

Unilateral Diaphragmatic Weakness After Stereotactic Radiotherapy of The Lung: A Case Report

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ABSTRACT

Stereotactic body radiation therapy (SBRT) is the treatment of choice for patients with stage 1 non-small cell lung cancer (NSCLC) who are medically unfit or those refusing surgery. SBRT is a modality which is well tolerated with respect to limitations on surrounding organs and contra-indications. With improving techniques and cancer treatments, patients have a longer life span, but it is known that radiotherapy can cause late-onset complications.

We are reporting the case of a 77-year-old woman who was treated with SBRT because of stage 1 NSCLC. She received a total dose of 51 Gy in three fractions, prescribed to the 78% isodose line. Eight months after SBRT she developed progressive dyspnea and the CT scan showed an elevated left hemi-diaphragm. Potential causes were ruled out. The SBRT treatment was performed without other complications.

To our knowledge this complication has not previously been described after SBRT. With constant improving cancer treatments and radio-therapeutic techniques, and better longevity, we could see an increase in long term toxicity in the future.

Keywords: Late Toxicity, Adverse Event, Stereotactic Radiotherapy, Lung Cancer

Introduction

The standard of care for patients with stage 1 non-small cell lung cancer (NSCLC) is surgery. For the medically unfit or those refusing surgery, stereotactic body radiation therapy (SBRT) is the treatment of choice. SBRT is a modality which is well tolerated with respect to limitations on surrounding organs and contra-indications. With improving techniques and cancer treatments, patients have a longer life span, but it is known that radiotherapy can cause late-onset complications.

Radiotherapy has been described as a rare cause of mostly bilateral paralysis of the diaphragm (Avila *et al.*, 2011; Brander *et al.*, 1997; Buzele *et al.*, 2011; Stoll and Andrews, 1966; Annede *et al.*, 2017). Unilateral elevation of the diaphragm can have multiple causes. A rare cause is a primary tumor of the phrenic nerve, this has been described in cases of neurofibromatosis. Furthermore, cervical compressive tumors or metastases, trauma (penetrating of the thorax of cervical plexus), stretching or cooling during cardiac surgery and suboptimal placement of central venous catheters or cardiac leads can cause hemiparalysis of the diaphragm due to phrenic nerve injury. Additionally, infections, for example herpes or poliomyelitis, can cause paralysis of the diaphragm (Bartolome *et al.*, 2022). Both unilateral and bilateral paralysees have the same etiology but the proportional probability is different (Bartolome *et al.*, 2022). Unilateral diaphragmatic paralysis is more common than bilateral and is often discovered incidentally because patients with unilateral diaphragmatic paralysis are usually asymptomatic at rest (Bartolome *et al.*, 2022).

In this report, we describe a case of a left diaphragmatic paralysis eight months after SBRT of a lesion in the left lung. Written consent for use of data and publication is obtained from the patient.

Case Presentation

A 77-year-old woman with a growing nodule with a solid component, in the left upper lobe underwent CT-guided needle biopsy. The lung biopsy showed diffuse interstitial fibrosis and non-specific chronic inflammation, no malignancy. This biopsy was presumably not representative according to the pathologist. The patient was considered unfit for surgery to obtain a definite diagnosis and the multidisciplinary oncology meeting advised a three month follow up. At follow up, the lesion had grown and became PET positive. The growing nodule was considered clinically suspect for T1N0M0 adenocarcinoma. Because of comorbidities, surgery was not a good option and SBRT was suggested as treatment alternative. Naturally, the patient has been included in the final decision-making process and agreed with the SBRT based on strong clinical suspicion, but without final pathological evidence.

She was subsequently treated with SBRT in 2020 to a total dose of 51 Gy in three fractions, prescribed to the 78% isodose line. The lesion was 8 x 10 mm on PET-CT in December 2019. She has a medical history of asthma and excision of a IgG4 related pseudo tumor in the left upper lobe of the lung in 2016 without any signs of systemic IgG4 disease or local recurrence. Several small pulmonary nodules and areas of groundglass were stable between 2016 and 2019. She further had a transcatheter aortic valve replacement in 2016.

