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The importance of subpleural fibrosis in the prognosis of patients with idiopathic interstitial pneumonias☆

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ABSTRACT

Purpose: To compare computer-aided diagnostic results with histological findings obtained by surgical biopsy and evaluate whether subpleural lesion volumes can aid identification of idiopathic pulmonary fibrosis (IPF).

Materials and
Methods: We retrospectively analyzed computed tomography (CT) images of 79 patients (43 with fibrosing nonspecific interstitial pneumonia (fNSIP) and 36 with IPF) using the Gaussian Histogram Normalized Correlation (GHNC) system. We determined the H-pattern based on honeycomb and/or fibrosis with traction bronchiectasis on CT, and measured the H-pattern volume ratio at the biopsy sites and in the subpleural area. The biopsy site CT data were compared with biopsy specimens using Spearman's correlation. H-pattern volumes in the subpleural area within 2 mm under the pleura (H_2) were analyzed to predict IPF diagnosis and patients prognosis.
Results: The H-pattern volume ratio at the biopsy sites showed significant correlation with histological honeycomb ($r = 0.355$, $p < 0.001$), subpleural collapse ($r = 0.410$, $p < 0.001$), and heterogeneity ($r = 0.484$, $p < 0.001$). Multivariate regression analysis, adjusting for age, sex, and CT results, revealed that the H2 was a significant independent predictor of IPF diagnosis (odds ratio: 1.073; $p = 0.048$). H2 correlated with patients' survival after adjusting for age ($p = 0.003$).
Conclusion: The computer-aided H-pattern volume ratio of the subpleural area indicates subpleural abnormalities quantitatively and may help diagnose IPF.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, primarily occurring in older adults; it is limited to the lungs, and is associated with the histopathological and/or radiological pattern of usual interstitial pneumonia (UIP) [1,2]. Recently, several anti-fibrosing drugs have been developed, and been shown to stabilize disease progression in patients with IPF [3,4]; accurate diagnosis of IPF can ensure prompt initiation of appropriate treatment. Computed tomography (CT) is an essential imaging modality for detecting and diagnosing IPF [1,5]. CT diagnosis of IPF by expert radiologists is satisfactory, and correlates well with patient prognosis [6]. Diagnoses made by general and less-experienced thoracic radiologists, however, show moderate inter-observer agreement of the UIP pattern on CT [7]; therefore, approaches that enhance diagnostic accuracy are needed.

We considered that subpleural fibrotic lesions may be useful in this respect [8]. Small opacities resembling thorns, located beneath the pleura, are characteristic of UIP, corresponding to fibrosis at the pleuroseptal junction [9,10]. We quantitatively measured the vol-

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ume of subpleural fibrotic lesions using a computer-aided system (CAD), and compared these with histological findings; we also compared CAD results with the multi-disciplinary diagnosis (MDD) and patient prognosis. We hypothesized that the lesion volume in the subpleural area may be a useful parameter for detecting the UIP pattern and distinguishing IPF from fibrosing nonspecific interstitial pneumonia (fNSIP), and would correlate with the patient prognosis.

2. Materials and methods

2.1. Subjects

This retrospective, single center study was approved by the institutional review board at our institution, and the requirement for informed consent was waived.

We selected 107 consecutive cases who underwent surgical biopsy from January 2007 to May 2011 in our hospital, whose initial MDD was IPF or fNSIP. We excluded patients who had previous thoracic surgery, previous acute exacerbation, were without follow-up CTs, or were diagnosed with connective tissue disease, and/or showed specific serology within the follow-up period [11].

All biopsy specimens were independently reviewed by two lung pathologists (35 and 20 years of experience), and a diagnosis of NSIP, UIP, or other was made based on the histologic criteria [1,2]. These pathologists independently categorized emphysema, overall fibrosis, spatial/temporal heterogeneity of the lesion, organizing pneumonia, traction bronchiectasis, cellular infiltration, subpleural collapse, fibroblastic foci, and honeycomb, based on the guidelines [1,2,12] as being either none, mild, middle, or severe, according to previous studies [13,14]. Disagreements were resolved by consensus.

2.2. Pulmonary function tests (PFTs)

All patients underwent PFTs before undergoing surgical biopsy. CHESTAC-33 (Chest MI Co., Tokyo, Japan) and Fudac-77 (Fukuda Denshi, Tokyo, Japan) were used to measure forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), total lung capacity (TLC), and diffusing capacity (DLCO) [15]. Results are expressed as a percentage of predicted performance based on standard values [15].

