Is volumetric 3-dimensional computed tomography useful to predict histological tumour invasiveness? Analysis of 211 lesions of cT1N0M0 lung adenocarcinoma

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Received 6 October 2015; received in revised form 12 January 2016; accepted 18 January 2016

Abstract

OBJECTIVES: The purpose of this study was to use Hounsfield unit (HU) thresholds of computed tomography (CT) images to predict pathological lymph node metastasis and tumour invasiveness of cT1N0M0 lung adenocarcinoma on 3D evaluations.

METHODS: Preoperative CT images of 211 lesions of surgically resected cT1N0M0 lung adenocarcinoma were retrospectively examined. The tumour size was calculated in 1D, 2D and 3D views. Tumours with −300 HU and over were defined as ‘solid tumours’, and those between −800 and −301 HU were defined as ‘ground glass opacity tumours’. Tumours with −800 HU and over were assumed to be the whole tumour entity. The proportion of ‘solid tumour’ within the whole tumour entity was also calculated as the ‘solid tumour ratio’. These were compared with pathological information.

RESULTS: Solid tumour size and ratio were positively correlated with microscopic invasion to pleura, vessels and lymphatics in all dimensional evaluations. Pathological lymph node metastases were also well predicted by solid tumour size and ratio in all dimensional evaluations. The P-values for the receiver operating characteristic (ROC) curves of 1D, 1D ×2, 2D and 3D evaluations were: solid tumour size P = 0.013, 0.014 and 0.032; and solid tumour ratio 0.016, 0.0032 and <0.0001. In comparisons of 1D, 2D and 3D evaluations, ‘solid tumour size’ of the area under the curve (AUC) of ROC to detect pathological lymph node metastases was not significant. However, strikingly, the 3D solid tumour ratio was found to be significantly more accurate for the prediction of pathological lymph node metastases than the 1D and 2D solid tumour ratios on ROC evaluation (AUC: 1D 0.736, 2D 0.803 and 3D 0.882; P-values for the AUC comparisons were P = 0.013 for 3D versus 1D and P = 0.022 for 3D versus 2D). The correlations of subtypes of adenocarcinoma and the 3D solid tumour ratio were also investigated. Subtypes of adenocarcinoma were well correlated with the 3D solid tumour ratio.

CONCLUSIONS: Preoperative 3D CT using threshold values of −800 and −300 HU was useful for predicting pathological lymph node metastases and tumour invasiveness of cT1N0M0 lung adenocarcinoma.

Keywords: Adenocarcinoma • Histology • Lung cancer • Radiology • Thoracic surgery • 3D CT

INTRODUCTION

Advances in radiological technology have disclosed the correlations between biological behaviour and CT findings of lung adenocarcinoma, such as contrast enhancement or nodule shape [1, 2]. In particular, the high-intensity area of a tumour, the so-called solid component, on chest CT has been reported as a prognostic factor in several studies [3–6]. However, previous reports might have shown variations in evaluating the exact size of whole tumours or the solid components of tumours due to single-slice CT evaluations and inter-radiologist evaluation bias. Single-slice CT evaluation is naturally incapable of using all of the information on CT images of a tumour, because lung cancer often shows asymmetric growth. Petrick et al. [7] reported that 3D volumetric sizing for lung phantom lesions using urethane and epoxy resins was more unbiased than 1D and 2D sizing. The
NELSON study, Europe’s largest lung cancer screening trial, showed the effectiveness of 3D volumetric evaluation in screening and follow-up for lung nodules [8, 9]. Furthermore, several studies evaluating the differences between the solid and ground glass opacity (GGO) components, the histogram pattern or the mean value of Hounsfield units (HU) in a tumour on CT images were designed to define the sizes of whole tumours or solid components depending on radiologists’ discretion [3–6, 10]. Thus, evaluations of the sizes of whole tumours or solid components might vary among radiologists.

