Mean Computed Tomography Value to Predict the Tumor Invasiveness in Clinical Stage IA Lung Cancer

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Background. The purpose of this study was to validate the ability of the mean computed tomography (m-CT) value to predict tumor invasiveness and recurrence, and further, to compare with other measurements such as consolidation/tumor ratio and solid tumor size.

Methods. A retrospective study was conducted of 494 patients with clinical stage IA lung cancer who had peripherally located lung adenocarcinoma. Receiver operating characteristic curve analysis was used to compare the ability to predict tumor invasiveness and recurrence between m-CT value, consolidation/tumor ratio, and tumor size. Multiple logistic regression analyses were performed to determine the independent variables for the prediction of pathologic, less invasive lung cancer. Disease-free survival was measured from the date of the operation until any recurrence.

Results. The m-CT values were 643.6 ± 9.4 Hounsfield units in the noninvasive cancer group and 365.9 ± 11.4 Hounsfield units in the invasive cancer group ($p < 0.0001$). The invasive cancer group was strongly associated with a high CT attenuation value, high consolidation/tumor ratio, large solid tumor size, large tumor size, and high standardized uptake value. Multiple logistic analyses, including the preoperatively determined variables, revealed that standardized uptake value and m-CT are independent predictive factors of less invasive lung cancer. In addition, the hazard ratio of the m-CT value was higher than that of the standardized uptake value value.

Conclusions. The evaluation of m-CT value is useful in predicting less invasive lung cancer. The m-CT value can potentially determine operative procedure, particularly limited resection for peripheral lung adenocarcinoma.

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With recent advances in diagnostic imaging technologies, ground-glass opacity (GGO) lesions are increasingly detected using high-resolution computed tomography (HRCT) scans [1, 2]. GGO is defined as a shadow that is completely occupied by a hazy area of increased attenuation in the lung with preserved bronchial and vascular lesion margins when assessed using HRCT [3]. Patients with GGO-dominant small lung adenocarcinoma are believed to have a good prognosis [4, 5]. However, there is no standard method for measuring the area of GGO, and evaluating the proportion of the solid area in mixed GGO lesions is not always possible [6].

Quantitative densitometric methodologies and mean computed tomography (m-CT) number have been reportedly used to evaluate GGO lesions [7–10]. We previously reported that the m-CT value of GGO lesions is a risk factor associated with their future change [11]. Ikeda and colleagues [8] reported that the 75th percentile CT value of GGO lesions, analyzed using three-dimensional computerized quantification, was optimum for differentiating between atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), and adenocarcinoma.

Few studies have investigated the m-CT value in lung adenocarcinomas at different invasive stages, which is of great significance for treatment decisions. The objectives of this study were to validate the ability of m-CT values to predict tumor invasiveness and compare with other measurements, such as proportion of GGO and solid tumor size.

Patients and Methods

Patients

This study was approved by the Kanazawa University Internal Review Board. Between October 2006 and October 2012, 873 consecutive patients underwent pulmonary resection for lung cancer. The study excluded patients who received preoperative treatment, such as radiotherapy or chemotherapy, or had multiple lung cancers. Included were 494 patients (220 men and 274 women) diagnosed with clinical stage IA lung cancer with peripherally located adenocarcinoma of the lung. The reason for focusing on adenocarcinoma was that GGO is usually observed only in this histologic type. The patients were a median age of 65 years (range, 19 to 90 years).

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Abbreviations and acronyms

AAH	= atypical adenomatous hyperplasia
AIS	= adenocarcinoma in situ
Ad	= adenocarcinoma
C/T ratio	= consolidation/tumor ratio
CI	= confidence interval
DFS	= disease-free survival
GGO	= ground-glass opacity
HRCT	= high-resolution computed tomography
HU	= Hounsfield units
INVC	= invasive cancer
m-CT value	= mean computed tomography value
MIA	= minimally invasive adenocarcinoma
NINVC	= noninvasive cancer
ROC	= receiver operating characteristics
SUV	= standardized uptake value

We reviewed their medical records, including the results of pathologic examination and recurrence status. The surgical specimens for each patient were reviewed and classified according to the newest 2015 World Health Organization classification criteria for lung adenocarcinoma as AAH, AIS, and minimally invasive carcinoma (MIA) [12]. We defined AAH and AIS as noninvasive lung cancer (NINVC). MIA and invasive adenocarcinoma were categorized as invasive cancer (INVC).

