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Research article

Quantitative CT density histogram values and standardized uptake values of FDG-PET/CT with respiratory gating can distinguish solid adenocarcinomas from squamous cell carcinomas of the lung

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ABSTRACT

Purpose: To assess the ability of parameters derived from computed tomography (CT) histograms and the maximum standardized uptake value (SUV_{max}) of 18F-fludeoxyglucose-positron emission tomography/CT (FDG-PET/CT) images to distinguish solid lung adenocarcinomas from squamous cell carcinomas and to determine if these parameters are correlated.

Methods: This study comprised 43 consecutive patients with solid lung cancer (< 3 cm in diameter), who underwent both plain chest CT and FDG-PET/CT (adenocarcinoma, n = 25; squamous cell carcinoma, n = 18). Density histograms of targeted lung cancers were created from chest CT images, and kurtosis and skewness were calculated. On FDG-PET/CT, the SUV_{max} without/with respiratory gating (RG) were calculated for each lesion. The values for the 4 parameters determined for patients in each diagnostic group were compared by the Mann-Whitney test. The diagnostic characteristics of the parameters were assessed by receiver operating characteristic (ROC) curve analysis. Differences between these parameters were assessed by the chi-square test. SUV_{max} with RG, kurtosis, and skewness were combined for binary logistic regression analysis, and the differences between the combined parameters and SUV_{max} with RG were also assessed. Spearman rank correlation analysis was used to determine the correlations for kurtosis or for skewness with SUV_{max} without/with RG.

Results: The differences in kurtosis and SUV_{max} without/with RG between the diagnostic groups were significant (kurtosis, $P < 0.004$; SUV_{max} without/with RG both $P < 0.0001$). ROC curve analysis indicated that each parameter (kurtosis value, skewness value, $SUV_{max,}$ without/with RG) provided low-high ability to differentiate between 2 groups (area under the curve [AUC]: 0.760, 0.593, 0.900, 0.931, respectively). The ROC of the combined parameters provided the highest ability (AUC: 0.949). Both kurtosis and skewness were significantly correlated with SUV_{max} without/with RG. Kurtosis and SUV_{max} with RG were most strongly correlated ($\rho = 0.618$).

Conclusion: Quantitative CT histogram values and SUV assessment can differentiate solid lung adenocarcinomas from squamous cell carcinomas. Kurtosis and SUV_{max} values were strongly correlated. The addition of RG and further combination of the parameters improved the results.

1. Introduction

Although the overall mortality of lung cancer has decreased with the reductions in smoking and advances in cancer prevention, early detection, and new treatments [1], lung cancer remains the major cause of cancer-related deaths worldwide [1,2]. An accurate diagnosis is crucial for treatment planning because chemotherapy regimens vary. However, an invasive procedure to obtain a histopathologic diagnosis of lung cancer may be difficult to perform for patients such as those with low performance status. Regimens are based on the histologic subtype of non-small cell lung cancer (NSCLC), of which there are several, according to the guidelines of the National Comprehensive Cancer Network (NCCN) for NSCLC [3,4]. Therefore, it would be very advantageous to establish a method for estimating a histopathologic diagnosis that is based on high-resolution CT, which is commonly used during the initial examination of lung cancer patients. Although the morphological evaluation of ground-glass nodules (GGNs) on high-resolution CT has been reported by some

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investigators [5–7], to our knowledge, the histopathologic differentiation between solid adenocarcinomas and squamous cell carcinomas, which are 2 major NSCLC subtypes, has not been well reported.

As reported in a previous study, kurtosis and skewness measurements from CT histograms were useful for morphologic assessments, even for solid lung cancers, and proved to be useful for differentiating malignant nodules from benign nodules [8]. In that study, the adenocarcinomas tended to have relatively low kurtosis values on CT histogram analysis [8]. Because of that finding, we hypothesized that differences between the kurtosis values and other parameters derived from CT histogram analysis might allow differentiating a solid-type adenocarcinoma from squamous cell carcinoma.

On the other hand, the difference between the standardized uptake values (SUVs) from 18F-FDG-PET/CT of adenocarcinomas and squamous cell carcinomas has been revealed to be significant because of the difference between the expression of glucose transporter type 1 (GLUT1) by both histological subtypes [9]. However, FDG-PET/CT is not easily applicable to all lung cancer patients because it remains expensive and is limited to certain institutions. Therefore, if we can verify that CT histogram analysis has high diagnostic ability comparable to that of FDG-PET/CT, CT histogram analysis could be useful for the pretreatment diagnosis of NSCLCs. In addition, if we find that the combination of SUVs and quantitative CT histogram values can improve the ability of histopathological diagnosis, it must be useful to improve the precision of pre-treatment diagnosis by imaging.