We hypothesized that 3D volumetric evaluations were useful for predicting tumour invasiveness of small lung adenocarcinomas. The present study retrospectively examined the preoperative CT images of patients with cT1N0M0 lung adenocarcinoma to predict lymph node metastases and tumour invasiveness with limited bias. To obtain less variance in measurements for tumour sizing, volumetric 3D evaluation was used to measure the whole tumour and the solid component of the tumour, and these were compared with 1D and 2D evaluations. Moreover, HU thresholds were strictly adopted for measuring tumour size. Accordingly, the correlation between preoperative 3D-CT using HU thresholds and pathological findings was investigated in cT1N0M0 lung cancer patients.

MATERIALS AND METHODS

Patients

From January 2011 to November 2012, 236 lesions of cT1a/bN0M0 lung adenocarcinoma were surgically resected in our institute, and 211 lesions of 193 patients were included in this study (age: 67.2 ± 9.5 years, male/female: 94/99). Twenty-five lesions were excluded because thin-slice images of these lesions were not available. The lesions were clinically staged according to the seventh edition of the tumor node metastasis (TNM) classification of lung cancer [11]. Almost all patients included in this study underwent 18F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) to confirm clinical N0. Invasive mediastinal stagings such as mediastinoscopy or endobronchial ultrasound-guided trans-bronchial needle aspiration were not performed at preoperative state in included patients. The clinical features of included patients are summarized in Table 1. The 193 cases underwent a total of 203 surgical procedures: 105 lobectomies for 71 lesions; 70 segmentectomies for 71 lesions and 28 wedge resections for 28 lesions. The clinicopathological features of the included cases are presented in Table 2. The extent of nodal dissection was surgically decided in each patient.

This study was approved by the Kyoto University Graduate School and Faculty of Medicine, Ethics Committee (approval no. E2140). The requirement for informed consent from each patient was waived because this study was part of a retrospective review of the database of included patients.

Pathological information reviews

Pathological information was reviewed from the database of pathology reports of included patients. Pathological lymph node metastases were described as pN. Microscopic invasion to pleura, vessels and lymphatics was described as p, v and ly factors, respectively (Table 2). Pleural invasion was considered to be positive when tumour cells extended beyond the elastic layer of the pleura, as determined by elastic staining [12]. Vascular and lymphatic invasions were considered to be positive when tumour cells were recognized in the lymphatic lumen and blood vessel, respectively [12]. The lesions were classified by the predominant histological subtype according to the IASLC/ATS/ERS classifications [13] (Table 3).

Computed tomography images

The preoperative CT images of 211 lesions of resected cT1N0M0 lung adenocarcinoma were analysed retrospectively. Enrolled patients underwent non-contrast-enhanced chest CT (Aquilion 64; Toshiba Medical Systems, Tochigi, Japan). Thin-slice images less than 1 mm thick were acquired during one breath hold with tube voltage of 120 kVp using automatic exposure control. The acquired CT data were then analysed by AZE Virtual Place (AZE Ltd, Tokyo, Japan). The sizing methods were as described below (1D, 1D ×2, 2D and 3D).

(i) 1D: The largest diameters of the whole and solid tumour parts were manually measured with electronic callipers.

(ii) 1D ×2: The largest perpendicular diameters of the whole and solid tumour parts in the same CT slice were also manually measured with electronic callipers. The product of 1D

Table 1: Clinical features of the included cases

<table>
<thead>
<tr>
<th>Value</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.2 ± 9.5</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>94/99</td>
</tr>
<tr>
<td>Smoking history (never/ex/current)</td>
<td>91/76/26</td>
</tr>
<tr>
<td>Prevalence of COPD</td>
<td>44</td>
</tr>
<tr>
<td>Total number of lesions</td>
<td>211</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td>Total 203 (193 cases)</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>105 for 112 lesions</td>
</tr>
<tr>
<td>Segmentectomy</td>
<td>70 for 71 lesions</td>
</tr>
<tr>
<td>Wedge resection</td>
<td>28 for 28 lesions</td>
</tr>
</tbody>
</table>

The data are presented as means ± SD. Total numbers of patients, lesions and surgical procedures did not match, because there were cases of multiple ectopic or heterochronous lesions. COPD: chronic obstructive pulmonary disease; SD: standard deviation.

