A new treatment option for stage IIIB lung squamous cell carcinoma-Hypofractionated brachytherapy combined with ICIs: A Case Report

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Research Article

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Abstract

Here, we present a case of a patient with stage IIIB squamous lung cancer with mediastinal and cervical lymph node metastases in the left lung with peripheral squamous lung cancer, who was selected for simultaneous immunotherapy with insertional radiotherapy at the primary site in the left lung, followed by intensity-modulated radiotherapy for mediastinal and cervical lymph node metastases and maintenance immunotherapy every 3 weeks. There was no treatment-related toxicity above grade 2 during the treatment. The response was PR, and PFS was more than 12 months. That provides a new therapeutic idea for treating advanced squamous lung cancer. Here, we present a case of a patient with stage IIIB squamous lung cancer with mediastinal and cervical lymph node metastases in the left lung with peripheral squamous lung cancer, who was selected for simultaneous immunotherapy with insertional radiotherapy at the primary site in the left lung, followed by intensity-modulated radiotherapy for mediastinal and cervical lymph node metastases and maintenance immunotherapy every 3 weeks. There was no treatment-related toxicity above grade 2 during the treatment. The response was PR, and PFS was more than 12 months. That provides a new therapeutic idea for treating advanced squamous lung cancer.

Introduction

Squamous-cell carcinoma accounts for about 18% of lung cancers [1], and it is difficult to benefit from targeted therapy because of fewer driver gene mutations. Chemoradiotherapy combined with Immune checkpoint inhibitors(ICIs) shows better response rates and longer overall survival than chemoradiotherapy [2]. However, treatment-related pneumonitis has the risk of death[3]. Radiotherapy combined with immunotherapy may produce overlapping toxicity, increase the incidence of pneumonitis, even threaten the patient's life [4]. High-dose-rate (HDR) brachytherapy has the advantage of providing a high radiation dose in a focal lesion, allowing apoptosis over an extended period[5]. Here, we present the case of an IIIB squamous-cell carcinoma patient receiving ICIs with Concurrent Hypofractionated brachytherapy for primary and sequential Volumetric Intensity Modulated Arc Therapy(VMAT) for mediastinal and cervical lymph node metastasis. The novel combination can significantly reduce the radiaton dose of normal lung tissue and avoid pneumonitis.

Case Presentation

In March 2021, a 40-year-old woman was admitted with a repeated cough for one month. Enhanced chest computed tomography (CT) revealed a peripheral pulmonary mass in the left lower lobe, about 3.4*3.2*4.0cm, and lymph nodes under the bulge >1.5cm in short diameter. Positron emission tomography CT scans found a pulmonary mass mediastinal node, and neck lymph node in Section IV had increasing metabolism. MRI Brain scanning was negative. The tumor Immunohistochemistry testing showed that TTF-1 - Napsin-A - P40 - CK5/6 - P63 + Ki67 +,60% . So patient was diagnosed with IIIB squamous-cell lung carcinoma (cT2aN3M0, AJCC8th).

After 2 cycles of chemotherapy of TP combined with Cindillizumab(aPD-1), The chest CT indicated the peripheral pulmonary mass, about 1.9*2.1*2.6cm in size. According to RECIST1.1 criteria, tumor diameter in the left lower lobe was reduced by 37% from baseline, evaluation of efficacy was PR Mediastinal, and Cervical lymph nodes were SD. In May 2021, the patient subsequently received Hypofractionated brachytherapy for the pulmonary mass: GTV D90:2790cGy; L-lung: V20=2.8%、V5=16.26%.In June 2021, 64Gy/30F mediastinal and cervical lymph node radiotherapy: GTVnd1 D95=6446.6cGy;GTVnd2 D95=6146.1cGy;CTV2 D95=6396.1cGy; L-lung: V5=51.98%、V20=8.28%;R-lung: V5=67.34%、V20=15.89%. Concurrent chemotherapy of TP combined with Cindillizumab for 1 cycle. Then, the patient regularly received Cindillizumab every 3 weeks. As of the last follow-up date of March 2022, The patient occasionally had cough and fatigue, but the degree was grade 1, and no immune pneumonia or immune myocarditis occurred.

