Case Report

The use of adaptive intensity-modulated radiotherapy in the treatment of small-cell carcinoma lung refractory to chemotherapy in a patient with preexisting interstitial lung disease

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ABSTRACT

This is a case report of a 60-year-old diabetic, hypertensive male with a good performance status and a history of bilateral interstitial lung disease with a left upper lobe lung mass diagnosed to be a Stage IIB mixed small-cell/squamous cell carcinoma which was refractory to carboplatin- and etoposide-based chemotherapy. The patient was then taken up for adaptive intensity-modulated radiotherapy with tighter margin under image guidance with a mid-treatment replanning done at 25#. Acute toxicities were assessed weekly and showed no Grade 3 or more reactions. Pulmonary function test showed no detrimental changes during or after radiation. Response assessment at 12 and 20 weeks showed a partial response with decrease in metabolic activity on serial scans.

KEY WORDS: Adaptive radiotherapy, image-guided radiotherapy, small-cell lung carcinoma, squamous cell lung carcinoma

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INTRODUCTION

Small-cell lung carcinoma (SCLC) has a gross burden of 13% with majority presenting as extensive stage SCLC.[1] The use of chemoradiation in limited stage SCLC has improved overall survival (OS) with tolerable increase in toxicities.[2] Recent evidence has shown OS advantage in extensive stage SCLC.[3] The most troublesome complication of thoracic radiotherapy (TRT) is radiation pneumonitis (RP). Preexisting interstitial lung disease (ILD) further complicates TRT planning and implementation. TRT is found to increase episodes of fatal RP in patients with subclinical ILD.[4] This case assesses the role of adaptive intensity-modulated radiotherapy (A-IMRT) in patient with preexisting ILD.

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CASE REPORT

A 60-year-old diabetic, hypertensive male with a good performance status (WHO 1) presented to outpatient department with preexisting ILD for the past 4 years and a history of coronary artery disease with the left lung mass. He was evaluated for incidental mass in the left lung apex on computerized tomography (CT) of the chest.

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A ^{18}fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET)-CT showed an FDG avid (SUV_{max} 13.1) enhancing mass in the apicoposterior segment of the left upper lobe, measuring 5.9 cm × 3.6 cm × 6.7 cm with no evidence of extrathoracic disease. Biopsy showed focal p40, synaptophysin, and cytokeratin positivity, thyroid transcription factor-1 negativity with morphological features compatible with a diagnosis of combined SCLC and squamous cell carcinoma, limited staged T2bN1M0, Stage IIB as per Veteran's administration, and AJCC 2009 staging.

Thoracic multispecialty board (MSB) ruled out radiotherapy in view of risk of ILD progression. The patient received 6 cycles of carboplatin- and etoposide-based chemotherapy. Post-6 cycles, PET-CT was suggestive of both metabolic and morphological progressions.

With the progression limited to the thorax, MSB decided to add radiotherapy. Planning 4D-CT showed a mean movement of <1 cm in X, Y, and Z coordinates. The patient was simulated with 3-mm CT slices in SOMATOM sensation open™ and immobilized with orfit-ray™ cast. The DICOM files were pushed into Varian Eclipse™ where the patient was planned with A-IMRT.

Contouring

Phase I

Gross tumor volume (GTV) was taken as a gross disease as seen on CT and PET scans after co-registration. A uniform margin of 1 mm was added along GTV to form the planning target volume 1 (PTV). Four-mm margin (reduced in comparison to current standards in view of ILD) was added uniformly with truncation along chest wall and normal mediastinal structures to form the clinical target volume (CTV). Elective nodal irradiation (ENI) was not included as per current standards. A setup margin of 2 mm (reduced to the account for ILD) was also added uniformly around to form the PTV2. The patient was planned for 50 Gy/25# to PTV1 and 44 Gy/25# to PTV2.

High-resolution computed tomography chest between two phases showed a partial response (RECIST 1.1) in lung primary, no interval change in the hilar lymph node.

Phase II

An adaptive planning CT scan was conducted after 23# for Phase II A-IMRT after 25#. GTV was recontoured, and CTVn and PTVn margins were reduced accordingly (PTV2 was removed). PTVn was prescribed 16 Gy at 2 Gy per fraction [Figure 1].

Plan evaluation

Phase I and Phase II were independently assessed for target delineation, and plan sum was assessed for organ at risk (OAR) [Tables 1-3 and Figure 2].

Weekly toxicity assessment

He had no Grade 3/4 toxicity. He had Grade 2 esophagitis which was managed conservatively. Antifibrotic therapy was discussed in MSB, and the patient was started on oral pirfenidone with weekly PFT assessment. The pirfenidone was started at 600 mg in three equally divided doses and was subsequently escalated to 1200 mg/day with weekly liver function tests.

