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# Clinical and CT characteristics of surgically resected lung adenocarcinomas harboring *ALK* rearrangements or *EGFR* mutations

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ABSTRACT

*Purpose:* To determine if clinical and CT characteristics of surgically resected lung adenocarcinomas can distinguish those harboring *ALK* rearrangements from *EGFR* mutations.
*Materials and methods:* Patients who had surgical resection and histologically confirmed lung adenocarcinoma were enrolled, including 41 patients with *ALK* rearrangements and 66 patients with *EGFR* mutations. Eighteen categorical and six quantitative CT characteristics were used to evaluate the tumors. Differences in clinical and CT characteristics between the two groups were investigated.
*Results:* Age ($P = 0.003$), histological subtypes ($P < 0.001$), pathological stage ($P = 0.007$), and five CT characteristics, including size ($P < 0.001$), GGO ($P = 0.001$), bubble-like lucency ($P = 0.048$), lymphadenopathy ($P = 0.001$), and tumor shadow disappearance rate ($P = 0.005$) were significantly different between patients harboring *ALK* rearrangements compared to patients with *EGFR* mutations. When we compared histologic components, a solid pattern was more common ($P = 0.009$) in tumors with *ALK* rearrangements, and lepidic and acinar patterns were more common ($P < 0.001$ and $P = 0.040$, respectively) in those with *EGFR* mutations. Backward elimination analyses revealed that age (OR = 0.93; 95% CI 0.89–0.98), GGO (OR = 0.14; 95% CI 0.03–0.67), and lymphadenopathy (OR = 4.15; 95% CI 1.49–11.60) were significantly associated with *ALK* rearrangement status.
*Conclusion:* Our analyses revealed that clinical and CT characteristics of lung adenocarcinomas harboring *ALK* rearrangements were significantly different, compared with those with *EGFR* mutations. These differences may be related to the molecular pathology of these diseases.


## Introduction

Over the last decade, advances in molecular testing have resulted in a paradigm shift whereby lung cancers are classified and treated based on genetic alternations that are critical to tumor growth and survival and can be exploited with targeted agents [1]. For example, the discovery that epidermal growth factor receptor (*EGFR*) mutations are effective targets for *EGFR* tyrosine kinase inhibitors (TKIs) has revolutionized therapeutic strategies [2]. More recently, the fusion oncogene of echinoderm microtubule-associated protein like 4 (*EML4*) and anaplastic lymphoma kinase (*ALK*) was newly identified in a subset of non-small cell lung cancer (NSCLC), primarily in lung adenocarcinoma [3]. *ALK*

*Abbreviations:* EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; TKIs, tyrosine kinase inhibitors; NSCLC, non-small cell lung cancer; PACS, picture archiving and communication system; CEA, serum carcinoembryonic antigen; TDR, tumor shadow disappearance rate; GGO, ground-glass opacity; OR, odds ratio; CI, confidence interval.

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fusions occur in approximately 5% of lung adenocarcinoma, typically occur in a mutually exclusive manner to *EGFR* mutations [4–6], and *ALK* inhibitors, such as crizotinib, have been developed and tumors with *ALK* rearrangements have shown striking responses [7].

Pathologically and biologically, lung adenocarcinoma is a heterogeneous disease. Genetic heterogeneity has been identified not only between individual tumors of the same histopathologic subtype but also between primary lesions and associated metastatic sites in the same patient, and even between spatially separated regions within a single tumor [8,9]. Hence, the tumor genomics landscape portrayed from single tumor biopsy samples obtained from primary or metastatic sites may be inaccurate and underestimated [8]. Sequential or multiple biopsies to identify subclones can rarely be implemented in routine clinical care because of logistical and financial barriers. Compared with molecular technologies, routine imaging provides a non-invasive and comprehensive view of the entire tumor and can be utilized to monitor tumor progression and therapy response, and potentially to identify locations for biopsy to provide the most actionable data.

To date there have been few published studies assessing the association between CT imaging features and *ALK* rearrangements among NSCLC patients [6,10–16], and the results were still somewhat conflicting. Most of these studies included advanced tumors whose histology and mutational status were obtained from biopsy samples of primary or metastatic sites that may not accurately reflect the pathological and molecular characteristics of the tumor [10–15]. To identify characteristics that are associated with *ALK*-positive lung adenocarcinoma, this study compared clinical and CT characteristics between lung adenocarcinomas harboring *ALK* rearrangements versus those with *EGFR* mutations in a cohort of patients whose histopathologic and molecular diagnosis were confirmed by surgical resection.

## 2. Materials and methods

### 2.1. Study population

The institutional review board of Tianjin Medical University approved this retrospective study. Written informed consent to undergo the pathological or gene mutational test was obtained from all patients beforehand.

