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Computed tomography characteristics of lung adenocarcinomas with epidermal growth factor receptor mutation: A propensity score matching study

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ABSTRACT

Objectives: We investigated the relationship between computed tomography (CT) characteristics and epidermal growth factor receptor (EGFR) mutations in a large Asian cohort who received surgical resection of invasive lung adenocarcinoma.

Materials and Methods: We retrospectively included 864 patients (524 with EGFR mutation and 340 with EGFR wild-type) who received surgical resections for invasive lung adenocarcinomas. After applying propensity score matching, 312 patients with mutated *EGFR* were matched with 312 patients with wild-type *EGFR*. CT characteristics, predominant histologic subtype, and CT measurement parameters (volume and estimated diameter of the total tumor and inner solid portion and ground-glass opacity [GGO] proportion) were compared within matched pairs.

Results: Tumors in the *EGFR* mutation group showed higher proportions of pure ground-glass nodules (4.1% vs 1.3%), GGO-predominant (23.7% vs 14.7%), and solid-predominant part-solid nodules (37.2% vs 31.7%) CT characteristics, whereas *EGFR* wild-type tumors predominantly presented as pure solid nodules (34.6% vs 52.2%, $P < 0.0001$). *EGFR* mutation tumors more frequently had a lepidic-predominant subtype than did *EGFR* wild-type tumors (20.2% and 11.9%; $P < 0.0001$), and showed a smaller whole tumor size and solid portion ($P < 0.0001$) with a higher GGO proportion ($P < 0.0001$). Tumors with exon 21 missense mutations showed the highest GGO proportion and the smallest inner solid portion size, followed by tumors harboring an exon 19 deletion, compared with *EGFR* wild-type tumors (*posthoc* $P < 0.01$).

Conclusion: Adenocarcinomas with *EGFR* mutations had a higher GGO proportion than those with wild-type *EGFR* after matching of clinical variables. Lesions with an exon 21 mutation had a higher GGO proportion than lesions with other mutations.

1. Introduction

Epidermal growth factor receptor (EGFR) mutation is the most common genetic mutation in non-small cell lung cancer, especially in adenocarcinoma [1–5]. *EGFR* mutations are frequently observed in women, non-smokers, and Asians [5]. Because *EGFR* mutations are associated with a good response to EGFR tyrosine kinase inhibitor therapy [2,3,6,7], acquiring information regarding *EGFR* mutation status prior to treatment is critical for targeted chemotherapy. Therefore, the International Association for the Study of Lung Cancer (IASLC) recommends molecular testing including *EGFR* mutation for lung adenocarcinomas [8].

The prediction of EGFR mutation from computed tomography (CT) imaging features has been studied, not only due to growing interest in "Radiomics" in terms of predicting patient outcome by imaging features [9–12], but also from clinical necessity in situations when tissue

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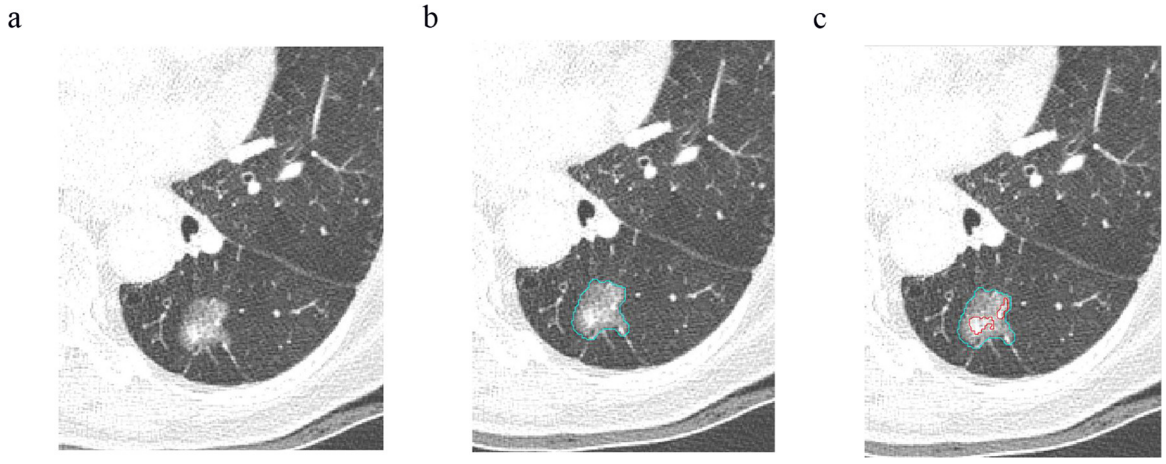