Table 2: Clinicopathological features of included lesions

<table>
<thead>
<tr>
<th>Value</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum diameter of whole tumour (mm)</td>
<td>18.7 ± 8.9</td>
</tr>
<tr>
<td>20 mm or less (cT1a)</td>
<td>13.2 ± 4.2 mm, 132 lesions</td>
</tr>
<tr>
<td>Over 20 mm (cT1b)</td>
<td>27.9 ± 6.9 mm, 79 lesions</td>
</tr>
<tr>
<td>Maximum diameter of solid tumour (mm)</td>
<td>13.1 ± 9.6</td>
</tr>
<tr>
<td>Positive cases of pathological lymph node metastasis (pN+)</td>
<td>8 lesions, 3.8%</td>
</tr>
<tr>
<td>Positive cases of microscopic pleural invasion (pl+)</td>
<td>20 lesions, 9.5%</td>
</tr>
<tr>
<td>Positive cases of microscopic vesical invasion (v+)</td>
<td>15 lesions, 7.1%</td>
</tr>
<tr>
<td>Positive cases of microscopic lymphatic invasion (ly+)</td>
<td>5 lesions, 2.4%</td>
</tr>
</tbody>
</table>

The data are presented as means ± SD. The maximum diameters of the whole and solid tumour part on CT are shown. Pathological lymph node metastases are shown as pN. Microscopic invasions to pleura, vessels and lymphatics are shown as pl, v and ly factors, respectively. SD: standard deviation; CT: computed tomography.
diameter multiplied by the perpendicular diameter × 0.75 was calculated as the estimated tumour area. This measurement of the area was defined as the 1D ×2 measurement.

(iii) 2D: The semi-automated area measurement of the whole and solid tumour parts of the CT slice including the largest tumour diameter was defined as the 2D measurement.

(iv) 3D: The semi-automated 3D volumetric measurement of the whole and solid tumour was defined as the 3D measurement.

The 2D and 3D measurements of tumour size were semi-automated calculations within AZE Virtual Place software. Examples of the tumour 2D and 3D measurements are shown in Fig. 1. For 2D measurement, the periphery of the tumour was roughly traced manually on the CT slice containing the largest tumour diameters, without chest wall or apparent vessels. Subsequently, according to the report by Nomori et al. [10], thresholds of −800 and −300 HU were applied to the inside of the traced area, and the area −800 HU and over and that −300 HU and over were automatically calculated. The area −800 HU and over was assumed to be the whole tumour. The area −300 HU and over was defined and calculated as ‘solid tumour’, and that between −800 and −301 HU was defined and calculated as ‘GGO tumour’. The 3D volumetric measurement involved semi-automated integral calculations of the 2D measurements of some slices around the tumour.

The proportion of ‘solid tumour’ size compared with whole tumour size was also calculated, and this was defined as the ‘solid tumour ratio’ in the 1D, 1D ×2, 2D and 3D measurements.

### Statistical analysis

Logistic regression analysis and comparisons of the area under the curve (AUC) of the receiver operating characteristic (ROC) curve were used for the statistical analyses of the categorical data, including pl, v and ly factors and pathological lymph node metastases. Welch’s t-test was used for comparisons of 3D solid ratio data and each subtype of adenocarcinoma. Multivariate logistic regression analysis for pN was performed with the factors; sex (male = 1, female = 0), age (in years), smoking history (current = 2, ex = 1, never = 0) and prevalence of COPD (yes = 1, no = 0) for each dimensional solid tumour size and ratio. The odds ratio for each risk factor was also calculated. The odds ratio for solid tumour size was described as ratio for every one unit (mm, mm² and mm³) increase, for solid tumour ratio as described as ratio for every 1% increase. Statistical analyses were performed using JMP® 11 (SAS Institute, Inc., Cary, NC, USA). A P value of less than 0.05 was considered significant.