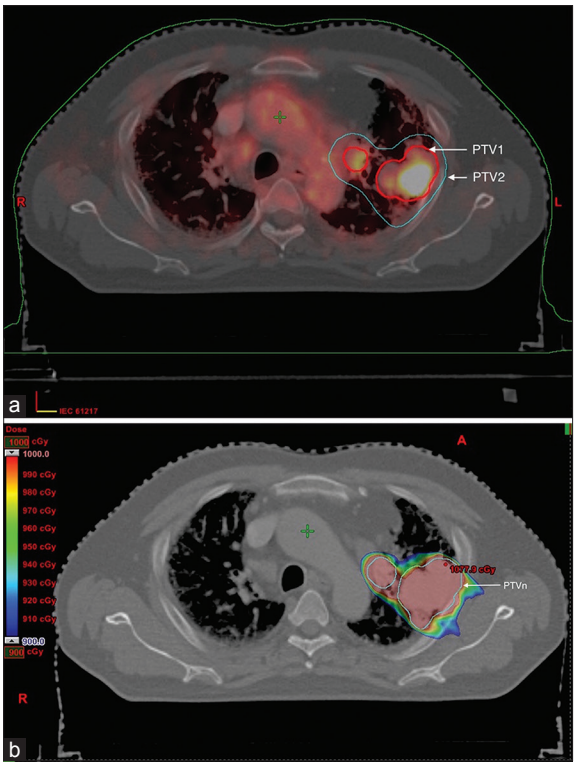

Figure 1: (a) Phase I contouring showing planning target volume 1 and planning target volume 2 with fluorodeoxyglucose-positron emission tomography co-registration. (b) Phase II contouring with planning target volume n

Table 1: Phase I dosimetry

	PTV1 (Gy)	PTV2 (Gy)
Volume	46.29 cc	168.25 cc
V95%	50.13	42.60
D110%	55.14	46.86
D93%	46.62	39.61
Hot-spot (>110%)	0%	42%
Cold-spot (<93%)	0%	0.02%
D2%	51.06	52.30
D98%	50.05	42.03
D50%	51.96	45.74
HI	1.9	22.4
CI	0.98	0.97

HI: Homogeneity index, CI: Conformity index, PTV: Planning target volume

Response evaluation

PET-CT was done 12 weeks after completion of radiotherapy showed an upper lobe metabolically active lesion (1.8 cm × 1.7 cm, maximum standardized uptake value [SUV_{max}] 9.3). A decrease in size and metabolic activity (30% decrease in SUV) was seen. Mediastinum showed a complete response. A repeat PET-CT scan at 20th-week postradiotherapy showed a further decrease

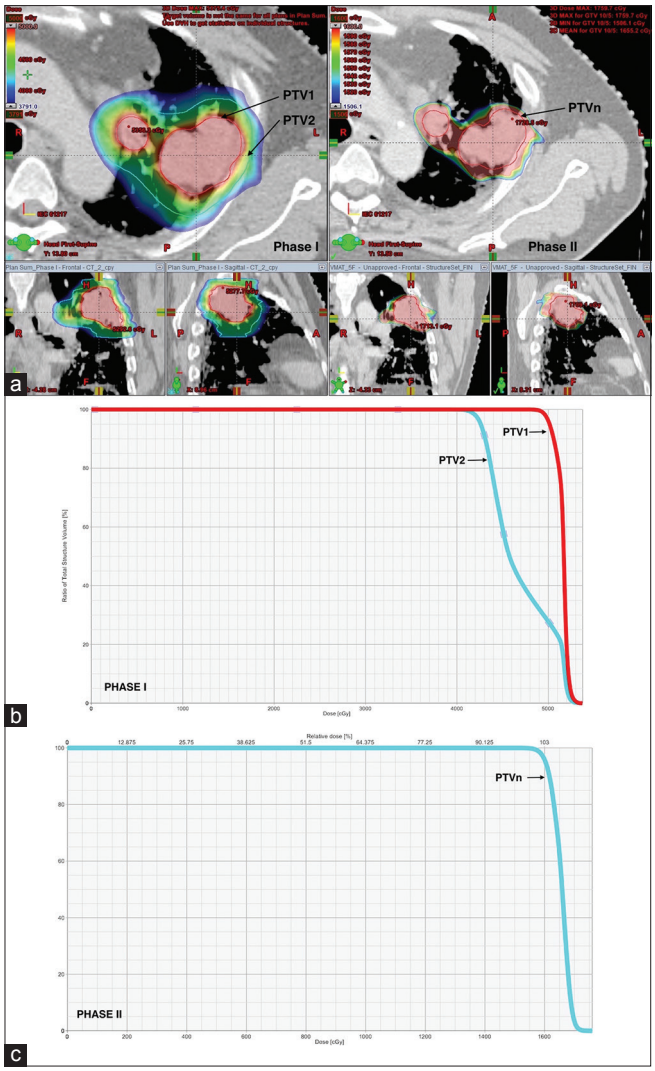

Figure 2: (a) Dose-color wash denoting Phase I and Phase II, respectively. (b) Dose-volume histogram showing Phase I planning target volume 1 and planning target volume 2. (c) Dose-volume histogram showing Phase II planning target volume n

in metabolic activity. No detrimental changes were noted in the PFTs and CT thorax at 12- and 20-week postradiotherapy [Figure 3].

