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Original research article

First report of pulmonary large cell neuroendocrine carcinoma treated with stereotactic body radiation therapy

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ABSTRACT

Introduction: Pulmonary large-cell neuroendocrine carcinoma (LCNEC) is a very rare disease, comprising approximately 3% of lung cancers. Even for Stage I disease, recurrence after resection is common, with a poor five-year overall survival. We present the first report of stereotactic body radiotherapy (SBRT) for pulmonary LCNEC.

Methods: A 54-year-old woman with a left upper lobe pulmonary nodule underwent a wedge resection with thoracoscopic mediastinal lymph node dissection, revealing a 2.3 cm pT1b N0 LCNEC. Approximately one year later, surveillance imaging demonstrated a new left upper lobe PET-avid nodule, resulting in completion left upper lobectomy revealing LCNEC, with 0/6 involved lymph nodes and negative staging studies. The patient subsequently chose surveillance over adjuvant chemotherapy; unfortunately 23 months later imaging revealed an enlarging 0.7 cm nodule adjacent to the previous resection site, despite the patient remaining in good health (KPS = 90). Subsequent restaging demonstrated no evidence of metastatic disease. Due to the morbidity of a third operation in this region, and based on the safety of SBRT for Stage I non small-cell lung cancer, the consensus decision from our thoracic oncology team was to proceed with SBRT as preferred management for presumptive second recurrence of LCNEC. The patient shortly thereafter underwent SBRT (50 Gy in 10 Gy/fraction) to this new nodule, 41 months following initial LCNEC diagnosis.

Results: Four months following SBRT, the patient remains in excellent clinical condition (KPS 90), with no evidence of disease spread on surveillance studies. The nodule itself demonstrated no evidence of growth following SBRT.

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Conclusions: This first report of SBRT for pulmonary LCNEC demonstrates that SBRT is a feasible modality for this rare disease. A multidisciplinary thoracic oncology approach involving medical oncology, thoracic surgery, radiation oncology and pulmonology is strongly recommended to ensure proper patient selection for receipt of SBRT.

1. Background

Stereotactic body radiotherapy (SBRT) is an evidence-based treatment modality for Stage I non-small cell lung cancer, having demonstrated comparable local control and overall survival to surgical resection in Phase III randomized trials.[1] Pulmonary large-cell neuroendocrine carcinoma (LCNEC) is a very rare disease, comprising approximately 3% of lung cancers.[2,3] Characterized by large cells with abundant cytoplasm, high mitoses, necrosis, and neuroendocrine features, LCNEC differs from small-cell lung cancer (SCLC) in that SCLC has smaller cells, a different pattern of invasiveness, and a low nuclear/cytoplasm ratio.[4] While the rarity of pulmonary LCNEC has precluded prospective analyses, retrospective studies have demonstrated that even for Stage I disease, recurrence after resection is common, with a poor five-year overall survival.[2] We present the first report of SBRT for pulmonary LCNEC.

2. Case report

A 54-year-old woman with a left upper lobe pulmonary nodule underwent a wedge resection with thoracoscopic mediastinal lymph node dissection, revealing a 2.3 cm pT1b N0 mass which on pathology demonstrated the characteristics of LCNEC (Fig. 1). Approximately one year later, surveillance imaging revealed a new left medial upper lobe PET-avid pulmonary nodule (SUV maximum 3.0), and she underwent completion lobectomy of the left upper lobe, with 0/6 involved lymph nodes, and negative staging studies; pathology once again revealed LCNEC. Postoperatively, the patient elected to continue with surveillance over adjuvant chemotherapy. Unfortunately over the next 23 months a nodule abutting the left upper lobectomy surgical suture line (Fig. 2) increased on chest CT from 0.1 cm (at 15 months) to 0.3 cm (at 19 months) to 0.7 cm (at 23 months) in an eight-month timespan, despite the patient remaining in good health (KPS 90). This nodule was PET-avid with maximum SUV of 4.3; restaging demonstrated no evidence of metastatic disease.