2.3. CT image analysis

Thin-section, volumetric CT images (0.5-mm-thick slices) were obtained during inspiration in the supine position, prior to surgical biopsy, using a 16-multi-detector CT (MDCT) (Aquilion-16, Toshiba, Tokyo, Japan) or a 64-MDCT scanner (Aquilion-64, Toshiba, Tokyo, Japan) at 120 kVp. A current of 250 mAs (16-MDCT) and variable mAs below 250 mAs (64-MDCT) was used. Images were obtained without contrast agents, and were reconstructed using a standard algorithm of filtered back projection.

2.4. Image analysis using the gaussian histogram normalized correlation (GHNC) system

We analyzed the CT images using the GHNC system as reported previously [16–18]. Briefly, the GHNC system divides lung pixels into six categories (normal [N], emphysema [E], ground glass opacity [GGO, G], consolidation [C], reticulation [R], and honeycomb [H]) along pre-designed samples using the CT attenuation values and their local histograms. These samples were selected from normal volunteers and patients other than subjects of this study.

The lung volume in each category and the total CT lung volume (CTLV) were computed automatically, and each category was indicated by a different color on GHNC images. Each category volume was expressed as a percentage of the CTLV. We measured mean CT attenuation values of the lung (CTmean) and the mean pixel values of the lung on the differential images (CTdmean). The differential image is Laplacian filtered image to stress the edge of figures [19]. CTdmean is the mean absolute pixel values on the lung on the Laplacian filtered images.

We determined the subpleural lung area as the outer part of the lung within 1–5 mm under the pleura (Fig. 1) and calculated these CT parameters in each subpleural lung area. We assumed that H_k is the H-pattern volume ratio in the subpleural lung area within k mm. For example, H_1 represents the H-pattern volume ratio within a 1-mm-width of the subpleural area, and so forth. The segmentation of the subpleural area is fully automated. One radiologist and one technician performed the CT analyses; we assessed inter-observer agreement.

2.5. CT measurement at the biopsy site

Biopsy sites were confirmed by comparing CT images before and after surgical biopsy. One radiologist determined regions of interest (ROIs) of approximately 2-cm diameter at the biopsy sites for measuring GHNC parameters (Fig. 2 a). Sagittal or coronal reformatting images were used to adjust the histological plane. We measured the pattern volume ratio, CTmean, and CTdmean of each ROI.

2.6. Statistical analysis

Inter-observer agreement between the two pathologists was assessed by weighted-kappa analysis. Inter-observer agreement was classified as slight ($\kappa = 0.00–0.20$), fair ($\kappa = 0.21–0.40$), moderate ($\kappa = 0.41–0.60$), substantial ($\kappa = 0.61–0.80$), or nearly perfect ($\kappa = 0.81–1.00$). Inter-observer agreements of CT measurements between the two observers were analyzed by calculating intra-class correlation coefficients (ICCs); an ICC > 0.75 indicates good agreement [20]. We used Bland – Altman plots to present the limits of agreement. We compared the histological scores and the CT results of the ROIs using Spearman's correlation analysis.

We divided the patients into two groups, i.e., the IPF and fNSIP groups, based on the MDD. We compared the patients' character-

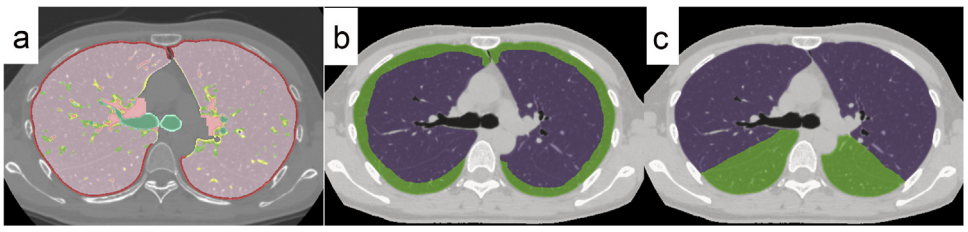

Fig. 1. Distribution pattern of the lesions and subpleural area on computed tomography (CT) images.
a) The red line along the pleura shows the 2-mm width of the subpleural area as determined by the computer-aided system. b) Schematic drawing of the peripheral distribution and c) the distribution along broncho-vascular bundles. The light-green area occupies 25% of the lung on both (b) and (c). In contrast, the light-green area comprises almost 100% of the subpleural area on (b), and 25% on (c).