Misjudgement of gefitinib efficacy in patients with central non-small-cell lung cancer due to obstructive atelectasis caused by stereotactic radiotherapy

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Abstract. Stereotactic body radiation therapy (SBRT) has been reported to be safe and effective for the treatment of central lung cancer, with mostly tolerable early complications. In this study, we report the development of severe obstructive atelectasis as a late complication in two patients with central lung cancer who received SBRT. This obstructive atelectasis interrupted the evaluation of efficacy of the subsequent gefitinib treatment for non-small-cell lung cancer (NSCLC). The two patients received a total dose of 40 Gy encompassing the planning target volume in 10 fractions (5 fractions/week) at 4 Gy per fraction at the central lesions. Obstructive atelectasis occurred when the patients received subsequent gefitinib treatment. Follow-up reviews or positron emission tomography-computed tomography examination of the two patients confirmed that obstructive atelectasis was actually caused by radiotherapy rather than disease progression. Misjudgement of the cause of ostructive atelectasis in one of the cases resulted in premature termination of gefitinib. Therefore, it is crucial to accurately determine the cause of late complications in NSCLC patients receiving sequential SBRT and gefitinib.

Introduction

Lung cancer is one of the most common and lethal types of cancer, accounting for 17% of the total new cancer cases and approximately one-fourth of the total cancer-related deaths worldwide (1). Non-small-cell lung cancer (NSCLC) includes adenocarcinoma, squamous cell carcinoma and large-cell carcinoma and is responsible for ~85% of newly diagnosed lung cancer cases (2). Approximately 80% of lung cancer cases have already advanced at the time of diagnosis, thus eliminating surgery as a treatment option. Multidisciplinary treatment is currently the main therapeutic approach for advanced NSCLC. The main method to quickly and effectively control tumor growth is a combination of local treatment and systemic therapy (3). However, the clinical outcomes for radiotherapy combined with chemotherapy, the main therapeutic regimen for advanced NSCLC under the traditional multidisciplinary approach, have been disappointing, with a 5-year survival rate of <20% (4-6).

With the increase of the application of targeted therapy for lung cancer, the combination of targeted therapy and radiotherapy has also become a popular therapeutic modality. Theoretically, due to its low toxicity, the combination regimen may be an effective approach, particularly suitable for elderly patients and those with additional underlying diseases (7,8).

However, certain specifications that have been traditionally used for chemotherapy may not be applicable to targeted therapy. Unless disease progresses significantly during the course of targeted therapy, the general recommendation is to continue medication without interruption, as treatment termination is likely to result in rapid disease progression (9). Nishie *et al* (9) reported a statistically significant difference in the median survival of NSCLC patients who continued epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) and those who discontinued such therapy after disease progression, indicating that the management strategy of targeted therapy should be differentiated from that of radiotherapy or chemotherapy.

Stereotactic body radiation therapy (SBRT) delivers high doses of radiation to the involved target field and diminishes the radiation fields by reducing the effects of tumor motion for accuracy and precision, thus contributing to a reduction in the volume of irradiation of normal tissues and an increase in the dose delivered to the target field (10). SBRT was recently used for lung cancer in patients for whom surgery is not a suitable option, with an efficacy comparable to that of surgery for early lung cancer (11). Rowe *et al* (12) expanded SBRT to central lung cancer and reported that the approach was safe and effective, with mostly tolerable early complications. However, late complications were not addressed in that study. In this study, we report the development of severe obstructive atelectasis as

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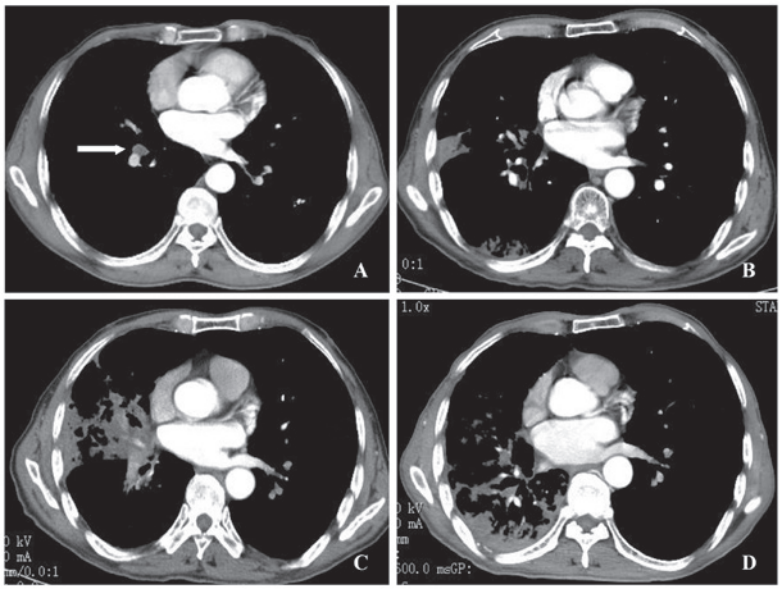

