CASE REPORT

Radiation-Induced Peripheral Neuropathy After Thoracic Stereotactic Ablative Radiotherapy: Case Report

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ABSTRACT

Stereotactic ablative radiotherapy (SABR) is a highly effective treatment for medically inoperable patients with early stage NSCLC. Because of its noninvasive nature and favorable toxicity profile, the use of SABR continues to expand for eligible patients. We present here two uncommon cases of peripheral neuropathy secondary to SABR-induced injury to recurrent laryngeal and phrenic nerves, resulting in unilateral vocal cord and diaphragmatic paralysis, respectively.

Keywords: Case report; Vocal cord paralysis; Recurrent laryngeal nerve; Diaphragmatic paralysis; SABR

Introduction

Advancements in treatment planning and delivery have facilitated the use of high-dose, ablative radiotherapy to optimize tumor control while minimizing normal tissue toxicity. Stereotactic ablative radiotherapy (SABR) has therefore evolved as the standard-of-care treatment for medically inoperable patients with stages I to IIA NSCLC, achieving remarkable outcomes with local control exceeding 90%. Accumulated experience with SABR in the past 10 to 15 years has informed clinical practice guidelines, and severe late toxicities to organ at risks (OAR), notably the esophagus, bronchial tree, great vessels, heart, chest wall, spinal cord, and brachial plexus, are largely avoided with careful treatment planning and patient selection. When performed by experienced centers, SABR is well tolerated and associated with low morbidity. Nevertheless, unexpected and uncommon toxicities can occur. Peripheral nerve damage has been previously reported as a rare but serious late sequelae of thoracic radiotherapy.[1,2] Although the radiosensitivity of the spinal cord and brainstem is well known, peripheral nerves have been traditionally regarded as more radioresistant. We herein report late development of vocal cord and diaphragmatic dysfunction from SABR-induced injury to ipsilateral recurrent laryngeal and phrenic nerves.

Case Presentation

Case 1

A 61-year-old female with 40+ pack-years smoking history, chronic obstructive pulmonary disease, and discoid lupus developed synchronous T1cN0M0 (2.3 cm, peripheral) right upper lobe and T1bN0M0 (1.5 cm, paramediastinal) left upper lobe (LUL) pulmonary adenocarcinomas. Results of positron emission tomography-computed tomography (CT) revealed avidity in the biopsy-proven nodules without regional or distant metastatic disease, confirmed by mediastinal lymph node sampling. On the basis of her poor pulmonary function and multidisciplinary recommendations, she opted for

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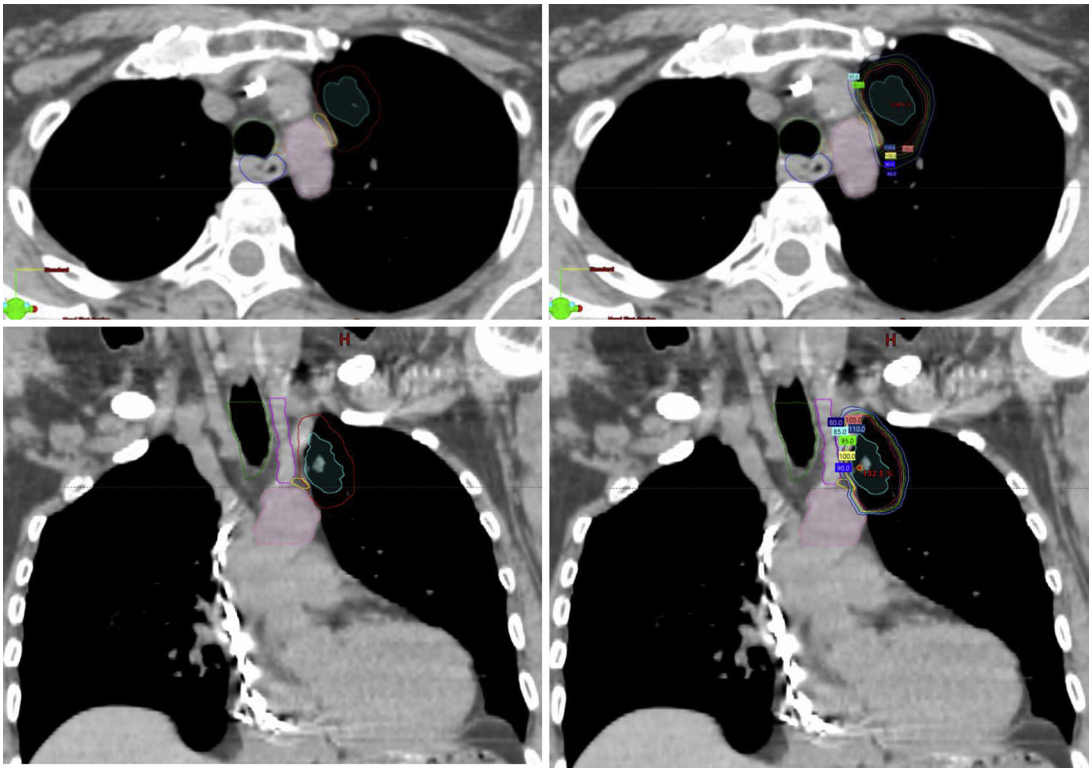