Fig. 1. Representative case of a lepidic-predominant invasive lung adenocarcinoma with epidermal growth factor receptor mutation (exon 21 missense) in a 74-year-old female never-smoker. (A–C) Computed tomography images showing a GGO-predominant part-solid nodule in the left lower lobe. (B) The contours of the outer region-of-interest of the tumor are manually drawn on the lung setting (blue line), and (C) are overlapped with the automatically segmented inner solid portion (red lines) on the representative transverse image. The total tumor volume and GGO volume percentage of this tumor were 3.62 cm^3 and 84.8%, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).
GGO, ground-glass opacity

sampling is not possible. Although there have been many reports that have investigated the CT findings of lung adenocarcinomas with *EGFR* mutation, the relationship between CT features and *EGFR* mutation remains unclear [13–22]. Some studies have concluded that tumors with *EGFR* mutation have more frequent ground-glass opacity (GGO) or a larger GGO proportion than do *EGFR* wild-type tumors [13–16,19,22], whereas others insist that the presence of GGO did not differ with *EGFR* mutation [17,18]. These conflicting results could be because interstudy differences in clinical characteristics of the study population affected the results. Because clinical variables such as sex and smoking history are frequently observed in lung cancers containing GGO (formally called bronchioloalveolar carcinoma [BAC] or adenocarcinoma with BAC features) as well as *EGFR* mutant tumors [23–25], they can be significant confounders when evaluating the relationship between *EGFR* mutation and CT features. Therefore, we hypothesized that the elimination of the confounding effects of clinical characteristics could allow the relationship between *EGFR* mutation and CT characteristics to be properly evaluated.

We aimed to investigate the correlation between CT characteristics and the presence of *EGFR* mutation in a large Asian cohort who received surgical resection for invasive lung adenocarcinomas, after adjusting for confounders with a propensity score matching analysis.

2. Materials and methods

2.1. Patients

This study was approved by the Institutional Review Board of our institution, and informed consent was waived for this retrospective study. From a surgical database of our institution, we identified 908 patients who received surgical resection for invasive lung adenocarcinoma at our institution between October 2007 and December 2013. All of the patients had one of the following predominant histologic subtypes: lepidic, acinar, papillary, solid, or micropapillary. We excluded 44 patients: 37 patients without reliable CT measurement due to absence of thin-section preoperative chest CT data, 6 patients without information of pathologic N stage, and 1 patient without size information on the pathologic report. Finally, a total of 864 patients comprised the study population (524 with *EGFR* mutation and 340 with wild-type *EGFR*).

2.2. Clinical characteristics

Medical records were reviewed, and baseline clinical characteristics such as sex, age, and smoking history were recorded. Patients were classified as never-smokers and smokers (including current and ex-smokers).

2.3. CT examinations

Chest CT was performed using one of the following scanners: Somatom Definition, Sensation-16 (Siemens Medical Solutions, Forchheim, Germany), Brilliance-64 (Phillips Medical Systems, the Netherlands), and Lightspeed Ultra (GE Medical Systems, Milwaukee, Wis). CT images were acquired with 120 kVp, 100–200 mA s, pitch of 0.875–1.5, and collimation of 1–2.5 mm, after administration of 100 mL of contrast medium at a rate of 2 mL/s. Images were reconstructed using a medium-sharp reconstruction algorithm with a thickness of 1–3 mm.

2.4. Visual interpretation of CT images

Preoperative CT images were reviewed by two thoracic radiologists. Lesion characteristics were assessed and classified into four categories according to the GGO proportion (pure ground-glass nodule [GGN], GGO-dominant part-solid nodule [PSN], solid-dominant PSN, and pure solid nodule). GGO was defined as increased opacity that did not obscure adjacent airway and pulmonary vascular structures. The proportion of GGO was calculated as the ratio of the maximum GGO diameter to that of the total tumor across the largest cross section. We classified lesion characteristics as follows: pure GGN, 100% GGO; GGO-dominant PSN, 50% $\leq$ GGO $<$ 100%; solid-dominant PSN, 0% $<$ GGO $<$ 50%; and pure solid nodule, 0% GGO [26]. If disagreement occurred between the two reviewers, a consensus reading was performed to reach the final conclusion.

2.5. Quantitative CT image analysis

Segmentation and measurement of the whole tumor and inner solid portion were performed with an in-house software developed in the Department of Biomedical Engineering, Gachon University College of Medicine, Incheon, Korea [27,28]. An inner solid segmentation algorithm was developed based on Microsoft Visual Studio (ver. 2010,

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