### RESULTS

In the retrospective review of the included lesions, the maximum diameter of whole tumour was 18.7 ± 8.9 mm, and the maximum diameter of the solid component of the tumour was 13.1 ± 9.6 mm (Table 2). The whole and solid tumour volumes were also calculated

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**Table 3:** The predominant adenocarcinoma subtypes of included lesions

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Adenocarcinoma in situ</td>
<td>25 lesions, 11.8%</td>
</tr>
<tr>
<td>Minimally invasive adenocarcinoma</td>
<td>7 lesions, 3.3%</td>
</tr>
<tr>
<td>Lepidic</td>
<td>52 lesions, 24.6%</td>
</tr>
<tr>
<td>Papillary</td>
<td>54 lesions, 25.6%</td>
</tr>
<tr>
<td>Acinar</td>
<td>51 lesions, 24.2%</td>
</tr>
<tr>
<td>Other (solid/micropapillary/invasive mucinous adenocarcinoma)</td>
<td>18 lesions, 8.5%/1 lesion, 0.5%/3 lesions, 1.4%</td>
</tr>
</tbody>
</table>

The lesions were classified to each predominant subtype of adenocarcinoma according to the IASLC/ATS/ERS classification.

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**Figure 1:** Definition of ‘solid tumour volume’ and ‘ground glass opacity (GGO) tumour volume’. Left: An example of the CT data of a lesion. Rough tracing around the tumour was performed in some slices of CT images, excluding chest wall or obvious vessels. Right: An example of the definition of tumour volume extracted from CT data. Yellow coloured area indicates the area –300 HU and over as ‘solid tumour volume’, and the red coloured area indicates the area between –800 and –301 HU as ‘GGO tumour volume’. GGO: ground glass opacity; HU: Hounsfield units; CT: computed tomography.
using 1D, 1D ×2, 2D and 3D measurements; 'solid tumour size' and solid tumour ratio with each dimension evaluation are shown as below: 1D 13.1 ± 9.6 mm, 0.65 ± 0.36; 1D ×2 136.5 ± 163.0 mm², 0.54 ± 0.39; 2D 119.3 ± 133.4 mm², 0.35 ± 0.22; and 3D 1683.7 ± 2866.0 mm³, 0.29 ± 0.18.

**Solid tumour size**

All dimension evaluations for solid tumour size were good predictors of pN, pl, v and ly, as shown in Fig. 2A–D (except for the evaluation to predict the pl factor by 3D measurement and the ly factor by 1D ×2, 2D and 3D measurements). The P-values for the ROC analyses of 1D, 1D ×2, 2D and 3D evaluations were: pN P = 0.0013, 0.0023, 0.0014 and 0.032; pl P < 0.001, 0.010, 0.0021 and 0.046; v P < 0.001, 0.0014 and 0.0033; and ly P = 0.027, P = 0.024 and P = 0.20, respectively. The ideal cut-off values for the ROC analyses of 1D, 1D ×2, 2D and 3D evaluations were: pN 15.1 mm, 146.1 mm², 260.8 mm³ and 2720 mm³; pl 13.3 mm, 87.9 mm², 109.3 mm² and 1090 mm³; v 16.8 mm, 70.8 mm², 133.9 mm² and 1670 mm³; ly 16.8 mm, 162.5 mm³, 260.8 mm³ and 2720 mm³, respectively.

