Original Study

Characterization of Computed Tomography Imaging of Rearranged During Transfection-rearranged Lung Cancer

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Abstract

Because rearranged during transfection (*RET*)-rearranged non–small-cell lung cancer (NSCLC) is rare, clarifying the computed tomography (CT) imaging characteristics is crucial. In 21 cases of advanced *RET*-rearranged NSCLC, the CT imaging characteristics revealed relatively small and solid primary lesions without air bronchogram or cavitation, located as peripheral lung lesions, frequently disseminated to the pleura. These findings could help to better understand the progression pattern of *RET*-rearranged NSCLC.

Background: Rearranged during transfection (RET)-rearranged non–small-cell lung cancer (NSCLC) is relatively rare and the clinical and computed tomography (CT) image characteristics of patients with an advanced disease stage have not been well documented. **Patients and Methods:** We identified patients with advanced-stage RET-rearranged NSCLC treated in the Cancer Institute Hospital, Japanese Foundation for Cancer Research, and analyzed the clinical and CT imaging characteristics. **Results:** In 21 patients with advanced RET-rearranged NSCLC, RET rearrangements were identified using fluorescence in situ hybridization and/or reverse transcriptase-polymerase chain reaction. The fusion partner genes were identified as KIF5B (57%), CCDC6 (19%), and unknown (24%). CT imaging showed that 12 primary lesions (92%) were peripherally located and all were solid tumors without ground-glass, air bronchograms, or cavitation. The median size of the primary lesions was 30 mm (range, 12-63 mm). Of the 18 patients with CT images before initial chemotherapy, 12 (67%) showed an absence of lymphadenopathy. Distant metastasis included 13 with pleural dissemination (72%), 10 with lung metastasis (56%), 8 with bone metastasis (44%), and 2 with brain metastasis (11%). **Conclusion:** Advanced RET-rearranged NSCLC manifested as a relatively small and peripherally located solid primary lesion with or without small solitary lymphadenopathy. Pleural dissemination was frequently observed.

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Keywords: Advanced stage, CT imaging characteristics, Non–small-cell lung cancer, Progression pattern, *RET* rearrangement

Introduction

The recent discovery of the driver mutation for advanced non–small-cell lung cancer (NSCLC) has changed its treatment strategy. For example, the use of epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors for NSCLCs harboring an *EGFR* mutation[1-5] and anaplastic lymphoma kinase (*ALK*) tyrosine kinase inhibitors for *ALK*-rearranged NSCLC[6,7] has resulted in remarkable response rates and prolonged progression-free survival compared with cytotoxic chemotherapy. Therefore, these molecular target therapies have become standard treatment for patients

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with these driver mutations with advanced-stage disease. Furthermore, several gene fusions were discovered in patients with NSCLC, including in *ROS1*,[8] *NTRK*,[9] and rearranged during transfection (*RET*) proto-oncogene genes.

RET rearrangement was first detected in NIH-3T3 cells transfected with lymphoma DNA,[10] followed by papillary thyroid cancers.[11,12] In 2012, 4 different research groups reported that the kinesin family member 5B (*KIF5B*)-*RET* fusion gene was present in ~1% to 2% of NSCLCs.[13-16] Several *RET* inhibitors were evaluated in clinical trials[17-19] after the identification of *RET*-rearranged NSCLCs in clinical practice. However, because of the rareness of *RET*-rearranged NSCLCs, clarification of the clinical and, in particular, computed tomography (CT) imaging characteristics of *RET*-rearranged NSCLCs are very important.

Recently, morphology has been used to predict the molecular biology in rare lung cancer subgroups. Previous studies evaluated the relationship between CT imaging features and genetic mutations of NSCLC, such as those in *EGFR* and *ALK*. They reported that NSCLC might exhibit distinct imaging characteristics. We evaluated the CT findings of advanced *RET*-rearranged NSCLC.

Patients and Methods

Patients

We used a database to identify patients with advanced *RET*-rearranged NSCLC, including stage III, stage IV, or postoperative recurrence, who had been treated in the Cancer Institute Hospital, Japanese Foundation for Cancer Research. Our institutional review board approved the present retrospective study, which waived the need for informed consent owing to the noninvasive nature of the study and patient anonymity. Clinical information was collected for each patient from the electronic medical records and included age, sex, smoking status, histologic type, and partner gene. *RET* rearrangements were identified using multiplex reverse transcriptase-polymerase chain reaction (RT-PCR) and/or a break-apart fluorescent in situ hybridization (FISH) assay.

CT Findings

For image analysis, we evaluated the CT scan at the initial diagnosis for patients with advanced-stage disease and at diagnosis of recurrence for patients with postoperative recurrence. One pulmonary oncologist and one radiologist (with 8 and 24 years' experience, respectively) assessed each patient's CT scan for each of the CT image traits in consensus. The CT features assessed included primary tumor, thoracic lymphadenopathy, and distant metastases. Screening of brain metastases had been performed using CT or magnetic resonance imaging (MRI) at the initial or recurrence diagnosis.

The size of the primary tumor was defined by measuring the longest axis on the lung windows. The location of the primary tumor was defined as either central (tumor involving segmental or larger bronchus) or peripheral (tumor involving subsegmental bronchus or smaller airway). The contour of the primary tumor was characterized as round, lobulated, or irregular. The density of the primary tumor was classified as solid attenuation, ground-glass attenuation, or part-solid attenuation. Air bronchogram, cavitation, calcification, and pleural indentation were also evaluated.

Table 1 Baseline Characteristics of *RET*-rearranged Lung Cancer (n = 21)

Characteristic	n (%)
Age, y	
Median	61
Range	34-79
Age ≥ 60 y	12 (57)
Sex	
Female	12 (57)
Male	9 (43)
Stage	
III	1 (5)
IV	13 (62)
Recurrence	7 (33)
Smoking	
Current or former	10 (48)
Never	11 (52)
Histologic type	
Adenocarcinoma	21 (100)
Other	0 (0)
RET test	
FISH	5 (24)
RT-PCR	6 (27)
FISH and RT-PCR	10 (48)
Partner gene	
KIF5B	12 (57)
CCDC6	4 (19)
Unknown	5 (24)

Lymphadenopathy was defined as the presence of a lymph node ≥ 10 mm in the short axis on the mediastinal window. For patients with multifocal lymphadenopathy, the size of the largest lymph node was recorded, and the properties of the lymphadenopathy were classified as either solitary or fusion. The location of the lymphadenopathies was recorded as mediastinal, ipsilateral hilar, contralateral hilar, axillary, and supraclavicular. The presence of nodal enlargement at each site was recorded and classified as absent, unifocal (present at 1 site), or multifocal (present at > 1 site).

The presence of metastatic disease in the predefined sites of pleura, lung, bone, liver, pericardium, brain, and adrenal gland were recorded at the diagnosis or at metastatic recurrence. Other sites of metastatic disease were noted but not formally analyzed owing to the predicted low prevalence.

A chest CT scan was performed for 10 patients at our institution and for 8 patients at a previous institution before their initial chemotherapy. The CT imaging used scanners with Revolution HD FREEdom or Discovery CT 750 HD with the following parameters: 50 to 150 mL of nonionic iodinated contrast material (350 mg iodine/mL) administered intravenously at a rate of 2 to 4 mL/s; detector collimation, 1 to 5 mm; beam pitch, 0.984; rotation time, 0.5 second; tube voltage, 120 kVp; and tube current, auto mA. The reconstruction thickness and intervals were 1.25 mm at our institution.