The SBRT was performed without complications. After radiotherapy the follow up at the pulmonologist continued with CT scans every three months. The CT scan of October 2020 demonstrated increase in some of the pre-existent areas of pulmonary groundglass, possibly related to IgG4 disease. The irradiated tumor lesion showed a complete radiological response. At this time the patient also complained about progressive dyspnea on exertion. Because of possible IgG4 activity and restraint to use invasive diagnostic procedures at this point, she was treated with corticosteroids (prednisone 30 milligram) for several weeks with no effect on the groundglass areas or dyspnea. In December 2020 the patient was referred to the emergency department because of persistent dyspnea and pain with respiration. Chest CT scan showed an elevated left hemi diaphragm (Fig. 1) and no pulmonary embolus.



Figure 1: CT-scan December 2020 shows an elevated left hemi diaphragm.

In retrospect, this elevation was already visible in the CT scan made in November 2020 (only less severe). Her lung function tests showed a steep decline in forced vital capacity (FVC) from 2.70L (101%) in July 2019 to 1.86L (71%) in December 2020. No electromyography (EMG) had been made. She had no suspected recent viral infection. A CT scan of the chest, head and neck was subsequently made to exclude other causes of phrenic nerve damage. Echo and fluoroscopic sniff test confirmed a paradoxical diaphragmatic elevation on the left side during inspiration. This indicates severe weakness or paralysis of the left hemi diaphragm. At this point, there were concerns that this could be late toxicity of the SBRT. Therefore, it could be considered to treat the patient with hyperbaric oxygen therapy. In this case, this was not a suitable option, because of chronic pain related to a broken vertebra. The treatment plan was reviewed and is shown in Fig. 2 and 3. Fig. 4 shows the target volumes in two planes. The phrenic nerve was mostly in the planning targeted volume receiving a total dose of 25-38 Gy in three fractions (BED 129-279 / EQD2 65-139 Gy with α/β of 2).

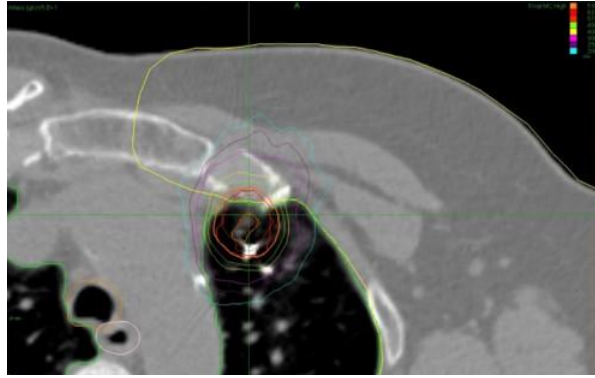


Figure 2: Treatment plan close up of cranial part of the target volume.

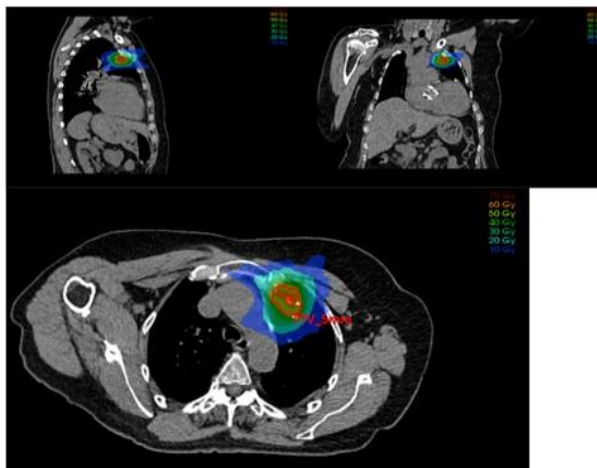


Figure 3: Treatment plan with 5mm PTV margin.