Figure 1. Thoracic computed tomography scan of an 83-year-old man with adenocarcinoma of the right lung. (A) Prior to radiotherapy; (B) 6 months after radiotherapy (mild obstructive pneumonia); (C) 9 months after radiotherapy and 2 weeks after gefitinib initiation (severe obstructive pneumonia in the middle lobe of the right lung); (D) 14 months after radiotherapy (obstructive pneumonia in the middle lobe of the right lung is relieved and obstructive pneumonia in the inferior lobe of the right lung is aggravated). White arrow, location of tumor.

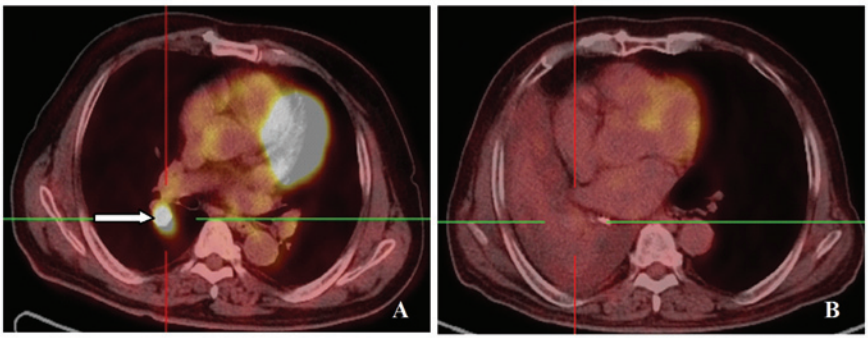

Figure 2. Thoracic PET-CT scan of a 77-year-old man with adenocarcinoma of the right lung. (A) Prior to radiotherapy; (B) 7 months after radiotherapy and 6 months after gefitinib initiation (obstructive atelectasis in the right lobe with no FDG metabolism). White arrow, location of tumor. PET-CT, Positron emission tomography computed tomography; FDG, fluorodeoxyglucose.

a late complication in two patients with central lung cancer who received SBRT. The obstructive atelectasis interrupted the evaluation of the efficacy of the subsequent gefitinib treatment for NSCLC. Informed consent was obtained from the two patients prior to the study. This study was approved by the Ethics Committee of Daping Hospital [(2012)NO.10].

Case reports

Case 1. An 83-year-old man was diagnosed with stage T2N1M1 adenocarcinoma of the right lung (Fig. 1A). Palliative γ-ray SBRT was administered to the lesions in the right lower lung, right hilum and left lower lung at doses and fractions as previously described (13). Briefly, computed tomography (CT)-guided simulation was available for delineation of the gross tumor volume (GTV). The planning target volume (PTV) was generated with an additional 0.5 cm to the GTV in the axial plane and 1.0 cm in the longitudinal plane. The γ-SBRT plan included a 50% isodose line covering >95% of the PTV and a 70% isodose line covering >90% of the GTV. A total dose of 40 Gy was prescribed encompassing the PTV in 10 fractions (5 fractions per week) at 4 Gy per fraction and the corresponding dose of 56 Gy was prescribed encompassing the GTV (5.6 Gy/fraction).

Considering the patient's age, pemetrexed monotherapy was administered 4 times intermittently after radiotherapy. A review conducted at 6 months indicated mild radioactive inflammation of the right lung on CT scan (Fig. 1B). Oral gefitinib was initiated at 9 months post-radiotherapy. Two weeks later, the cough of the patient was exacerbated. A second CT scan revealed obstructive atelectasis in the lateral segment of the right middle lobe (Fig. 1C). The atelectasis was attributed to disease progression and gefitinib was terminated. Given the patient's age, no further treatment options (chemotherapy, radiotherapy, or surgery) were contemplated. A CT scan at 14 months post-radiotherapy revealed that the obstructive atelectasis was mitigated in the lateral segment of the right middle lobe (Fig. 1D). However, the obstructive

atelectasis in the posterior segment of the right upper lobe, the dorsal segment and the basal segment was aggravated. Metastasis to the contralateral lung was identified 6 months later, indicating disease progression.