We searched our database for those patients who had surgical resection for primary lung cancer and undergone both *ALK* fusion and *EGFR* mutation detection at our institution between January 2014 and July 2015. Inclusion criteria were those cases who had histologically confirmed lung adenocarcinoma with *ALK* rearrangements or *EGFR* mutations and available preoperative CT images on our picture archiving and communication system (PACS) performed less than 1 month before the subsequent surgery. Since the mutational rate of *EGFR* was much higher than that of *ALK* (20% to 50% for *EGFR* vs. 5% for *ALK*) in lung adenocarcinomas of Asian populations [6,17], we then randomly selected 25% of those cases with *EGFR* mutations for comparison. Two cases underwent chemotherapy or radiotherapy before surgery and one case that harbored both mutations were excluded. Finally, 41 patients with *ALK* rearrangements and 66 patients with *EGFR* mutations were included in this study. For *EGFR* mutations, exon 21 mutation was most frequent (31/66, 47.0%), other mutations were located in exon 19, 20, or 18 (26, 8, and 3 cases, respectively).

### 2.2. Clinical and pathological characteristics

For each patient, age, gender, smoking status (never, former, and current smokers), preoperative serum carcinoembryonic antigen (CEA) level, histological subtypes and pathological TNM stage were extracted from patient medical records. Tumors were histologically classified according to the 2015 WHO classification, and each component was documented by making a semiquantitative estimate of all of the different histologic patterns present in 5% increments [18]. Tumors were pathologically staged according to the seventh edition of the Union for International Cancer Control and American Joint Committee on Cancer TNM classification system [19].

### 2.3. CT characteristics

Chest CT examinations were performed before surgery by using one of three multi-detector CT systems: Somatom Sensation 64 (Siemens Medical Solutions, Forchheim, Germany), Light speed 16, and Discovery CT750 HD (GE Healthcare, Milwaukee, WI, USA) scanner. Scanning parameters were as follows: 120 kVp with tube current adjusted automatically, 1.5 mm reconstruction thickness with 1.5 mm reconstruction interval for 64-detector scanner; and 120 kVp, 150–200 mA, 1.25 mm reconstruction thickness with 1.25 mm reconstruction interval for the other two scanners. Additional contrast-enhanced CT was performed for 96 patients. Non-ionic iodine contrast material (Ultravist, 300 mg of iodine per milliliter, Bayer Pharma, Berlin, Germany) was injected into the antecubital vein at a dose of 1.3-1.5 mL per kilogram of body weight at a rate of 2.5 ml/s by using an automated injector with a 70-s delay.

The images were reconstructed with high-resolution reconstruction algorithm for a pulmonary window setting (Width 1,200HU, Level −500HU) and with standard reconstruction algorithm for a mediastinal window setting (Width 320HU, Level 35HU).

Two radiologists with 9 and 6 years of experience in chest CT diagnosis independently reviewed all of the CT images on our PACS. Both radiologists were aware that patients had surgically resected lung adenocarcinomas but were unaware of the clinical data as well as the histological subtype or mutational status. As shown in Table 1, 18 characteristics were rated as categorical variables by assessing all slices and reporting with a standardized scoring sheet. Final conclusions were reached in consensus by discussion for discrepancy. The maximum dimension of the tumor (Dmax) and the largest dimension perpendicular to the maximum axis (Dper) on both pulmonary and mediastinal settings (pDmax, pDper, mDmax, and mDper) were measured and tumor shadow disappearance rate (TDR) was calculated. TDR was used to describe the GGO ratio of the tumor, and was regarded as a criterion for evaluating radiological invasiveness of lung cancer. TDR was calculated using the following formula: $TDR = 1-(mDmax \times mDper/pDmax \times pDper)$ [6]. CT attenuation value was measured by placing a region of interest (ROI) as large as possible and avoiding the air-containing space within the confine of the tumor. The degree of contrast enhancement was calculated by subtracting the CT value of pre-contrast from that of post-contrast for those patients performed contrast-enhanced CT scanning.

### 2.4. Statistical analyses

Statistical analyses were performed by using Stata/MP 14.1 (StataCorp LP, College Station, TX). To compare patients with *EGFR* mutant tumors versus patients with *ALK* positive tumors, Fisher's exact test was used for categorical variables and Student's *t*-test was used for continuous variables. Multivariable logistic regression analysis was used to generate odds ratios (ORs) and 95% confidence intervals (CIs). The dependent variable was mutational status (*EGFR* mutation versus *ALK* positivity) and the clinical and CT characteristics were the independent features. Backward elimination analyses were used to select the most informative variables into a single parsimonious model. The clinical and CT characteristic that was sta-