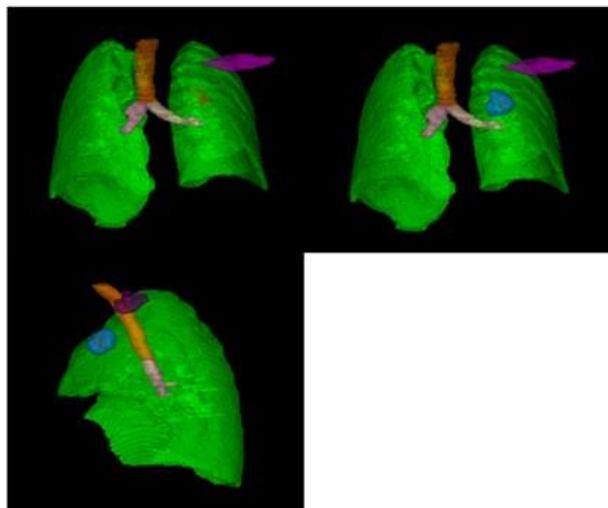


Figure 4: Target volume three dimensional: GTV (red) (left), PTV (blue) (right), PTV sagittal plane (lower). Brachial plexus in purple. Trachea in orange. Bronchi in pink.

Currently, 2.5 years after the SBRT, the patient has continued shortness of breath on exertion and a persisting elevated left hemi diaphragm is seen on chest CT scan.

Discussion

To the best of our knowledge, elevation of the diaphragm due to dysfunction or weakness of the phrenic nerve after SBRT has not previously been described as late toxicity. In some rare cases bilateral weakness of the diaphragm after radiotherapy is described (Buzele *et al.*, 2011). Generally, this was after radiotherapy for Hodgkin lymphoma or mammary carcinoma and did not concern SBRT as in our case, but conventional radiotherapy. For example, Buzele, *et al.* (2011) described a case of malnutrition from esophageal and phrenic dysfunction 20 years after radiotherapy with 40 Gy (supraclavicular, mediastinal and cervical) for Hodgkin's lymphoma (Buzele *et al.*, 2011). Brander, *et al.* (1997) described a case of bilateral diaphragmatic weakness 30 years after radiotherapy for Hodgkin's lymphoma (Brander *et al.*, 1997). A total dose of 100 Gy was given at the supraclavicular and axillar regions and mediastinum, a dose which is now obsolete. They conclude that minor and unilateral weakness must often have been overlooked in previous studies. Avila, *et al.* (2011) described a case of a 55-year-old female with progressive dyspnea and unilateral elevation of the diaphragm (but with bilateral damage of the phrenic nerve) 37 years after radiation for Hodgkin's lymphoma (Avila *et al.*, 2011). She received 36 Gy in 18 fractions on peri-aortal and mantle fields. The D-max of the phrenic nerve was 44 Gy. Annede, *et al.* (2017) reported a case of gastroparesis two years and seven months after radiotherapy with 30 Gy in ten fractions (Annede *et al.*, 2017). For the brachial plexus there is a five percent chance to develop complications in the following five years when one third of the irradiated volume receives 62 Gy (Emami *et al.*, 1991). Stoll and Andrews (1966) states that 73% developed neurological symptoms after a total dose of 63 Gy in twelve fractions (EQD2=114). After 57.75 Gy in eleven fractions (EQD2=105), 15% got symptoms. Kori, *et al.* (1981) stated that a total dose of 60 Gy or more, and a fraction size of >2 Gy is associated with an increased risk of brachial plexus neuropathy (Kori *et al.*, 1981). The constraint for the phrenic nerve is not described in earlier literature. In many studies the brachial plexus is used as a surrogate for the phrenic nerve. Emami, *et al.* (1991) did not describe this nerve either, only the brachial plexus. Because of this, we used the same constraints as for the brachial plexus. Considering the evidence, we conclude that total dose and fraction size are important predictors of damage to the phrenic nerve.

