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Three-dimensional mean CT attenuation value of pure and part-solid ground-glass lung nodules may predict invasiveness in early adenocarcinoma

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AIM: This study evaluated the relationship between three-dimensional (3D) mean computed tomography (CT) attenuation values of ground-glass nodules (GGN) and pathological invasiveness in early lung adenocarcinoma. The diagnostic accuracy of 3D CT attenuation values was compared with that of two-dimensional (2D) CT attenuation values and standardised uptake value on positron-emission tomography (PET).

MATERIALS AND METHODS: Surgical and radiological data from 96 pure or part-solid GGNs of <20 mm were analysed retrospectively. Mean 2D and 3D CT attenuation values of the tumours were obtained with semi-automated volumetric software. Pathological invasiveness was diagnosed according to the International Association for the Study of Lung Cancer (IASLC))/American Thoracic Society (ATS)/European Respiratory Society (ERS) classification. Pre-invasive lesions and minimally invasive adenocarcinomas were classified as non-invasive adenocarcinoma. Univariate and multivariate analyses determined relationships between pathological invasiveness and clinical/radiological findings. Receiver operating characteristic (ROC) analysis was performed to determine the optimal cut-off value for detecting invasive adenocarcinoma.

RESULTS: A total of 66 non-invasive and 30 invasive adenocarcinoma cases between 2010 and 2016 were analysed. Univariate analysis revealed four tumour invasiveness-associated predictors: maximum diameter, SUVmax, mean 2D CT attenuation value, and mean 3D CT attenuation value ($p<0.05$). Multivariate analysis revealed that the maximum diameter, SUVmax, and mean 3D CT attenuation value were significant predictors of pathological invasiveness ($p=0.023$, 0.022, 0.004). The area under the ROC curve to predict invasive adenocarcinoma for mean 3D CT attenuation value was 0.838 and the cut-off value was −489 HU.

CONCLUSION: The mean 3D CT attenuation value could distinguish pre-invasive lesions and minimally invasive adenocarcinoma from invasive adenocarcinoma.

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Introduction

Early-stage lung adenocarcinoma nodules often feature ground-glass opacity (GGO) associated with a pathological lepidic growth pattern.[1] These GGO-dominant adenocarcinomas are termed ground-glass nodules (GGN) and could be optimal candidates for sublobar resection as an alternative to lobectomy.[2–4] Histological evaluation by biopsy for small and hazy pulmonary nodules is generally difficult; therefore, an accurate radiological evaluation of the aggressiveness of lung adenocarcinoma is essential. Previous studies have reported radiological parameters to distinguish pre-invasive lesions and minimally invasive adenocarcinoma from other types of lung cancer with tumour shadow disappearance rate or a maximum standardised uptake value (SUVmax) with positron-emission tomography (PET) used to estimate the malignancy of pulmonary tumours featuring GGO components.[5–7] Computed tomography (CT) attenuation value analysis can also be used as a discriminatory parameter for invasive adenocarcinoma[8,9]; however, previous studies have relied on two-dimensional (2D) axial, radiological evaluation. As most lung nodules are irregularly shaped in both axial and other dimensions, sole reliance on axial 2D CT imaging might be inappropriate. Therefore, direct three-dimensional (3D) evaluation could be more accurate than axial 2D measurements because every axis is evaluated. With the development of imaging technology and the optimisation of CT parameters, 3D analyses of lung tumours have been used to evaluate volumetric parameters, including 3D quantitative CT attenuation values. Therefore, the objective of the present study was to evaluate the relationship between CT attenuation values obtained with 3D CT and pathological invasiveness in lung adenocarcinoma.

Materials and methods

This retrospective study was approved by the Institutional Review Board and informed consent for research use of surgical specimens was obtained from all patients. Between January 2010 and December 2016, a total of 721 patients with non-small cell lung cancer underwent pulmonary resection. A total of 95 patients were included in the study on meeting the following criteria: a maximal tumour diameter of <20 mm on thin-section CT, pure or part-solid GGN, CT image section thickness of <2 mm, no internal tumour calcification, and complete surgical resection without neoadjuvant chemotherapy and radiotherapy. Pure solid nodules were excluded because most were pathologically diagnosed as invasive adenocarcinoma. The medical records of all patients were reviewed to determine age, gender, smoking habits, serum carcinoembryonic antigen (CEA) levels, and histopathologies. Radiological parameters included maximum tumour diameter, mean attenuation for both 2D CT and 3D CT, and SUVmax with 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG)-PET. Clinical characteristics and radiological findings were compared retrospectively with the pathological invasiveness of the adenocarcinomas.