Discussion

In patients with unresectable stage III non-small cell lung cancer, previous treatment with platinum-based concurrent radiotherapy has resulted in 5-year survival (OS) rates of 15%-32%[6]. For locally, concurrent radiotherapy with sequential dulvalizumab, with treatment-related toxicity within acceptable limits, has resulted in a 5-year OS of 42.9% [7, 8], which is the current standard of care for unresectable locally advanced NSCLC.

However, investigators have not stopped advancing and based on retrospective analyses, and phase 2 studies[9, 10]、phase 3 clinical studies of ICIs with concurrent radiotherapy have been conducted (e.g., ECOG-ACRIN EA5181, DART, etc.). However, treatment-related toxicity is of concern, especially in patients with a history of chest radiotherapy, chronic obstructive pulmonary disease, pneumonia, pulmonary fibrosis, and elevated absolute peripheral eosinophil counts, who may have a higher incidence of grade 3 or higher pneumonitis [11].

The immune-activating effect and immunosuppressive effect of radiotherapy need to be considered when radiotherapy is combined with ICIs. Therefore, the segmentation pattern, dose, and site of radiotherapy treatment need to be further investigated.MDACC trial adding radiotherapy to pembrolizumab treatment significantly improved response and prognosis in patients with metastatic non-small cell lung cancer[12].In the stratification of RT, it was concluded that the out-of-field ORR was 38% in the SBRT group and 10% in the conventional RT group (p=0.11), with mPFS times of 20.8 and 6.8 months, respectively (p=0.03). Many scientific trials have also indicated that higher doses of radiotherapy are necessary to induce systemic immunity but are also accompanied by higher treatment-related toxicity. In a study on the relationship between radiotherapy and the development of immune pneumonitis, immune pneumonitis occurred predominantly in lung volumes treated with moderate and low doses of radiotherapy, rather than in areas treated with high doses of radiotherapy[13]. Many scientific experiments have shown that higher doses are necessary to induce systemic immunity but are also associated with higher treatment-related toxicity. In a study on the relationship between radiotherapy and the occurrence of immune pneumonia, immune pneumonia mainly occurred in the lung volume receiving medium or low dose era but not in the area receiving high dose era [14]. It has become a challenge to

control the medium and low radiation doses to the lungs and thus reduce the occurrence of immune pneumonia when ICIs are combined with cCRT.

Computed tomography(CT)-guided Hypofractionated brachytherapy, direct irradiation of tumor lesions. Quality assurance is significant for brachytherapy because of the characteristic high-dose gradients within and adjacent to an implant or applicator[5]. Moreover, the applicator ensures that the radiation source remains motionless for the tumor lesion during treatment, reducing the effects of respiratory dynamics and positional errors. In one study, a single dose of 30Gy (BED = 120Gy) for primary lung lesions resulted in a lung V20 of 4.1% to 11.1%, which created an opportunity for intensity-modulated lymph node radiotherapy, resulting in a 2-year local control rate of 83.3% and 77.6% for primary and metastatic lymph nodes, respectively, and a 2-year survival rate of 67% for patients.[5], creating an opportunity for intensity-modulated radiotherapy of the lymph nodes.

In this case, radiotherapy with simultaneous immunotherapy showed good feasibility and safety, with no recent toxicity occurring. Radiotherapy was administered by interposition radiotherapy to treat the primary tumor foci and VMAT to treat mediastinal metastatic lymph nodes, with reasonable control of normal lung tissue exposure (V20 less than 20%) and avoidance of pneumonitis that may be caused by radiotherapy combined with ICIs. To the best of our current knowledge, this case is the first case to date in which radiotherapy with interstitial tissue insertion, combined with immunotherapy for stage IIIB squamous lung cancer, was able to avoid pneumonitis well, and there were no cases of serious adverse effects such as grade 2 or higher pneumonitis or myocarditis. Although limited, the currently available data, pairing interstitial radiotherapy with chemotherapy and ICIs may be a safe and potentially efficacious treatment approach based on a sequential model.

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Declarations

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Ethics approval and consent to participate :The study was approved by the Human Research Ethics Committees of the Affiliated Hospital of Southwest Medical University, China. the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent to publish: The authors affirm that human research participants provided informed consent for publication of the images in Figure 1-6.