Figure 1. Case 1. PTV (red) delineated with segmentation of expected path of VN (yellow) and RLN (orange) (left column, upper and lower panels); dosimetric distribution of treatment plan targeting left upper lobe tumor treated with 55 Gy in five fractions (right column, upper and lower panels). Isodose curves displayed as a percentage of prescription dose. Windowing optimized for mediastinal structures underrepresents the true borders of the primary tumor. PTV; planning computed tomography with target volume; RLN, recurrent laryngeal nerve; VN, vagus nerve.

treatment with SABR. She was treated with 5000 cGy in four fractions and 5500 cGy in five fractions to the right upper lobe and LUL adenocarcinomas, respectively (Fig. 1). She tolerated treatment well with only mild esophagitis after course completion which resolved spontaneously. Routine follow-up with chest CT revealed stable postradiation changes without evidence of recurrence at her 2-year follow-up. After 1 year and 10 months from radiation treatment, she developed hoarseness associated with loss of vocal strength. Result of flexible endoscopy revealed decreased adduction and mobility of her left true vocal cord (TVC). Result of CT neck suggested left TVC paralysis with enlarged laryngeal ventricle and medialization of the left TVC. No cervical adenopathy was observed. Result of CT chest revealed a new area of left basilar atelectasis with stable post-treatment changes. The expected anatomical path of recurrent laryngeal and vagus nerves was retrospectively contoured on the radiation treatment planning scan (RTCT; Fig. 1) for dosimetric analysis (Table 1).

Case 2

A 74-year-old female with multiple co-morbidities was diagnosed with having stage I NSCLC of the LUL treated with SABR (5250 cGy in five fractions; Fig. 2). Ongoing surveillance imaging revealed radiation fibrosis within the LUL with no evidence of tumor recurrence within the treated field. One-year post-treatment, she developed progressive left hemidiaphragm elevation evidenced on subsequent chest CT and chest radiograph (Fig. 3). Results of pulmonary function tests revealed a 37% and 6% decline in forced vital capacity and total lung capacity, respectively. No systemic neuromuscular condition developed during this interval. Clinically, the patient reported worsening dyspnea, which was moderately improved with rehabilitation. The expected path of the phrenic nerve was retrospectively contoured on the RTCT (Fig. 2) for dosimetric analysis (Table 1).

Discussion

Radiation-induced peripheral neuropathy (RIPN), though uncommon, has been increasingly observed with improved long-term cancer survival. RIPN is most frequently reported as brachial plexopathy after breast irradiation and less frequently after irradiation to head and neck and apical thoracic tumors.[1,3] Vagal and recurrent laryngeal nerve palsy has been more recently linked to thoracic SABR, especially in the setting of