DISCUSSION

In ILD, lung carcinoma occurs in 3.3% at 1 year and 15.4% at 5 years. Furthermore, the presence of ILD predisposes to higher probability of RP.[5] With lack of standard classification, it becomes difficult to interpret studies such as cryptogenic fibrosing alveolitis, interstitial pneumonia, and idiopathic pulmonary fibrosis are different terms for ILD used in the UK, Japan, and the USA, respectively.[6] Lack of standardized diagnostic approach, confounding factors such as tuberculosis, along with perceived phobia, hesitancy, lack of financial resources, lead to current conservative approach to the diagnosis and treatment of new onset of ILD in India without any formal documentation.[7]

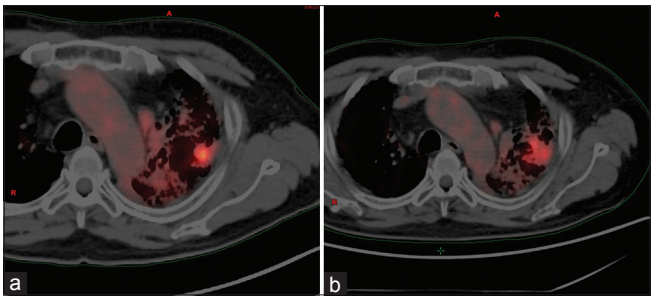

Figure 3: (a) Response evaluation with fluorodeoxyglucose-positron emission tomography at 12 weeks of completion of radiotherapy. (b) Response evaluation with fluorodeoxyglucose-positron emission tomography at 20 weeks of completion of radiotherapy

Table 2: Phase II dosimetry

	PTVn (Gy)
Volume	39.68 cc
V95%	16.03
D110%	17.63
D93%	14.90
Hot-spot (>110%)	0%
Cold-spot (<93%)	0%
D2%	16.25
D98%	15.93
D50%	16.58
HI	1.93
CI	0.98

HI: Homogeneity index, CI: Conformity index, PTV: Planning target volume

Table 3: Organ at risks

Organs	Volume Radiated	D_{max} (Gy)	D_{mean} (Gy)
Lungs	V_{20Gy} - 16.88%	-	9.19
Esophagus	-	27.89	7.84
Heart	V_{25Gy} - 0%	-	1
Spine	-	12.99	-

Radiation leads to the production of free radicals, leading to DNA damage and further cause fibrotic changes on healing. Preclinical studies have shown that the combination of gene therapy with chest irradiation to increase the expression of manganese superoxide dismutase which limits the evolution of radiation-induced pulmonary damage.[8] Traditionally, RP was pathologically divided into five distinct groups.[9] Immediate phase – occurs within hours to days and is characterized by hyperemia and congested mucosa with leukocytic infiltrations, leading to pulmonary edema. Latent phase – represents the phase with accumulations of thick secretions with ciliary dysfunction. Acute exudative phase – occurs 3 to 12 weeks after exposure and results in sloughing of endothelial and epithelial cells. This phase is clinically most significant. This phase leads to intermediate phase and fibrotic phase. However, clinically and radiologically, only acute and chronic phase is relevant which may warrant a medical intervention in the form of steroids and mucolytics.[10]

Antifibrotic therapy with pirfenidone has been used in clinical trial setting to improve the results of radiation

pneumonitis.[11] Nintedanib, a tyrosine kinase inhibitor, is being studied to decrease the incidence of RP after thoracic radiotherapy. Preclinical studies have shown the efficacy of nintedanib in controlling ILD and decreasing the risk of RP.[12] A Phase II has recently been opened by Memorial Sloan Kettering Cancer Center (MSKCC) which assess the role of nintedanib in the development of RP after TRT.

Four most important factors responsible for the development of RP are method of irradiation, volume of irradiated lung, dosage, and time-dose factor. With the use of respiratory motion management techniques, conformity and discontinuation of ENI, two important factors responsible for RP are inferior lung irradiation and increasing lung mean dose (volume receiving >20 and >30 Gy and mean lung dose act as predictors for the development of symptomatic RP).[13]

In our patient, both factors of limiting the lung volume irradiated using A-IMRT and location of the tumor in the upper lobe theoretically restricts the risk of both acute RP and classical RP. Lack of prospective randomized trials assessing various dosimetric parameters in correlation with clinical parameters in a setting of preexisting ILD, especially in the era of IMRT limits standardization of these atypical cases.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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