Figures

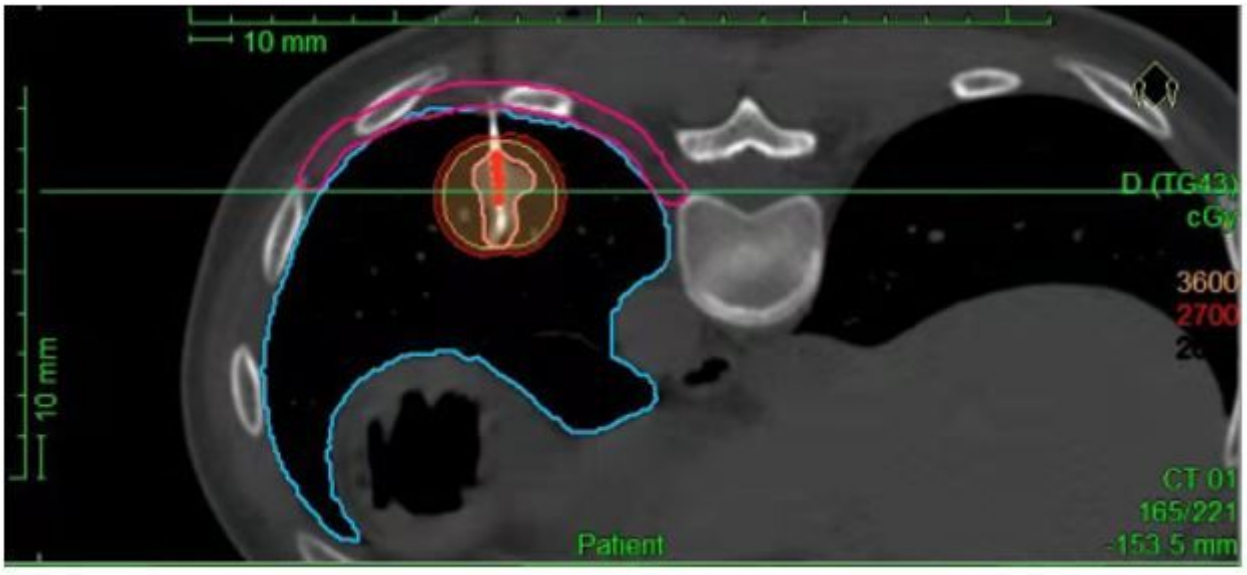

Figure 1

Hypofractionated brachytherapy for the pulmonary mass

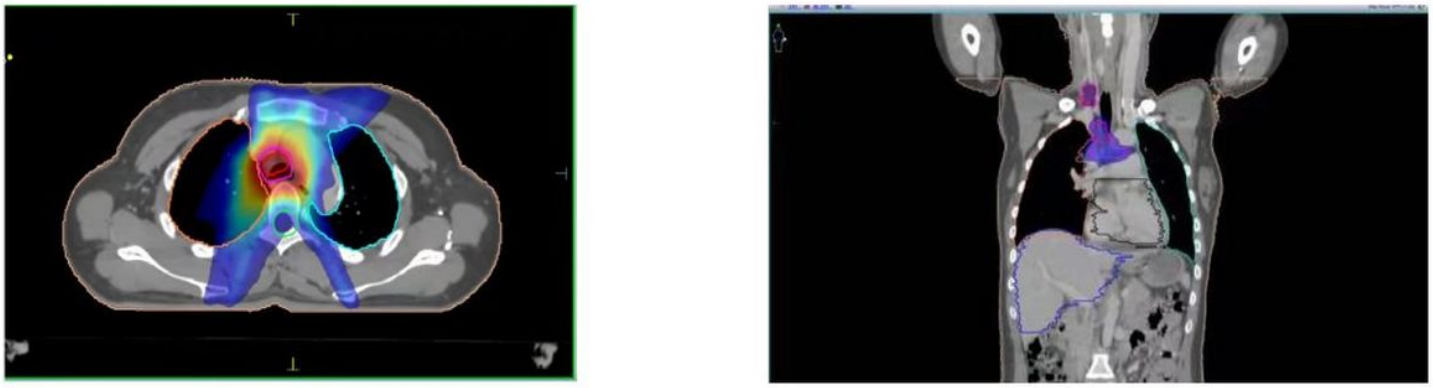

Figure 2

