are more likely to respond early to treatment.³ When considering treatment with SABR, where efficacy depends on the precision and accuracy of the set-up, understanding how a tumor may respond during the course of treatment is paramount. This report describes some unique diagnostic and technical considerations encountered with a stage I high-grade neuroendocrine lung cancer treated with SABR and reviews the relevant published literature.

Case

A 71-year-old woman was found to have a solitary pulmonary nodule in the right lower lobe on computed tomography (CT) scans during work-up for an episode of pleuritic chest pain. This 1.4-cm, 18F-fluorodeoxyglucose-avid (maximum standardized uptake value: 5.5) lesion was biopsied, and results revealed a high-grade neuroendocrine tumor. Multiple extrapulmonary lesions on positron emission tomography, including a colonic lesion and adenopathy within the mediastinum and abdomen, were biopsied and found to be consistent with the patient's history of sarcoidosis.

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Postbiopsy, the patient developed a pneumothorax requiring a chest tube and 2-day hospital admission. Given the patient's poor pulmonary function (forced expiratory volume in 1 second: 1.1 L; 43% of predicted), the patient was deemed medically inoperable. She was referred to radiation and medical oncology where options including radiation therapy alone, sequential chemoradiotherapy, and concurrent chemoradiotherapy were discussed. The patient refused any treatment involving chemotherapy, and given the size and location of the lesion, the patient consented to move forward with SABR of 6000 cGy delivered over 8 fractions on alternate days.

A 4-dimensional CT simulation was performed on a 16-slice Philips Big Bore CT Scanner (Philips Healthcare, Cleveland, OH). During respiration, the tumor moved 11 mm in the superoinferior direction, greater than our institutional standard of 10 mm for requiring respiratory gating. The internal target volume (ITV) was delineated on the axial slices of a subset average CT scan, composed of phases between 40% and 60% of the respiratory cycle. The planning target volume (PTV) was created using a 5 mm uniform margin around the ITV (Fig 1). The ITV and PTV were 4.2 cm³ and 17.0 cm³, respectively. A dose of 6000 cGy was prescribed to the PTV using a single isocenter, with a maximum point dose of 8170 cGy within the ITV. Treatment was delivered on alternate days, with daily cone beam CT, gated 2-dimensional kV/kV image guidance, and respiratory gating.

After four fractions, cone beam CT scans revealed a change in location, shape, and size of the lung mass. The treating radiation oncologist decided to replan the patient using the same technique described previously. At the time of re-simulation, the GTV was determined to have shifted approximately 8 mm inferiorly, 9 mm posteriorly, and 1 mm laterally (3-dimensional distance: 12 mm; Fig 2). The new ITV and PTV were 1.4 cm³ and 9.0 cm³, respectively. The patient completed the remaining four fractions without incident, and her treatment was restarted 4 days after re-simulation was initiated.

Discussion

SABR for stage I pulmonary neuroendocrine cancer is still in the early stages, with little efficacy and toxicity data. Upon review of the literature, we identified 2 multi-institutional retrospective analyses and 3 single-institution case series that reported on SABR for stage I SCLC (summarized in Table 1). The technical aspects of treating pulmonary neuroendocrine cancer with SABR have not been well described. Analogs are made to treatment of NSCLC, where SABR has become the standard treatment for inoperable stage I disease.¹⁰ Typical 3-dimensional interfraction tumor motion of stage I NSCLC has been reported in the range of 0.3 to 4.5 mm, with an average motion of <2 mm.^{11,12} The motion in the current case is greater than double the motion reported in these studies. We hypothesize that this movement is related to an untethering effect as the tumor responded to treatment.

In the described case, a 67% decrease in tumor volume was noted after the first 4 fractions of radiation therapy (ITV: 1.4 cm³; previously 4.2 cm³). A similar phenomenon has been reported in NSCLC, though the magnitude of reduction tends to be <10%.^{11,12} High-grade neuroendocrine cancers are known to be very radiosensitive,³ and a rapid reduction in tumor volume is expected. However, this could introduce image guidance considerations because tumor localization for later fractions may become challenging. Similar challenges have been reported in subcentimeter NSCLC, where tumor localization throughout treatment requires inference of tumor location based on the surrounding soft tissue landmarks on approximately 10% of cone beam CT images.⁴ In the described case, inferring tumor position based on surrounding landmarks would not have been possible as there was tumor motion relative to these landmarks.