The purposes of this study were to assess the diagnostic ability of parameters derived from CT histograms, SUVs from 18F-FDG-PET/CT, and parameters obtained by combining SUVs and CT histogram analysis values for distinguishing between adenocarcinoma and squamous cell carcinoma; and to investigate the correlations between these parameters.

2. Materials and methods

This study was approved by the Institutional Review Board and written informed consent was obtained from every study patient.

2.1. Patient selection

For this prospective study, 164 consecutive patients with a clinical diagnosis of probable lung cancer who underwent both plain chest CT and FDG-PET/CT from July 2015 to December 2016 were assessed. During the enrollment process, 9 patients with incomplete studies were excluded. Fifty-eight patients with nodules that did not fulfill the nodule criteria for size and number (4 patients with no nodules, 4 patients with multiple nodules and no observable main nodule, 50 patients with nodules > 3 cm in diameter) and 37 patients with nodules other than squamous cell carcinoma or adenocarcinoma (25 patients with no histological confirmation, 3 lung cancers other than squamous cell carcinoma or adenocarcinoma, 1 patient with malignant lymphoma, 5 patients with metastatic tumours, and 3 patients with histopathologically diagnosed benign nodules) were also excluded. Histopathological diagnosis was performed by surgery, transbronchial biopsy, or CT-guided biopsy. Among the remaining 60 patients with squamous cell carcinoma or adenocarcinoma ≤3 cm in diameter, 14 patients with partly-solid GGNs and 3 patients with pure GGNs were excluded. A total of 43 patients (25 patients with adenocarcinoma and 18 with squamous cell carcinoma) were finally enrolled in this study (Fig. 1).

2.2. CT and FDG-PET/CT scanners

2.2.1. Chest CT

The CT scans were performed by the Biograph mCT-S(64)4R (Siemens Healthcare, Erlangen, Germany) scanner with a 64-row-detector. The parameters of CT scans were as follows: tube voltage 120 kVp; tube current 240 mA; rotation time 0.5 s; beam pitch 1.2, 512 × 512 matrix; slice thickness 1 mm. Images were reconstructed with a B31f kernel (mediastinum). Contrast was not used for this examination. All patients were scanned by the same protocol.

2.2.2. FDG-PET/CT

The Biograph mCT-S(64)4R (Siemens Healthcare, Erlangen, Germany) scanner was also used for FDG-PET/CT. Every patient fasted for longer than 5 hours before the examination. Whole-body PET/CT images were acquired 1 h after intravenous injection of ^{18}F FDG (3.7 MBq/kg BW, max 340 MBq). The whole-body CT scan parameters were as follows: voltage 120 kVp, tube current based on automatic exposure control, beam pitch 1.5, rotation time 0.5 s, 512 × 512 matrix, slice thickness 2.00 mm; kernel = B31f. After the whole-body CT scan was completed, an emission scan for a duration of 120 s/bed position (1 bed position 216 mm; each covering 92.88 mm) was immediately performed. PET data sets were reconstructed iteratively using time-of-flight (TOF)-three-dimensional ordered subsets expectation-maximization (3D-OSEM) (2 iterations, 21 subsets) from the CT data. An automated amplitude-based gating method (HD-Chest; Siemens Medical Solutions, Hoffman Estates, USA) was used for respiratory gating during FDG-PET/CT (RG-PET). RG-PET images were obtained immediately after the emission scan (approximately 14-min delay). All patients were scanned by the same protocol.

2.3. Image analysis

All CT image sets were transferred to a commercial workstation (Synapse Vincent V4.1; Fujifilm Medical, Tokyo, Japan) for histogram analysis. CT images were displayed with a window level of −500 Hounsfield units (HU) and a window width of 1,500 HU. Software integrated with the workstation was used by 2 radiologists (MT and YT, with 10 and 2 years, respectively, of experience in diagnostic radiology). The workstation automatically performed three-dimensional entire nodule contouring to set the volume of interest (VOI) of each nodule by drawing a nodal diameter on an axial CT image. The 2 radiologists (MT and YT) cooperatively determined the nodal diameter of each nodule and performed minor corrections on the contoured VOI in all 3 dimensions if necessary. Density histograms of these VOIs were automatically created by the workstation. Kurtosis and skewness of the histogram were calculated by statistical software (JMP Pro 12.1.0; SAS Institute Inc., Cary, NC).

On FDG-PET/CT, maximum standardized uptake values (SUV_{max}: SUV of the hottest voxel within a VOI) with and without respiratory gating (RG) were measured by a commercially available workstation (Syngo via VB10; Siemens Healthcare, Erlangen, Germany). The VOI of each nodule was automatically determined on the workstation by an isocontouring threshold of 40% of the SUV_{max} of the entire nodule. These measurements were cooperatively performed by the 2 radiologists (MT and YT).

2.4. Statistical analysis

The patients were classified into 2 groups based on the histopathological diagnosis of adenocarcinoma and squamous cell carcinoma. Differences between the proportions of each of the 2 groups for