VMAT for Mediastinal and Cervical lymph nodes

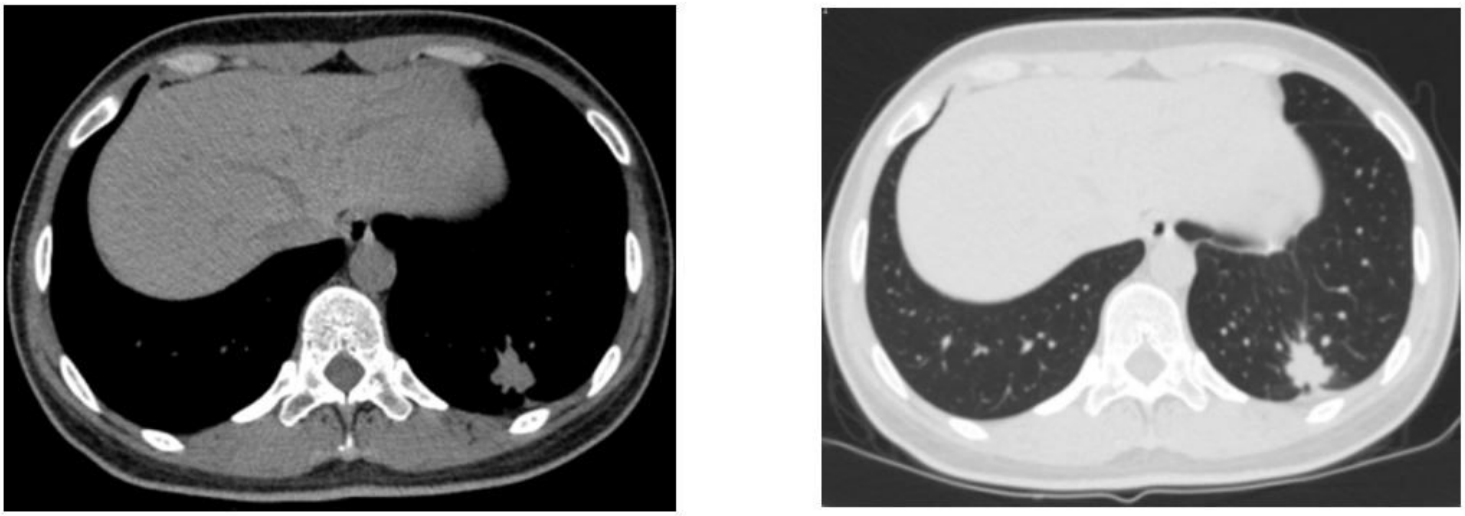

Figure 3

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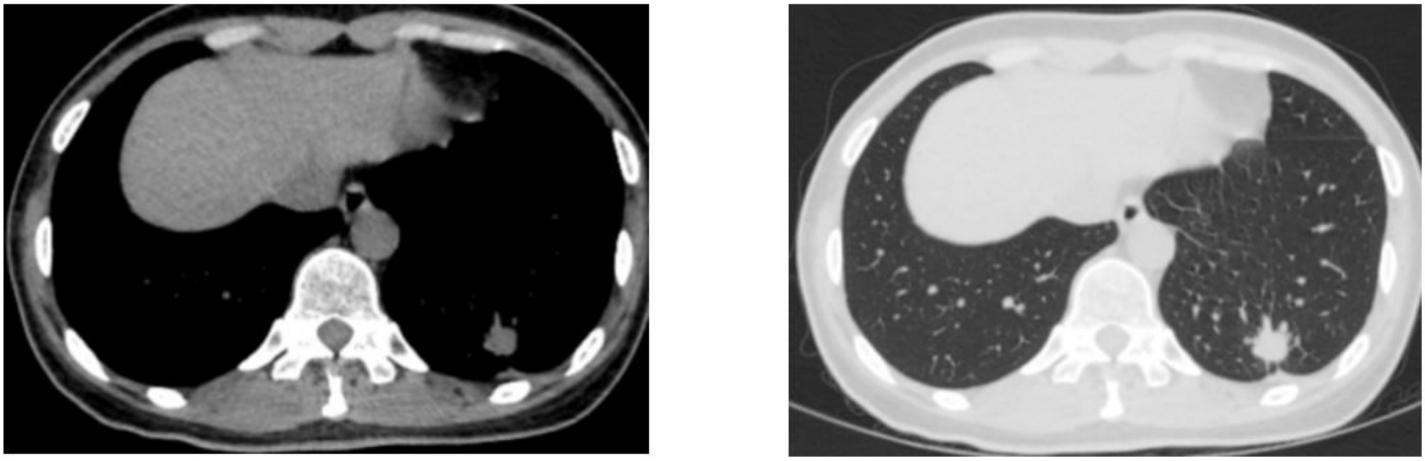