Due to the morbidity of a third operation in this region, and based on the safety of SBRT for Stage I non-small cell lung cancer, the consensus decision from the thoracic oncology tumor board was to proceed with SBRT as preferred management for presumptive second recurrence of LCNEC. The patient shortly thereafter underwent SBRT (50 Gy in 10 Gy/fraction) to this new nodule, 41 months following initial LCNEC diagnosis (Fig. 3). Treatment planning was performed utilizing four-dimensional CT to delineate the target volume through all phases of the respiration cycle as previously described.[5]

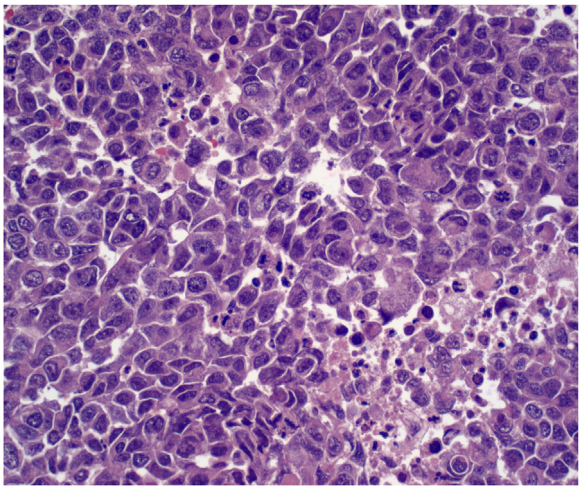


Fig. 1 – H&E stain of tissue from original left upper lobe wedge resection, demonstrating large cells with abundant cytoplasm, necrosis, mitoses and neuroendocrine features: the constellation of findings comprising the hallmark of large cell neuroendocrine carcinoma.

Given the less than 0.5 cm movement of the tumor throughout respiration on the 4DCT scan, contours were created from the average 0–90 simulation CT scan and the patient was treated utilizing a free breathing approach. A volumetric modulated arc therapy plan was used, with 95% of the PTV receiving 99% of the dose and a maximum ITV dose of 116.1%.

Four months following SBRT, the patient remains in excellent clinical condition (KPS 90), with no evidence of disease spread on surveillance studies. The nodule itself demonstrated no evidence of growth following SBRT.

3. Discussion

The propensity for pulmonary LCNEC to metastasize is a large component of its poor five-year overall survival, and is the main reason surgical resection is the standard of care following initial diagnosis.[3] Our patient first underwent wedge resection, followed by complete lobectomy after initial recurrence, with both lesions proven to be LCNEC by tissue diagnosis (Fig. 1). Given the known propensity of pulmonary LCNEC to recur despite operative resection, it was the strong belief of our thoracic oncology team that the second recurrence on imaging (Fig. 2) was overwhelmingly likely to be LCNEC; this prompted imaging to rule out metastatic disease, after which the decision regarding optimal therapy for the nodule was discussed by our team. Although resection

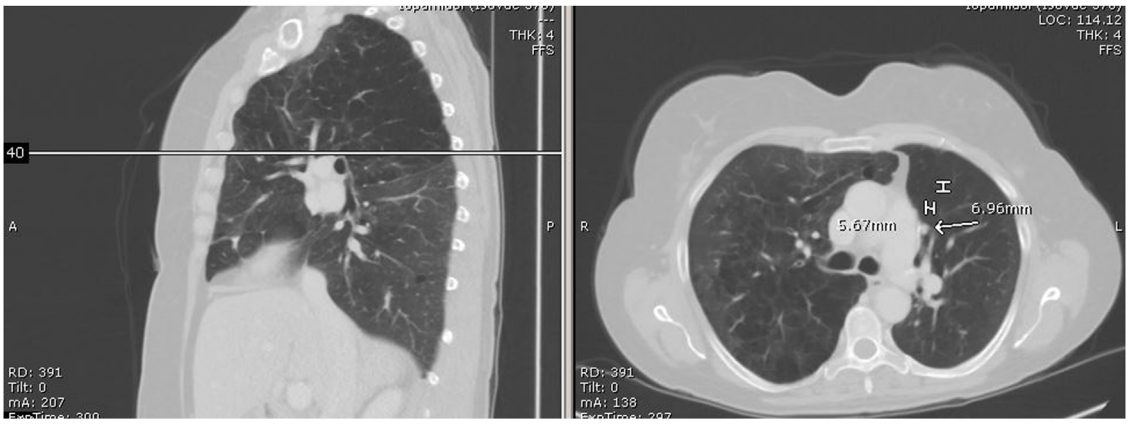
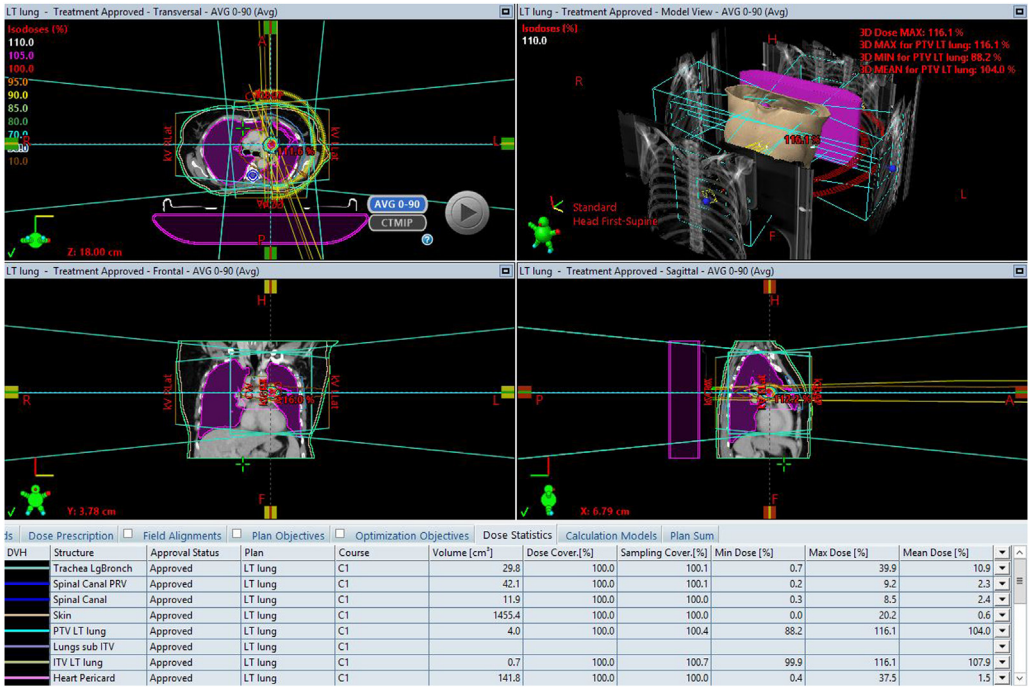