Fiducial markers have been used to allow for tumor tracking in the setting of NSCLC being treated with SABR. Risks associated with the use of fiducials include infection, arrhythmia, and pneumothorax secondary to marker placement, in addition to the risk of marker

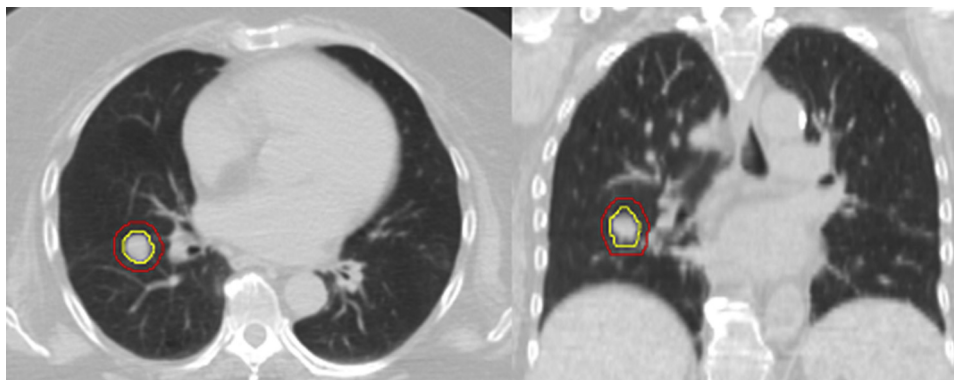


Figure 1 Original planning computed tomography scan. Yellow indicates internal target volume, and red planning target volume.

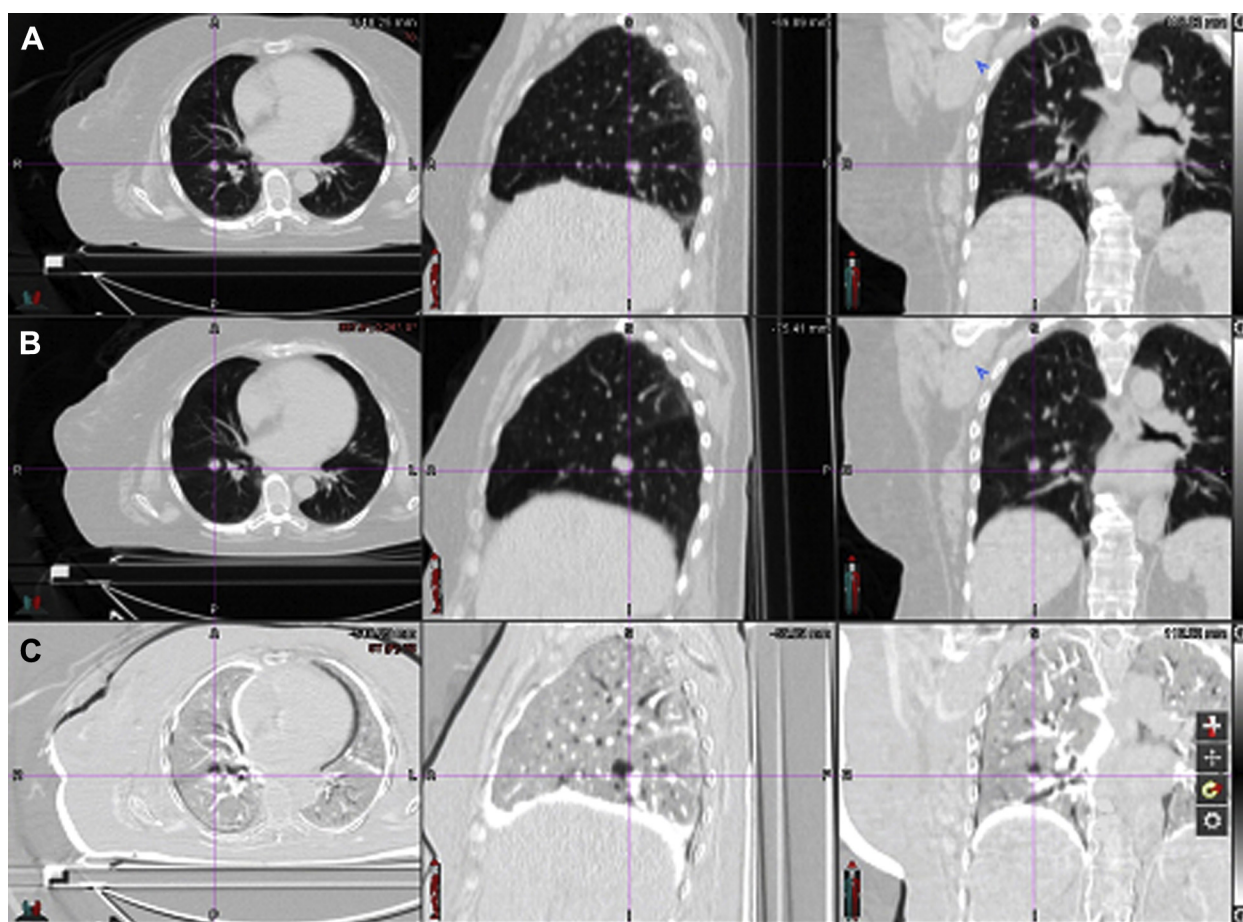


Figure 2 Comparison of the original and repeat 4-dimensional computed tomography (CT) scans. (A) Four-dimensional CT scan after change in tumor position noted on daily cone beam CT scan. (B) Four-dimensional CT scan performed for original planning purposes. (C) Fused image of the original and repeat 4-dimensional CT scans showing tumor changes.

migration, decreasing image guidance accuracy.¹³ With increasing evidence that fiducial-less treatment allows for comparable tumor control rates in NSCLC,¹⁴ fiducials have been used less frequently. The same, however, is not known for neuroendocrine lung cancer, and there may still be a role for fiducial placement before SABR in treating this spectrum of diseases. Four-dimensional cone beam CT can also be considered for real-time tracking of respiratory and tumor motion improving the accuracy of tumor localization.¹⁵