Table 1. Dosimetric Values Associated With Nearby OARs

Case	OAR	Max to 0.035 cm^3 (cGy, [% Rx])	Point Max (cGy, [% Rx])
Case 1[a]	Recurrent laryngeal nerve[b]	1427.5 [25.0]	1818.4 [33.1]
	Vagus nerve	5753.8 [104.6]	6203.0 [112.8]
	Aorta	5504.4 [100.1]	5921.1 [107.7]
Case 2	Phrenic nerve	4675.8 [89.1]	5291.8 [100.8]
	Aorta	5420.6 [103.2]	5566.9 [106.0]

[a]The concurrently treated right upper lobe tumor was noncoplanar with the treated left upper lobe tumor and was significantly far enough away such that any scatter dose contributed to listed OARs was negligible.
[b]Nerve fibers constituting the RLN originate from the vagus nerve; therefore, dose to the vagus nerve could contribute to the total dose of the RLN.
Max, maximum; OAR, organ at risks; RLN, recurrent laryngeal nerve; Rx, prescribed radiation dose.

reirradiation, but the true incidence is unknown.[2,4] Our report is the first to establish phrenic nerve palsy as a late toxicity after a single course of SABR to the lung.

The pathophysiology of RIPN remains an ongoing subject of debate. At least two mechanisms have been proposed, which are as follows: (1) nerve compression from radiation-induced fibrosis and (2) direct nerve injury from axonal damage and demyelination.[1] Regardless of pathogenesis, RIPN is usually an irreversible late sequela that may take many months to develop. It can complicate the diagnostic workup for neuropathy and compromise treatment options, especially when prior history of radiation treatment is overlooked.

Several factors contribute to the risk and severity of RIPN. Treatment-related factors such as fraction size, delivery technique, OAR dose distribution, and tissue tolerance for reirradiation should be considered to reduce toxicity.[1] For thoracic SABR, special caution is taken when treating central lesions adjacent to critical structures such as the bronchial tree, esophagus, heart, great vessels, and spinal cord.[5] Nevertheless, the RLN, vagus, and phrenic nerves are typically not well visualized on diagnostic imaging and doses to these structures