One of the reasons why this paper contributes to this subject is because most studies on this subject are out of date (Brander *et al.*, 1997; Kori *et al.*, 1981; Stoll and Andrews, 1966). Higher total doses and different techniques were used in comparison with current treatment plans. Fig. 2 and 3 show the stereotactic dose plan for February 2020 of the patient. She was treated with 51 Gy in three fractions of 17 Gy. It is apparent that the tumor is close to the left phrenic nerve. The phrenic nerve derives from cervical nerve roots three, four and five. This is close to the brachial plexus, which derives from cervical root five, six and seven and thoracic nerve root one. The phrenic nerve innervates the diaphragm and takes care of

the sensible and motoric innervation of the diaphragm. The nerves continue in the caudal direction, the right phrenic nerve passes the brachiocephalic vein and superior vena cava on the lateral side. On the left side the nerve travels laterally from the aortic arc. It then passes the hili on the anterior, and laterally passes by the mediastinum to the diaphragm where the nerves fan out (Aquino *et al.*, 2001). We can conclude that the left phrenic nerve is partially in the target volume and most likely received between 25-38 Gy. We have no information about the irradiated volume of the nerve, because the nerve was not treated as an organ at risk. In our institute, the constraint for plexus brachialis nerves is: D-max of 24 Gy. The threshold of the nerve is thus exceeded, as we use this constraint as a surrogate for the phrenic nerve.

Our patient presented with progressive dyspnea, similar to previously described cases in literature. The main difference being that our patient received SBRT, to a small volume, but a locally high dose (up to 51 Gy in total) was applied. Furthermore, the patients described in previous studies had bilateral paralyses and our patient unilateral. The lung function (FVC) decreased 30% in our patient, which has been described in relation to unilateral diaphragm weakness before (Kokatnur and Rudrappa, 2018).

According to Avila, *et al.* (2011), there are four criteria to set the diagnosis of phrenic nerve injury secondary to radiation treatment (Avila *et al.*, 2011). First, it is a diagnosis of exclusion. Second, the radiation field must be at the location of the nerve, furthermore, an adequate latent period must have passed and the tolerance threshold of the nerve must be exceeded. In our case no other cause of the nerve injury was found. On the CT scan no signs of malignancy or other causes of compression or damage to the cervical or high thoracic nerves or roots were seen. As shown in Fig. 2 and 3 and as described above, the nerve is partially in the radiation field. Most injuries after radiotherapy usually occur within two years, but very late onset has also been reported i.e. 37 and 30 years after radiation (Avila *et al.*, 2011; Brander *et al.*, 1997). In our case, the patient developed symptoms within two years, namely, eight months after SBRT. As described earlier, the threshold of 24 Gy (D-max) was exceeded. For this complication it was advised to try hyperbaric oxygen therapy, but at that moment the patient was in no clinical condition to receive this treatment due to chronic pain related to a broken vertebra.

Conclusion

A 77-year-old patient presented with progressive dyspnea and an elevated left hemi diaphragm eight months after SBRT of the left upper lobe for clinically suspect stage 1 NSCLC. There is an anatomical correlation of the nerve in the radiation field. Also, the elimination of other diagnosis and a tolerance threshold that was exceeded, allows us to link this case of hemi lateral weakness of the diaphragm to radiotherapy, despite the fact that our patient received a conventional fractionation and a total dose that is generally considered to be safe. To the best of our knowledge, this complication has not previously been

described after SBRT. Possibly, this occurs more frequently than reported because not every patient becomes symptomatic. Other constraints for the phrenic nerve should be considered, especially when the radiation is bilateral or when it concerns re-radiation. With constantly improving techniques, better cancer treatments and longevity, an increase in long term toxicity could be seen in the future.

Ethics Statement: Written consent for use of data and publication is obtained from the patient.

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