CT examination

All CT examinations were obtained using 64- and 256-row, multisection, helical CT machines (Brilliance 64 and Brilliance iCT 256; PHILIPS Electronics, Tokyo, Japan). A standard contrast-enhanced imaging protocol was performed to evaluate the lung apex to upper abdomen using the following parameters: 120 kVpeak, 180–280 mAs tube current–time product, 0.515 and 0.758 beam pitch, 512×512 pixel resolution, and 0.5 second scanning duration. Axial images were reconstructed with a 1- or 2- mm section thickness. The images were viewed using a window level of −500 to −700 HU with a window width of 1,000–2,000 HU (lung window setting) and a level of 30–60 HU with a window width of 350–600 HU (mediastinal window setting).

Radiological evaluation

The maximum diameter of the tumour was defined as the longest diameter, including GGO lesions, on lung window settings. GGO refers to a focal capacity of increased attenuation, which did not obscure vessels in the lung window setting. All preoperative CT data were transferred to a computer workstation (SYNAPSE VINCENT version 3.0, FUJIFILM, Tokyo, Japan) which displays a CT density profile across the tumour. The 3D shapes of the tumour were semi-automatically visualised by tracking the edge of the pure or part-solid GGN from all axial images (Fig 1). Additionally, any structures overlapped with GGNs, such as pulmonary vessels, were excluded from the calculation target by drawing ROI manually in the axial image. The 3D image of the tumour was coloured dependent on the CT attenuation values (Fig 2). The voxel-based, 3D CT attenuation value histograms were generated automatically from which the mean attenuation value was calculated by multiplying the 3D CT attenuation value of the tumour by its volume (Fig 3). The mean 2D CT attenuation value the tumour on the axial plain of the largest nodule area was also obtained from pixel-based CT attenuation value histograms by multiplying the 2D CT attenuation value by its area. The SUVmax values by PET-CT were established by a radiologist before surgery who was blinded to the surgical outcomes.

Pathological evaluation

All patients underwent pulmonary resection, including wedge resection, segmentectomy, or lobectomy. Surgical intervention was recommended for nodules with GGO that increased in size during CT follow-up or when new solid components were found inside of GGN. Patients with tumours mainly composed of GGO underwent surgical excision without preoperative diagnosis by CT-guided or transbronchial biopsy. Pathological findings of adenocarcinoma were classified according to the International Association for the Study of Lung Cancer (IASLC))/American Thoracic Society (ATS)/European Respiratory Society (ERS) classification. Pre-invasive lesions (PL) and minimally invasive adenocarcinomas (MIA) were classified as non-

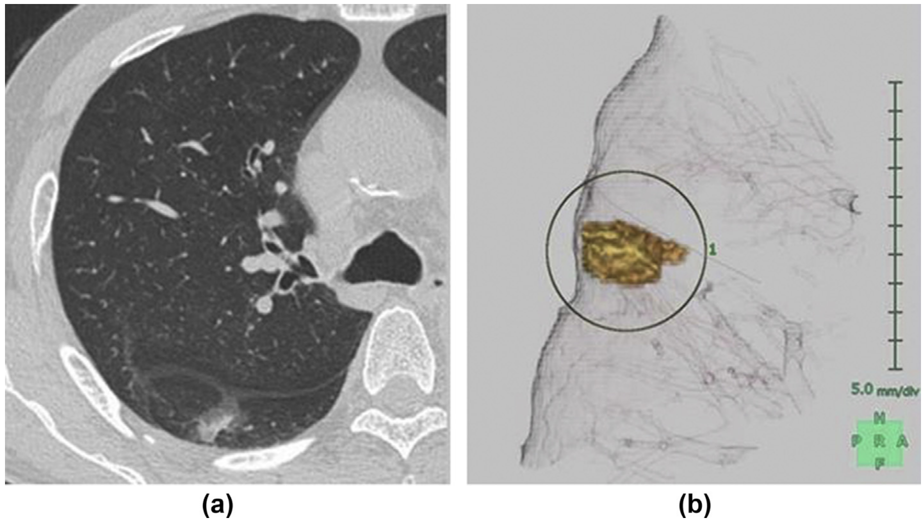

Figure 1 (a) Representative example of a tumour with a GGO lesion. (b) 3D image of a tumour segmented by the automated volumetric software.