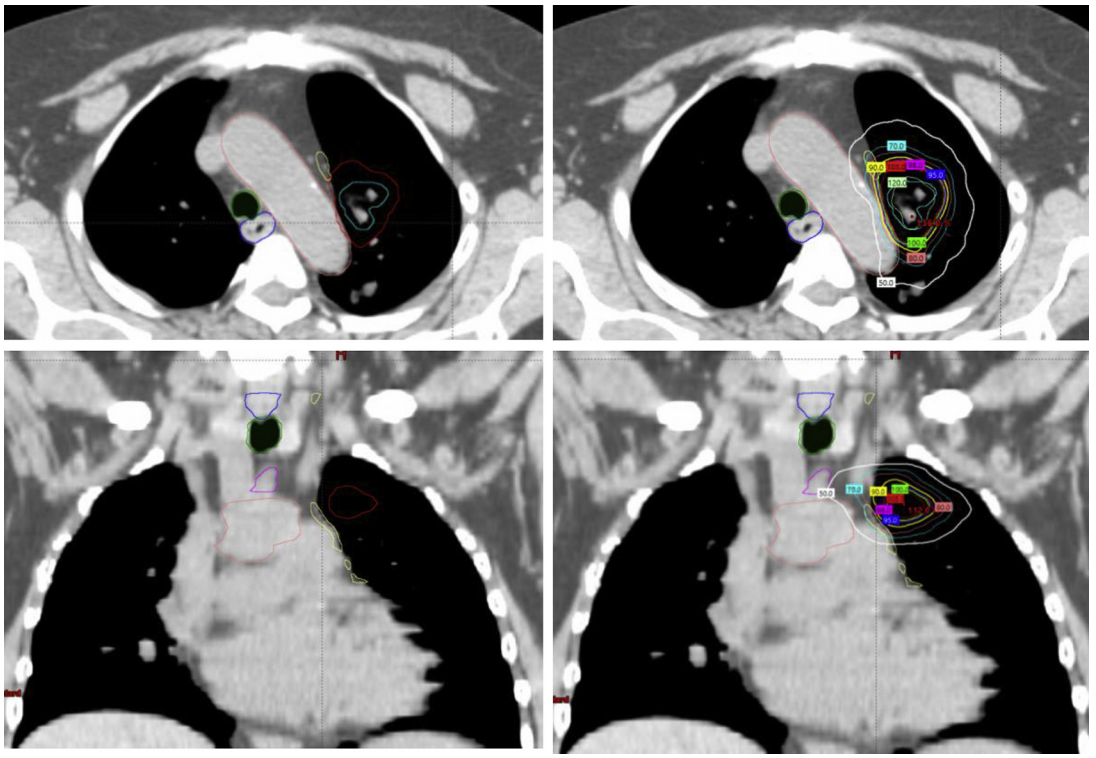

Figure 2. Case 2. PTV delineated with segmentation of expected path of PHN (yellow) (left column, upper and lower panels); dosimetric distribution of the treatment plan targeting left upper lobe tumor treated with 52.5 Gy in five fractions (right column, upper and lower panels). Isodose curves displayed as a percentage of prescription dose. Windowing optimized for mediastinal structures underrepresents the true borders of the primary tumor. PHN, phrenic nerve; PTV; planning computed tomography with target volume.

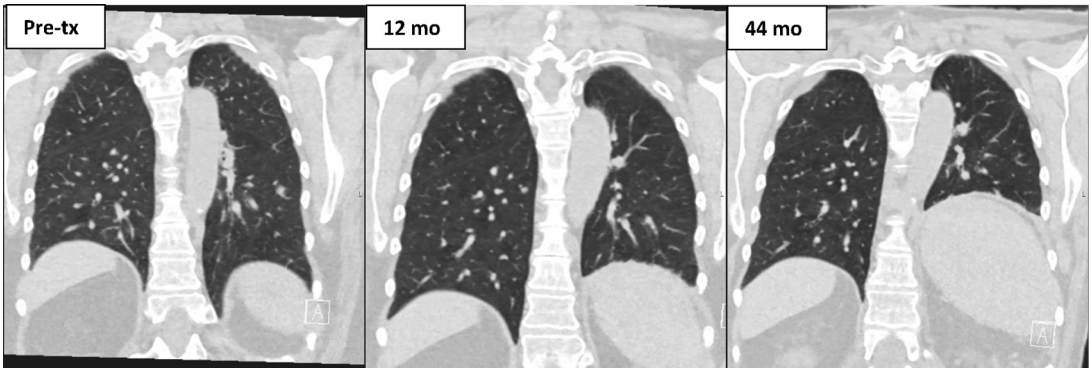

Figure 3. Coronal views of serial CT chest of patient described in case 2 revealing progressive elevation of left hemidiaphragm after SABR (middle and right panels) compared with pre-tx (left panel). CT, computed tomography; mo, months post-treatment; SABR, stereotactic ablative radiotherapy; tx, treatment.

are not routinely evaluated during treatment planning. Furthermore, the radiotolerance of these structures remains unknown. Last, patient-related factors likely play a role in lowering OAR radiotolerance, as previously reported for patients with autoimmune-related disease.

Conclusion

Vocal cord and diaphragmatic paralyses secondary to peripheral nerve injury are potential late toxicities of thoracic SABR. Although both patients remain disease free and express no regret in their decision to pursue SABR, careful pretreatment counseling and risk benefit discussion are essential, as is long-term follow-up for early symptom recognition. Management should aim to improve the patient's quality of life. In the absence of validated dosimetric constraints for peripheral nerves, it is unclear whether such toxicities are avoidable, especially for directly abutting tumors when using ablative doses to maximize tumor control. Future work developing dose constraints for recurrent laryngeal and phrenic nerves may enhance the safe practice of SABR for central thoracic tumors. Although these toxicities are uncommon, RIPN should be incorporated into the informed consent discussion for central lung tumors treated with SABR.

CRediT Authorship Contribution Statement

Ha H. Pham: Validation, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing—original draft, Visualization.

Neil Newman: Investigation, Resources, Writing—review and editing.

Evan C. Osmundson: Conceptualization, Methodology, Verification, Formal analysis, Investigation, Writing—review and editing, Supervision, Project administration.

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All patients described in this report provided written informed consent for therapy received and the inclusion of their deidentified data for use in research analyses.

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