In the comparisons of 1D, 1D ×2, 2D and 3D evaluations of solid tumour size to detect pN, pl, v and ly, the highest AUC of the ROC curve to predict pN does not show a significant difference for solid tumour size evaluation [AUC with 95% confidence interval (CI) and P-values of each curve: 1D 0.807 (0.607–0.919) P = 0.0013, 1D ×2 0.826 (0.644–0.926) P = 0.0023, 2D 0.826 (0.645–0.930) P = 0.0014 and 3D 0.819 (0.623–0.925) P = 0.032]. (B) Each AUC of the ROC curve to predict pl does not show a significant difference for solid tumour size evaluation [AUC with 95% (CI) and P-values of each curve: 1D 0.762 (0.659–0.842) P < 0.001, 1D ×2 0.766 (0.667–0.842) P = 0.010, 2D 0.779 (0.683–0.852) P = 0.0021 and 3D 0.787 (0.690–0.859) P = 0.046]. (C) The AUC of the ROC curve to predict v shows significant differences for 3D versus 1D, 3D versus 1D ×2 and 3D versus 2D (P = 0.020, 0.021 and 0.042, respectively) [AUC with 95% (CI) and P-values of each curve: 1D 0.780 (0.667–0.862) P < 0.001, 1D ×2 0.779 (0.663–0.864) P = 0.0014, 2D 0.797 (0.684–0.878) P < 0.001 and 3D 0.850 (0.758–0.910) P = 0.0033]. (D) Each AUC of the ROC curve to predict microscopic invasion to lymphatics (ly) does not show a significant difference [AUC with 95% (CI) and P-values of each curve: 1D 0.772 (0.480–0.925) P = 0.027, 1D ×2 0.772 (0.519–0.914) P = 0.072, 2D 0.820 (0.529–0.949) P = 0.024 and 3D 0.809 (0.522–0.943) P = 0.20]. AUC: area under the curve; CI: confidence interval; ROC: receiver operating characteristic; 1D: one-dimensional; 2D: two-dimensional; 3D: three-dimensional; pN: pathological lymph node metastases; pl: microscopic invasion to pleura; v: microscopic invasion to vessels; ly: microscopic invasion to lymphatics.
ROC of these measurements did not show a significant difference (except for the evaluation to predict v factor, 3D versus 1D, 3D versus 1D ×2 and 3D versus 2D with \( P = 0.020, 0.021 \) and 0.043, respectively).

Multivariate logistic regression analysis for pN with the factor of sex, age, smoking history and prevalence of COPD for 1D, 1D ×2, 2D and 3D evaluations showed the prevalence of COPD in 1D, 1D ×2, 2D and 3D (with \( P = 0.0099, 0.011, 0.012 \) and 0.0095) and solid tumour size in 1D, 1D ×2 and 2D (with \( P = 0.0065, 0.0068 \) and 0.0047) were independent risk factors for pN. Solid tumour size in 3D evaluation was not independent risk factor for pN (\( P = 0.10 \)). The odds ratio for prevalence of COPD in 1D, 1D ×2, 2D and 3D were 39.03, 33.27, 34.11 and 29.00. The odds ratio for solid tumour size in 1D, 1D ×2 and 2D were 1.13, 1.01 and 1.01 for every one unit increase, respectively.

**Solid tumour ratio**

The proportion of solid tumour size compared with whole tumour size was also calculated and defined as the solid tumour ratio in 1D, 1D ×2, 2D and 3D measurements.

All dimension evaluations for the solid tumour ratio were good predictors for pN, pl, v and ly, as shown in Fig. 3A-D (except for the evaluation to predict the ly factor by 1D and 1D ×2 measurements). The \( P \)-values for the ROC analyses of 1D, 1D ×2, 2D and 3D evaluations were: pN \( P = 0.016, 0.017, 0.0032 \) and <0.0001; pl \( P < 0.001, <0.001, <0.0001 \) and <0.0001; v \( P < 0.001, <0.001 \) and <0.0001; ly \( P = 0.087, 0.074, 0.0084 \) and <0.001, respectively. The ideal cut-off values for the ROC analyses of 1D, 1D ×2, 2D and 3D evaluations were: pN 1.0, 1.0, 0.40 and 0.42; pl 1.0, 0.84, 0.39 and 0.39; v 0.9, 0.84, 0.39 and 0.38; ly 0.84, 0.84, 0.47 and 0.48, respectively.