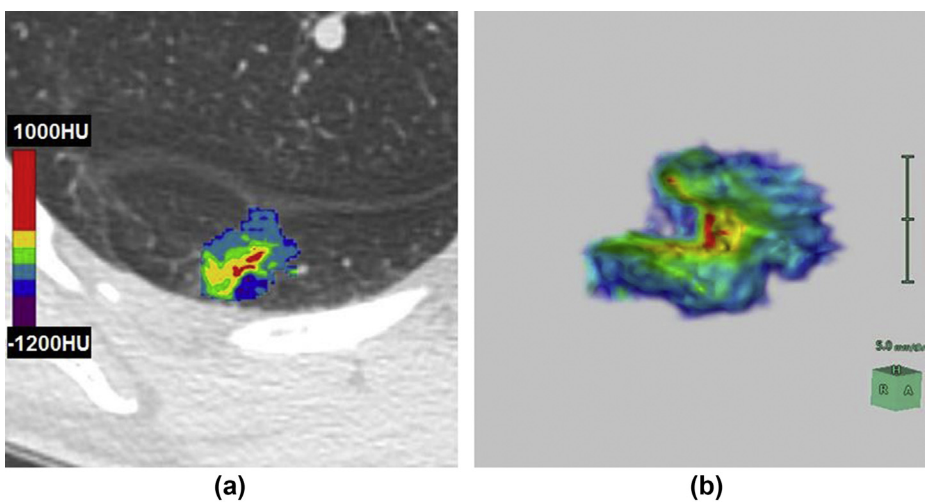

Figure 2 (a) Visualisation of the axial plain of the tumour and (b) 3D image of the tumour with the upper half removed. Internal tumour tissue colouration is dependent on the CT attenuation value.

invasive adenocarcinoma and other types were categorised as invasive adenocarcinoma.

Statistical analysis

All statistical analyses were performed with SPSS® version 21.0 (IBM Corporation, Armonk, NY, USA). Results are given as mean ± standard deviation (SD) or median and range values. A χ^2 test was used to compare categorical variables. Mann–Whitney U testing was used for non-parametric data. Variables with a *p*-value <0.05 in the univariate analysis were placed into a logistic regression multivariate analysis. Furthermore, a receiver-operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off value for detecting invasive adenocarcinoma. Statistical analyses were considered significant when the *p*-value was <0.05.

Results

Over the observation period, a total of 96 nodules with GGO components on thin-section CT were detected in 95 patients. Of these, two lesions were detected in one patient. The clinical and radiological characteristics of the patients are summarised in Table 1. There were 25 men (26%) and 70 women (74%) ranging in age from 35 to 87 years (mean age 67 years). Of the 95 total patients, 32 (34%) had a history of smoking. The mean diameter of the primary tumours on thin-section CT was 15.3±3.4 mm (range 8–20 mm). Surgical procedures included lobectomy in 49 cases and segmentectomy plus wedge resection in 46 cases. The pathological diagnoses demonstrated pre-invasive lesions in 17 nodules (18%), minimally invasive adenocarcinoma in 49 nodules (51%), and invasive adenocarcinoma in 30 nodules (31%). None of the tumours had lymphatic, blood

Figure 3 A CT value histogram showing a density profile across the tumour with the vertical axis representing tumour volume and horizontal axis representing CT attenuation value.

vessel, or pleural invasion, and lymph node metastases were not observed.

Based on our univariate analysis, maximum diameter, SUVmax, mean 2D CT, and mean 3D CT attenuation values were significant predictors for invasive adenocarcinoma ($p<0.05$ for all four variables) whereas no significance was seen in age, gender, smoking habits, or serum CEA levels. Table 2 shows the results of the multivariate analysis for predictors of invasive adenocarcinoma. The maximum diameter, SUVmax, and mean 3D CT attenuation value were significant factors for predicting pathological invasiveness in small adenocarcinoma (p=0.023, 0.022 and 0.004, respectively).

The ROC curve analysis revealed that the optimal cut-off values of SUVmax, mean 2D CT, and mean 3D CT attenuation value for predicting invasive adenocarcinoma in patients with purely or partly solid GGN were 1.27, −456 HU, and −489 HU, respectively (Fig 4). The area under the ROC curves of the SUVmax, mean 2D CT, and mean 3D CT attenuation value were 0.765, 0.810, and 0.838, respectively. These cut-off values yielded a sensitivity of 0.885 and a specificity of 0.566 for SUVmax, a sensitivity of 0.967 and a specificity of 0.576 for the mean 2D CT attenuation value, and a sensitivity of 0.967 and a specificity of 0.591 for the mean 3D CT attenuation value.

Table 2
Results of multivariate analysis for predictors of invasive adenocarcinoma.