Adaptive radiation therapy has been achieved using daily imaging to adjust the target volume on the basis of position and morphology without fiducial markers, reoptimizing the image guided radiation therapy plan accordingly.¹⁶ Historically, this has been a time-intensive process and has not gained widespread clinical acceptance; however, with improvements in computational algorithms, optimization time has decreased, allowing for increased clinical use, especially for scenarios such as the case described.¹⁷

The dose fractionation schedule of 60 Gy in 8 fractions on alternate days is a common schedule used in Canada

and Europe for central lung tumors.^{18,19} Based on the interfraction target changes in this case, shorter fractionation schemes may be preferred. Single-fraction radiation therapy has been minimally studied in primary lung cancer, with 2 recent phase 2 trials. Radiation Therapy Oncology Group study 0915 compared 34 Gy in a single fraction with 48 Gy in 4 fractions for stage I, medically inoperable NSCLC. The long-term results of this study have only been published in abstract form; however, they do show similar tumor control, overall survival (OS), and toxicities between the 2 arms at 5 years.²⁰ A second study (National Cancer Institute study I-124407) comparing 30 Gy in a single fraction with 60 Gy in 3 fractions for stage I NSCLC has closed to accrual but has not yet published results.²¹ To our knowledge, single-fraction radiation therapy has not been studied in the pulmonary neuroendocrine cancer setting; however, may be worth considering to avoid changes in tumor volume and position between fractions, with recognition that the efficacy in this setting is currently unknown.

When treating a patient with localized pulmonary neuroendocrine cancer, resection should be the primary

Table 1 Summary of reported retrospective analyses and case series on the use of SABR for stage I small cell lung cancer

Study	Patients	SABR dose in Gy/no. of fractions	Chemotherapy	Outcomes	Toxicities (grade ≥ 3)
Verma et al ⁵	n = 74 (76 lesions), multi-institution	50/5, 50/4, 54/3	n = 45 after RT (typically PE)	LC 97.4% at 1 year, 96.1% at 3 years DFS 59.1% at 1 year, 54.0% at 3 years OS 71.1% at 1 year, 34.6% at 3 years	n = 1 grade 3 pneumonitis
Shioyama et al ⁶ (abstract form only)	n = 64, multi-institution	35-60/3-19 (most commonly 48/4)	n = 36 received PE or CpE	DSS 79.1% at 2 years PFS 49.3% at 2 years OS 76.3% at 2 years	n = 0
Videtic et al ⁷	n = 6, single institution	50/5 (n = 2), 60/3 (n = 3), 30/1 (n = 1)	n = 4 received PE or CpE after RT	LC 100% at 1 year DFS 75% at 1 year OS 63% at 1 year	n = 0
Shioyama et al ⁸	n = 8, single institution	48/4	n = 6 received PE or CpE either before or after RT	LC 100% at 3 year DSS 86% at 3 years OS 72% at 3 year	n = 0
Ly et al ⁹	n = 8, single institution	50/4	n = 4 received PE after RT n = 1 received PE before RT	DFS 50% at 1 year, 38% at 3 years OS 88% at 1 year, 37% at 3 years	Not reported

Abbreviations: CpE = carboplatin-etoposide; DFS = disease-free survival; DSS = disease-specific survival; LC = local control; OS = overall survival; PE = cisplatin-etoposide; PFS = progression-free survival; RT = radiation therapy; SABR = stereotactic ablative radiotherapy.

treatment option. If the patient is unable to or refuses to undergo surgery, SABR should be considered as a viable alternative, keeping in mind the considerations outlined previously. Shorter courses of SABR could be considered to minimize interfraction target volume changes. In cases in which longer courses are required because of an inability to meet normal tissue constraints, awareness of the need for replanning during the course of treatment in response to target volume adjustments is paramount.

Chemotherapy and prophylactic cranial irradiation (PCI) are controversial in this early stage setting. Currently, the National Comprehensive Cancer Network recommends that patients with SCLC, no matter the stage, receive chemotherapy if medically suitable. Furthermore, if patients have a partial or complete response to initial therapy, PCI should be offered.⁵ Verma et al.⁶ attempted to answer the question of the role of chemotherapy and PCI in patients with stage I SCLC treated with SABR using a multi-institutional database of 74 patients (76 lesions). The results showed improved OS and disease-free survival ($P = .01$) with the addition of chemotherapy to SABR and a trend toward improved OS ($P = .08$) and disease-free survival ($P = .12$) in patients who received PCI. Of note, this study was retrospective, and patients

who received chemotherapy and PCI tended to be younger and have a better baseline performance status.

Conclusions

SABR as the primary treatment for stage I neuroendocrine lung cancer is not yet well understood, and there are important considerations that are unique to the treatment of this spectrum of diseases compared with NSCLC. In addition to better understanding the efficacy, further investigation into methods to account for interfraction target volume changes during SABR for pulmonary neuroendocrine cancer is required.

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