However, strikingly, in comparisons of 1D, 1D ×2, 2D and 3D evaluations of the solid tumour ratio, the 3D solid tumour volume ratio was found to be more accurate for prediction of pN than the 1D solid tumour length ratio and the 1D ×2 and 2D solid tumour area ratio on ROC evaluation (AUC, 1D 0.736, 1D ×2 0.741, 2D 0.803 and 3D 0.882; 3D versus 1D, 3D versus 1D ×2 and 3D versus 2D with \( P = 0.013, 0.023 \) and 0.022, respectively). Moreover, the 3D solid tumour volume ratio was found to be more accurate for prediction of pl, v and ly than all of the other dimensional measurements. The \( P \)-values for the comparison of the AUC of ROC analyses of 3D versus 1D, 3D versus 1D ×2 and 3D versus 2D evaluations were: pl \( P < 0.0001, <0.001 \) and 0.015; v \( P < 0.001, 0.0031 \) and 0.021; and ly \( P = 0.015, 0.023 \) and 0.0068, respectively.

The 3D solid tumour ratios of each subtype of adenocarcinoma are shown in Fig. 4. Subtypes of adenocarcinoma were well correlated with the 3D solid tumour ratio.

In summary, a higher solid tumour ratio in 3D measurement was a better predictor of histological malignancy in patients with lung adenocarcinoma than the other dimensional measurements.

Multivariate logistic regression analysis for pN with the factor of sex, age, smoking history and prevalence of COPD for 1D, 1D ×2, 2D and 3D evaluations showed the prevalence of COPD in 1D, 1D ×2, 2D and 3D (with \( P = 0.012, 0.013, 0.021 \) and 0.045) and solid tumour ratio in 1D ×2, 2D and 3D (with \( P = 0.042, 0.0087 \) and 0.0036) were independent risk factors for pN. Solid tumour ratio in 1D evaluation was not independent risk factor for pN (\( P = 0.078 \)). The odds ratios for prevalence of COPD in 1D, 1D ×2, 2D and 3D were 27.16, 27.59, 21.19 and 14.97, respectively. The odds ratios for solid tumour ratio in 1D ×2, 2D and 3D were 1.03, 1.08 and 1.15 for every 1% increase.

**DISCUSSION**

Several studies have noted the correlation between biological behaviour and CT findings such as the solid or the GGO component of lung adenocarcinoma [1-4]. Most of these studies used 1D or 2D evaluation on single slices of CT images. However, studies of the correlations between 3D evaluation of lung cancer and pathological tumour invasiveness have not been widely performed.

Solid lesions tend to progress faster than GGO-mixed lesions, and GGO-mixed lesions tend to grow faster than pure GGO lesions [14]. Tsutani et al. [3] reported that the solid area diameter was more effective in predicting high-grade malignancy and prognosis than whole tumour diameter. Matsuguma et al. [4] reported that a tumour with the same solid area diameter, but a greater proportion of GGO is much less invasive than that with a smaller proportion of GGO. In the present data, it was remarkable that comparisons of 1D, 2D and 3D evaluations of solid tumour size did not show a significant difference to predict pathological invasiveness, whereas the 3D solid tumour ratio was found to be more accurate for predicting pathological invasiveness than 1D or 2D evaluations. However, comparison of the 3D volume and ratio as predictors did not show a significant difference (AUC, 3D volume: 0.819, 3D ratio: 0.882, \( P = 0.31 \)). These outcomes resulted in the following suggestions:

(i) The accuracy of ROC analysis of solid tumour size was equal on 3D evaluation and 1D evaluation (Fig. 2A-D). Thus, detection of solid tumour size in 1D is appropriate.