Variables	Odds ratio (95% CI)	p-value
Whole tumour size (mm)	1.296 (1.037–1.621)	0.023
SUVmax	2.135 (1.116–4.085)	0.022
Mean 2D CT value (HU)	0.988 (0.974–1.001)	0.078
Mean 3D CT value (HU)	1.022 (1.007–1.038)	0.004

CI, confidence interval; SUVmax, maximum standardised uptake value; 2D CT, two-dimensional computed tomography; 3D CT, three-dimensional computed tomography.

Discussion

According to the IASLC/ATS/ERS classification, lung adenocarcinoma is categorised into three subtypes, including pre-invasive lesions (PRE), minimally invasive adenocarcinoma (MIA), and invasive adenocarcinoma.[10] For PRE and MIA, patients would have near 100% disease-free survival if these lesions were completely resected.[11,12] In previous studies, most GGO-dominant lung adenocarcinoma was reported to be PRE or MIA, both of which are suitable for sublobar resection[13–16]; however, lung adenocarcinoma with a GGO component occasionally exhibits pathological invasiveness. Therefore, accurate preoperative prediction of lung adenocarcinoma aggressiveness is crucial for the selection of the appropriate surgical procedure.

Previous studies of small lung adenocarcinomas have demonstrated a correlation between radiological findings and pathological features. The ratio between GGO and solid areas, tumour doubling time, CT attenuation values, and SUVmax on FDG-PET have been reported to be independent factors for lung adenocarcinoma to predict tumour characteristics for stage, recurrence, and survival.[17–20] Although previous studies were based on 2D radiological evaluation, leading to the possibility that 2D CT imaging might be

Table 1
Relationship between clinical features and pathological invasiveness of GGO-dominant tumours.

Clinical factors	Total (n=96)	Invasive (n=30)	Non-invasive (n=66)	p-Value
Age	68 (35–87)	68 (45–87)	68 (35–84)	0.566
Gender, male	26 (27%)	5 (17%)	21 (32%)	0.122
History of smoking	32 (33%)	7 (23%)	25 (38%)	0.161
CEA (ng/ml)	2.3±1.3	2.2±1.3	2.3±1.3	0.713
Whole tumour size (mm)	15.3±3.4	16.5±3.2	14.8±3.3	0.025
SUVmax	1.6±1.0	2.2±1.2	1.4±0.8	<0.01
Mean 2D CT value (HU)	−429±164	−306±126	−486±148	<0.01
Mean 3D CT value (HU)	−444±168	−307±114	−506±152	<0.01

Data are expressed as number of patients or mean±SD.
GGO, ground-glass opacity; CEA, carcinoembryonic antigen; SUVmax, maximum standardised uptake value; 2D CT, two-dimensional computed tomography; 3D CT, three-dimensional computed tomography; SD, standard deviation.

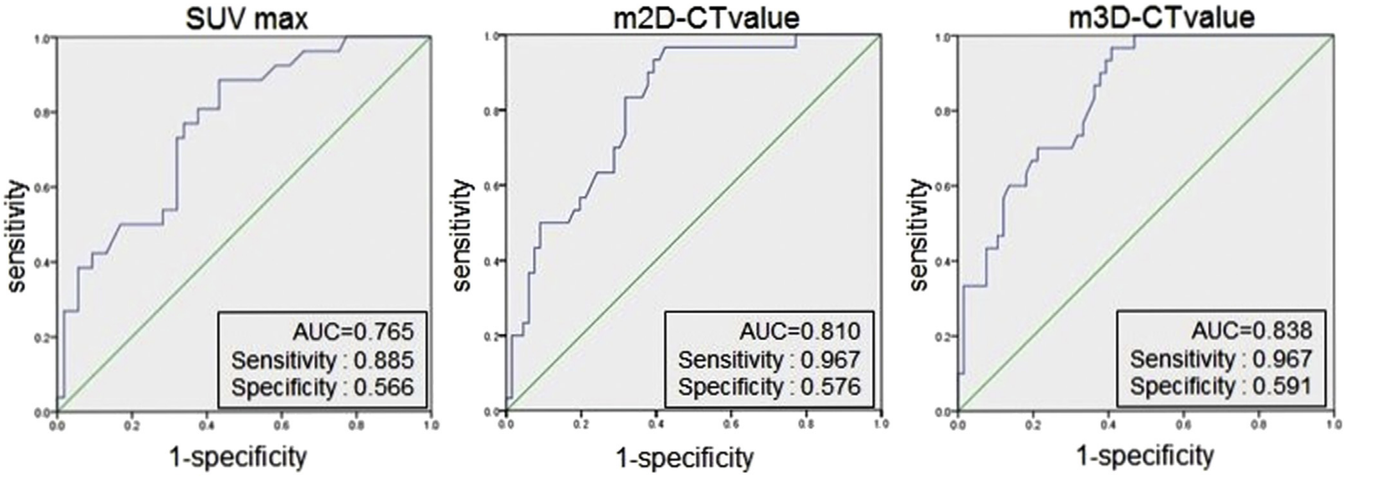

Figure 4 ROC for the (a) SUVmax, (b) mean 2D CT, and (c) mean 3D CT attenuation value showing the area under the curve for differentiation between invasive and non-invasive adenocarcinoma.