Fig. 2 – Sagittal and axial thoracic CT imaging nearly two years following left lobectomy, demonstrating a 0.7 cm nodule adjacent to previous resection.



DVH	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [%]	Max Dose [%]	Mean Dose [%]
	Trachea LgBronch	Approved	LT lung	C1	29.8	100.0	100.1	0.7	39.9	10.9
	Spinal Canal PRV	Approved	LT lung	C1	42.1	100.0	100.1	0.2	9.2	2.3
	Spinal Canal	Approved	LT lung	C1	11.9	100.0	100.0	0.3	8.5	2.4
	Skin	Approved	LT lung	C1	1455.4	100.0	100.0	0.0	20.2	0.6
	PTV LT lung	Approved	LT lung	C1	4.0	100.0	100.4	88.2	116.1	104.0
	Lungs sub ITV	Approved	LT lung	C1						
	ITV LT lung	Approved	LT lung	C1	0.7	100.0	100.7	99.9	116.1	107.9
	Heart Pericard	Approved	LT lung	C1	141.8	100.0	100.0	0.4	37.5	1.5

Fig. 3 – SBRT treatment plan for recurrent pulmonary LCNEC.

would technically be considered standard of care, the operative morbidity of a third resection in the same anatomic region combined with the Stage I nature of this lesion made SBRT an ideal noninvasive yet potent treatment option for her disease, particularly since retrospective data has indicated the median survival of Stage I lung cancer treated with observation is approximately 13 months.[6] Due to the proximity of the lesion to the arch vessels (Figs. 2 and 3), SBRT was administered to 50 Gy over five fractions as opposed to 54 Gy over three fractions, which is our current institutional preference.[7] Despite the relatively short period of post-SBRT follow-up (the recurrences in this patient occurred approximately one year and two years after resection), the absence of metastatic disease in combination with the patient retaining her pre-treatment KPS of 90 are indicators thus far that the choice of SBRT has been optimal in treating her disease without compromising her quality of life.

4. Conclusion

This first report of SBRT for pulmonary LCNEC demonstrates that SBRT is a feasible modality for this rare disease. A multidisciplinary thoracic oncology approach involving medical oncology, thoracic surgery, radiation oncology and pulmonology is strongly recommended to ensure proper patient selection for receipt of SBRT. Further follow-up is required to determine whether the prognosis of this patient will represent an improvement over that grimly reported in the retrospective literature.

Author contribution

Conception and design: McClelland, Lautenschlaeger. Data collection: McClelland, Musto. Data analysis and interpretation: McClelland, Durm, Birdas, Musto, Lautenschlaeger. Manuscript writing: McClelland. Final approval of manuscript: McClelland, Durm, Birdas, Musto, Lautenschlaeger.

Conflict of interest

None declared.

Financial disclosure

None declared.

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