Image Acquisition and Analysis

CT scans were performed from the lung apex to base during breath holding at midinspiration using an Asteion 4 CT scanner (Toshiba, Tokyo, Japan) with a section thickness of 1.25 or 2.5 mm. Two radiologists with 20 and 15 years of experience independently viewed these images and subjectively classified the nodules. Pure GGO was defined as a shadow that was completely occupied by a hazy area of increased attenuation of the lung, with preserved bronchial and vascular margins of the lesion and with no solid regions on HRCT.

The longest diameters of the GGO lesions and solid portion were measured. The proportion of GGO was calculated using a previously published method [13] and defined as the consolidation/tumor (C/T) ratio. The maximum diameter and one-dimensional m-CT value of this diameter were measured using a computer graphics support system (Synapse PACS; Fujifilm, Tokyo, Japan). The shape of the region of interest was standardized for each patient and configured by freehand drawing. The m-CT value was evaluated in the slice with the highest density. The interobserver variation was corrected by calculating the mean value of the 2 observers.

Statistical Analysis

Receiver operating characteristic curve analysis was used to compare the ability to predict the invasiveness of the lung cancer using the m-CT value, C/T ratio, and solid and whole tumor size. Univariate and multivariate analysis were performed to investigate pretreatment predictors of INVC. The Fisher exact test was used for the univariate analysis and a logistic regression model for the multivariate analysis. The 95% confidence interval (CI) was calculated. All p values were two-sided. Gender, age, tumor size, m-CT value, C/T ratio, standardized uptake value (SUV) value, carcinoembryonic antigen value, and solid tumor size were included in univariate analysis. The variables for the univariate analysis were selected before beginning statistical analysis based on the specific question being addressed and on prior publications [4–8]. Univariate factors with a p value of less than 0.05 were included in the multivariate analysis. Disease-free survival (DFS) was calculated using the Kaplan-Meier method. Continuous variables are expressed as mean ± SD. Significant differences were assessed using the t test for continuous variables and the χ^2 test for categoric variables. Analyses were performed using SAS software (SAS Institute, Inc, Cary, NC). A p value of less than 0.05 was considered statistically significant.

Results

Clinical and pathologic characteristics are reported in Table 1. Forty-two (8.5%) patients were upstaged of T status, and 32 (6.5%) were upstaged of N status. A total of

Table 1. Patient Clinical and Pathologic Characteristics

Factors	No. (%) or Mean ± SD (range) (N = 494)
Age, y	64.9 ± 11.2 (19–90)
Gender	
Male	220 (44.5)
Female	274 (55.5)
Clinical T stage	
T1a	359 (72.7)
T1b	135 (27.3)
Pathologic T stage	
T1a	345 (69.8)
T1b	85 (17.2)
T2a	64 (13.0)
Pathologic N stage	
N0	462 (93.5)
N1	20 (4.1)
N2	12 (2.4)
Pathologic stage	
IA	412 (83.4)
IB	48 (9.7)
IIA	19 (3.9)
IIB	3 (0.6)
IIIA	12 (2.4)
IASLC classification	
AAH	7 (1.4)
AIS	133 (26.9)
MIA	186 (37.7)
Invasive adenocarcinoma	168 (34.0)

AAH = atypical adenomatous hyperplasia; AIS = adenocarcinoma in situ; IASLC = The International Association for the Study of Lung Cancer; MIA = minimally invasive adenocarcinoma.