Figure 4

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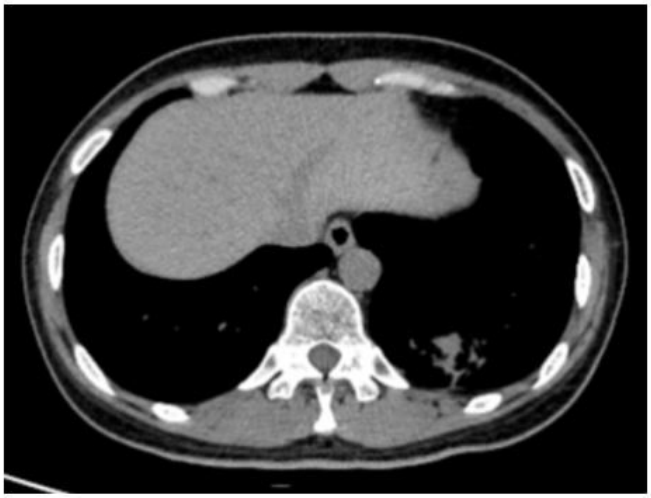

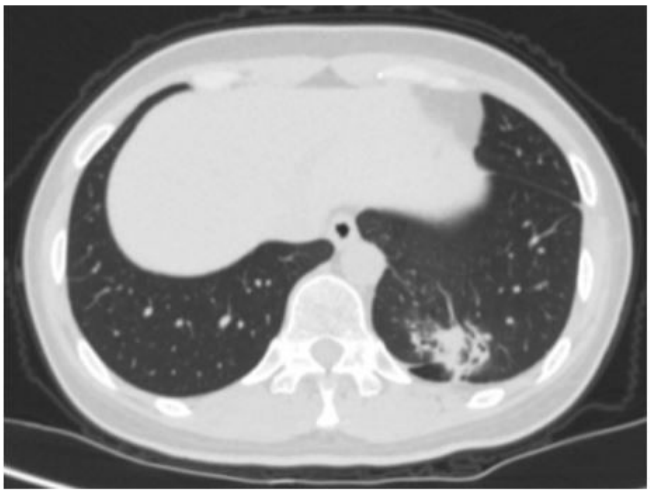

Figure 5

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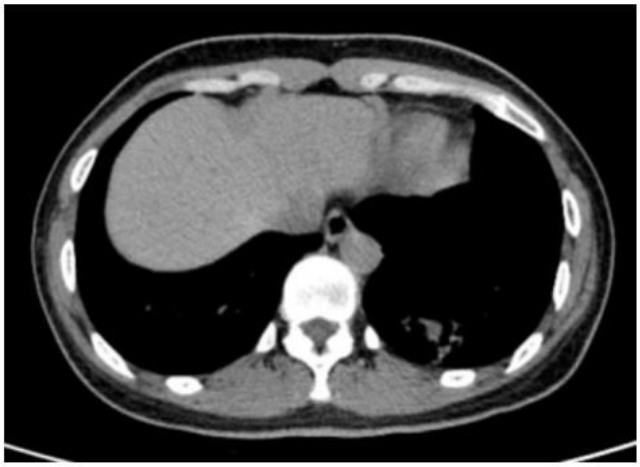

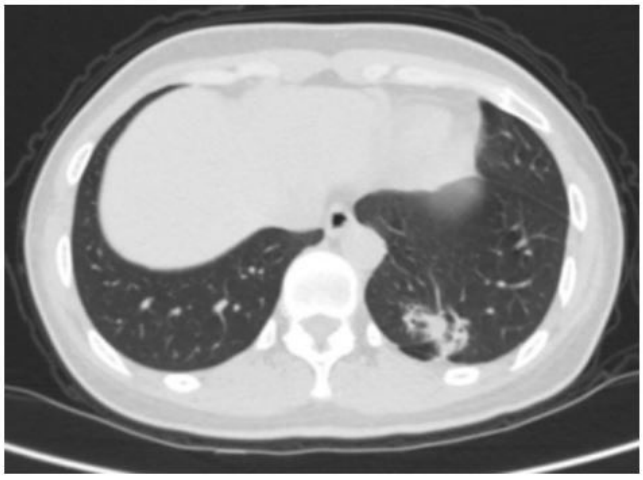

Figure 6

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