(ii) The accuracy of ROC analysis of the solid tumour ratio was higher on 3D evaluation than on 1D and 2D evaluations (Fig. 3A-D). Thus, GGO component detection appears better with 3D evaluation than with 1D and 2D evaluations.

More studies are needed to identify the differences among 1D, 2D and 3D evaluations of lung adenocarcinoma.

Tsutani et al. [3] reported that the maximum standardized uptake value on FDG-PET/CT was useful for predicting pathological malignancy and disease-free survival in clinical stage IA lung adenocarcinoma. Moreover, they noted that FDG uptake was more closely related to solid tumour size than whole tumour size. It is widely accepted that higher FDG uptake of cancer shows higher glucose uptake and correlates with more aggressive phenotypes and poorer clinical outcomes because of aerobic glycolysis in the tumour microenvironment (The Warburg effect) [15]. Their result suggested that the solid component of tumour was the main area of aerobic glycolysis. Thus, distinguishing the solid component from the GGO component on CT images with minimal bias is very important to predict the biological behaviour of the cancer. Further studies are required to explore the importance of FDG-PET/CT to predict the biological behaviour of lung adenocarcinoma.

The advantage of the present study was the strict use of the thresholds of -800 and -300 HU, thus avoiding bias and the variations in measurements of the whole and the solid part of tumour size among radiologists. The thresholds of -300 and -800 HU were determined according to the report by Nomori et al. [10], who reported that the histogram patterns of cT1N0M0 lung adenocarcinoma were correlated with pathological tumour invasiveness. The histogram patterns were classified into three groups as one peak at low density, one peak at high density and two peaks at low and high densities. What was of greatest interest in their paper for the purposes of this study was the appropriate HU thresholds to distinguish the GGO part and the solid part of adenocarcinoma. There was ‘a dip’ around -300 HU in the histogram of the two peaks of...
the low- and high-density groups, which might represent the solid-GGO-mixed type of tumour, in their report. In the present study, similar histogram patterns were also found on 3D analysis of some of the cases. Thus, the threshold of $-300$ HU was very useful to distinguish the solid part from the GGO part of tumours.

Thin-section CT findings have been shown to reflect histological findings [16]. IASLC/ATS/ERS classified lung adenocarcinoma based on the extent of lepidic lesions and invasive lesions [13]. Noguchi et al. [17] classified the histology of small lung adenocarcinoma and reported a correlation between histological subtypes such as fibroblastic proliferation and 5-year survival rates. We also previously reported the correlations between histological subtypes of adenocarcinoma and their prognosis [12]. The histological subtype perspective showed the importance of distinguishing lepidic lesions from invasive or fibrotic lesions to understand the malignant biological behaviour of lung adenocarcinoma. The results of the present study showed the correlation between the 3D solid tumour ratio and subtypes of adenocarcinoma (Fig. 4), and this matched the tumour invasiveness of each subtype well. Although the exact HU ranges and configurations on CT imaging for invasive or fibrotic lesions of tumour extent in histology were not identified, we might presume that high-intensity areas such as...
In conclusion, both the solid tumour size and the solid tumour ratio of 3D-CT evaluation were significantly correlated with tumour invasiveness. In particular, a higher solid tumour ratio in 3D measurement was a better predictor of histological malignancy in patients with lung adenocarcinoma than the other dimensional measurements. Moreover, subtypes of adenocarcinoma were well correlated with the 3D solid tumour ratio. Volumetric 3D CT applying thresholds of −800 and −300 HU were useful for predicting tumour invasiveness and lymph node metastases of cT1N0M0 lung adenocarcinoma.

ACKNOWLEDGEMENTS

The authors thank Kei Murakami, the radiological technologist from AZE Ltd, for providing technical advice.

Funding

This work was supported by Grants-in-Aid for scientific research (C) (No. 26462126) from the Japan Society for the Promotion of Science.

Conflict of interest: none declared.

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