Case 2. A 77-year-old man was diagnosed with stage T2N3M0 adenocarcinoma of the right lung. Positron emission tomography (PET)-CT examination revealed nodules in the right lower lobe, enlargement of the lymph nodes at the right hilum and above the left supraclavicular fossa, with increased standardized uptake values (SUV) of fluorodeoxyglucose (Fig. 2A). Palliative γ-ray SBRT was administered to the right hilum, right lower lobe and lymph nodes on the left supraclavicular fossa with a similar dose schedule to that of Case 1. Following radiotherapy, the patient received bevacizumab, pemetrexed, and nedaplatin. At the 1-month review, the CT scan revealed multiple small nodules in the right middle lobe and disease progression was considered. The patient declined further chemotherapy. Second-line oral gefitinib was initiated, with a decrease in the number of nodules in the right middle lobe 1 month after gefitinib treatment initiation. Partial regression was achieved. Gefitinib was continued for a further 7 months, when the patient experienced worsened post-exertional shortness of breath. A CT scan review revealed obstructive atelectasis in the right lung (Fig. 2B). Progressive disease was contemplated by an outpatient respiratory physician, who recommended terminating gefitinib. However, the PET-CT revealed a mass in the right lower lobe and enlargement of the lymph nodes in the right hilum and left supraclavicular fossa. No increase in SUV was observed in either area, indicating that the activity of the lesions was inhibited. Thus we recommended continuing gefitinib treatment.

Discussion

As interstitial pneumonia is one of the most severe side effects of EGFR-TKIs and radiotherapy, EGFR-TKIs and concurrent radiotherapy have been used with caution in clinical practice. Wang *et al* (13) reported only a low incidence rate (4%) of third-degree radiation pneumonitis in NSCLC patients receiving EGFR-TKI treatment plus radiotherapy. Okamoto *et al* (6), however, reported radiation pneumonitis in 2 of 7 stage III unresectable NSCLC patients. Onal *et al* (14) also reported on a patient who received erlotinib after radiotherapy, which induced radiation pneumonitis. Due to the aforementioned reasons, combination therapy was not prescribed for our two patients. Rather, additional EGFR-TKI treatment was administered sequentially after the completion of radiotherapy.

The main advantage of SBRT is its short radiation time and less damage to the surrounding tissues, resulting in a decreased risk of radiation pneumonitis in lung cancer. Wang *et al* (15) reported that in 14 patients with advanced NSCLC, SBRT combined with gefitinib resulted in a disease remission rate of up to 57.1%. The median time of disease remission was 8 months, while the 1-year survival rate was 69.6%, suggesting that this regimen may improve local control and disease remission rates with few side effects. Compared to 3D-RT or intensity-modulated radiotherapy, SBRT in combination with EGFR-TKIs may be a more suitable treatment option for elderly patients or those with diseases that are a contraindication to radiotherapy, such as chronic obstructive pulmonary disease (16).

However, our two patients with central lung lesions developed severe obstructive atelectasis while on gefitinib after undergoing SBRT, which interrupted our evaluation of gefitinib efficacy. Our analysis indicated that the occurrence of obstructive atelectasis mainly resulted from SBRT for lesions located in the hilum of the lung, which caused the late complication of radioactive bronchial fibrosis, in turn leading to bronchial stenosis. However, such severe obstructive atelectasis cannot exclude the synergistic role of gefitinib. Due to the misjudgement of obstructive atelectasis as a result of disease progression in Case 1, gefitinib was wrongly terminated after 2 weeks, depriving the patient of the opportunity to receive effective treatment. Case 2 was slightly more complicated. The patient did not undergo any gene mutation detection tests. The clinical trial from IPASS (17), suggested that the majority of the patients developed drug resistance within 6-8 months of taking the medication. This patient developed atelectasis exactly 7 months after gefitinib initiation. A PET-CT examination confirmed that there was no progression of the original lesions. Hence, we did not adopt the suggestion by outpatient physicians to discontinue the medication. In fact, Takeda *et al* (18) reported that, for patients with NSCLC after SBRT, the SUV from PET-CT are of higher diagnostic value regarding local recurrence compared to those from CT.

Our experience with patients who have recently undergone radiotherapy suggests that, if disease progression occurs at the site of radiotherapy during the course of EGFR-TKI treatment, the decision to discontinue the medication should be based on PET-CT rather than CT alone. Furthermore, radioactive atelectasis differs from radiation pneumonitis. If the patient is able to tolerate the condition without severe breathing difficulties, the recommendation is to continue medication. However, our empirical findings must be substantiated and confirmed through further clinical trials.

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