inappropriate. As most lung nodules that display GGO are irregularly shaped and distributions of solid components are often heterogeneous, any nodule assessments should be carried out in multiple planes. Three-dimensional evaluations that reflect the tumour directly and evaluate every axis could therefore be more accurate than conventional 2D measurement. These 3D parameters have also been used to evaluate tumour malignancy with the development of imaging technology. Bak *et al.*[21] reported a quantitative CT analysis via voxel-based CT number histogram and concluded that the 97.5th CT attenuation value of the tumour could be helpful in predicting the change in further CT and growth rate of pure GGNs.

Based on the World Health Organization classification, invasive adenocarcinoma is defined as a tumour that contains an invasive component >0.5 cm[22]; however, in the present study, some part-solid nodules without a solid component of >0.5 cm (axial slice) were pathologically diagnosed as invasive adenocarcinoma. The 2D solid size on the axial plane of the greatest area might differ from a pathological evaluation in a fixed specimen, giving rise to discrepancies between the 2D radiological solid diameter and pathological status. The present study showed that the mean attenuation based on 2D and 3D CT were both significant predictors of invasive adenocarcinoma in univariate analysis. Radiological invasive areas generally appear to be high CT number zones on high-resolution CT, indicating the growth of tumour cells along the alveolar septa and the central alveolar fibrosis. Therefore, the mCT attenuation value shows the tumour density that would more accurately reflect pathological invasiveness. According to the multivariate analysis, the mean 3D CT attenuation value was an independent predictor of pathological invasiveness of tumours with a GGO component whereas the mean 2D CT attenuation value was not significant. This result suggests that quantitative densitometric evaluation is superior to 2D plain image analysis.

The detection rate of GGO lesions has increased in recent years and whether GGO lesions should be resected or followed up remains controversial. Changes in both size and density are important for any decision to observe or intervene in patients with GGO lesions. Objective densitometric evaluation with 3D CT-attenuation value analysis could therefore be helpful in determining not only what operation to do but also when to stop follow-up of GGO lesions. In the ROC curve analysis, the CT cut-off value for differentiation from invasive adenocarcinoma was −489 HU in 3D analysis with high sensitivity (0.967). Sublobar resection could therefore be considered for GGO lesions showing less than −489 HU as those lesions are mostly diagnosed as non-invasive adenocarcinoma. In contrast, some nodules showing more than −489 HU in 3D analysis were pathologically diagnosed as non-invasive adenocarcinoma. This lower 3D specificity (0.591) is most likely due to solid components reflecting benign changes (e.g., benign scar or alveolar collapse), which are not related to the tumour invasion as complete differentiation between malignant invasion and alveolar collapse is difficult even with 3D analysis. In the ROC curve analysis, SUVmax, which is often performed preoperatively to predict tumour invasiveness, also had low specificity (0.566). The utility of FDG-PET in predicting the biologic features of early adenocarcinomas might therefore be reduced as it can be obscured by low metabolic activity of small lung adenocarcinomas with GGO components.

This study has several limitations. Firstly, the population studied was relatively small and localised to one academic hospital. Patients with pure solid nodules on high-resolution CT were excluded because the aim was to distinguish between radiologically low malignancy adenocarcinoma and pathologically invasive adenocarcinoma. Secondly, the segmentation of GGO lesions compared with solid nodules was difficult in some cases because of contrast obscuration with the lung parenchyma. In addition, automated, computerised measurements were used for the evaluation of tumours, which may have reduced data variabilities and manual manipulation was added only to exclude the effect of the underlying vascular structures to minimise segmentation errors. Thirdly, the size of the solid components was did not evaluated, which is a new T factor in the 8th edition of the TNM classification. Many pure GGN were included in this study and the sample size of part-solid nodules was so small that solid component size was not included as a radiological factor.

In conclusion, the mean 3D CT attenuation value of tumours with GGO components was well correlated with pathological features defined by the IASLC/ATS/ERS classification. This could lead to both more accurate prediction of the invasiveness of small lung adenocarcinoma and selection of candidates for sublobar resection.

Conflict of interest

The authors declare no conflict of interest.

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