Prognostic Impact of Tumor Size Eliminating the Ground Glass Opacity Component

Modified Clinical T Descriptors of the Tumor, Node, Metastasis Classification of Lung Cancer

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Introduction: The presence of ground glass opacity (GGO) on high-resolution computed tomography (HRCT) is well known to be pathologically closely associated with adenocarcinoma in situ. Recently, measuring the tumor diameter including areas of GGO on HRCT has been reported to possibly overestimate the T status. The purpose of this study was to evaluate the significance of the tumor size measured eliminating the area of GGO on HRCT as a prognostic factor and to propose a refined TNM classification based on modified T descriptors.

Methods: Four hundred seventy-five patients with clinical T1a-T2bN0M0 non-small-cell lung cancer underwent surgical resection. All tumors were reclassified based on the diameter measured eliminating the GGO area on HRCT according to the seventh TNM classification of lung cancer. We defined this new classification as modified T descriptors categorizing into five groups: mTis, mT1a, mT1b, mT2a, and mT2b. The overall survival rates of the patients in the current and modified staging groups were evaluated.

Results: The 5-year survival rates were 88% and 82% in the patients with T1a and T1b tumors and 90% and 75% in the patients with mT1a and mT1b tumors, respectively. The differences in the survival rate of the patients classified by using mT1a and the other modified T descriptors were more clearly separated statistically than those of the patients classified by using the current T1a and other T descriptors.

Conclusion: The modified T descriptors of the tumor size measured eliminating the GGO component on HRCT more clearly classified the prognoses of patients with early lung cancer than did the current T classification.

Key Words: Tumor, node, metastasis classification, Lung cancer, Staging, Tumor size, Ground glass opacity.

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Since the introduction of low-dose helical computed tomography (CT) in lung cancer screening, small primary lung cancers that could not previously be detected with conventional radiography have become identifiable at earlier and potentially more curable stages.[1,2] Among the small nodules detected during CT screening, many cases of adenocarcinoma have been found.[1,3] The prevalence of adenocarcinoma, especially that of adenocarcinoma with a lepidic growth pattern, has markedly increased in recent years as the most frequent histologic subtype of lung cancer.[4–6]

Some cases of adenocarcinoma exhibit areas of ground glass opacity (GGO) on high-resolution CT (HRCT) which reflect a lepidic growth pattern of tumor cells microscopically.[7] Therefore, lung tumors that display areas of focal GGO on HRCT contain components of pathologic lepidic tumor growth.[8] The majority of areas of pure GGO on HRCT have been shown to be adenocarcinoma in situ lesions pathologically.[9,10] Lung adenocarcinomas exhibiting part-solid nodules with a large proportion of GGO have also been demonstrated to tend to be less invasive than solid or mostly solid tumors of the same size.[7,8,11,12] These findings are reflected in the recently revised international multidisciplinary classification of lung adenocarcinoma sponsored by the International Association for the Study of Lung Cancer, American Thoracic Society and European Respiratory Society.[13] In these new criteria, the radiologic features are described as part of a multidisciplinary approach to the comprehensive classification of adenocarcinoma. With respect to early adenocarcinoma in particular, a crucial question has been raised: *How should the tumor size be measured?*

Since mid-1970s, the tumor size has been a primary descriptive and significant prognostic factor for lung cancer in the tumor, node, metastasis (TNM) classification of the Union for International Cancer Control (UICC) staging system.[14] According to the present classification[15] revised in 2009, the T classification of T1a to T3 was changed as follows: tumors with diameter of 2 cm or less are classified as T1a, tumors with diameter of greater than 2 cm but not more than 3 cm are classified as T1b, tumors with diameter of greater than 3 cm but more than 5 cm are classified as T2a, tumors with diameter of greater than 5 cm but not more than 7 cm are classified as T2b,

and tumors with diameter of greater than 7 cm are classified as T3. Recently, suggestions for the next revisions of the UICC and American Joint Committee on Cancer staging systems have been proposed. Tsutani et al.,[16] Matsuguma et al.,[17] and Maeyashiki et al.[18] demonstrated that the solid-area diameter without GGO on HRCT is a more effective measurement of tumor nodules for predicting the prognoses of patients with non–small-cell lung cancer and proposed the measurement of the solid-area diameter as the T descriptor in the future revision of the TNM classification.

The purpose of this study was to evaluate the significance of the tumor size measured eliminating the area of GGO as a prognostic factor based on modified T descriptors.

PATIENTS AND METHODS

This study was approved by the institutional review board of Nagoya University Hospital, Nagoya, Japan. Between January 2005 and December 2010, 700 patients with primary lung cancer underwent surgical resection with curative intent at our institution. Of these patients, 490 were given a clinical diagnosis of T1aN0M0 to T2bN0M0 non–small-cell carcinoma. Among them, 475 underwent HRCT and provided follow-up data; these patients constituted the study population. All patients underwent physical examination, chest radiography, and magnetic resonance imaging of the brain and CT of the chest and abdomen for tumor staging and an evaluation of resectability before surgery. The patients were scheduled for checkups every 1 to 3 months for 2 years after surgery and every 6 months thereafter. In patients with a high risk of recurrence, chest CT was performed every 6 to 12 months by physician's recommendation. Furthermore, when the occurrence of recurrence was suspected, additional imaging surveys were performed.

HRCT images were obtained with use of 4- or 16-row multislice CT scanners (Aquilion; Toshiba Medical Systems, Tokyo, Japan) without contrast medium. An image sliced transversely at the center of the nodule was selected to measure the tumor diameter. For image reconstruction, we used a 0.5- to 2.0-mm slice thickness and a lung algorithm (FC50, FC82, FC83). The image size was 512 × 512 pixels. Image data stored in the Digital Imaging and Communications in Medicine format were transferred from the CT scanner to a personal computer for the image analysis. The images were displayed at lung window settings of a level of −600 HU and a width of 1,500 HU. Two authors (SN and TF) manually measured the maximum diameter of the pulmonary nodules on a computer screen and distinguished areas of GGO from solid regions, removing air space, air bronchograms, and large vessels.

GGO was defined as the presence of a hazy increased opacity of the lung with preservation of the bronchial and vascular margins. The solid area of the tumor was defined as the area observed after eliminating all regions of GGO in the entire nodule. We defined the size of the solid component as the maximum dimension of the solid component after excluding the areas of GGO at the lung windows (Fig. 1). The tumor size calculated eliminating the GGO component was primarily measured on axial slices, and when the maximum size was obtained on a coronal or sagittal slice of HRCT, the largest size on the slice was selected. Discrepancies in evaluating the diameter of the solid component were resolved by averaging. All tumors were reclassified on the basis of the diameter

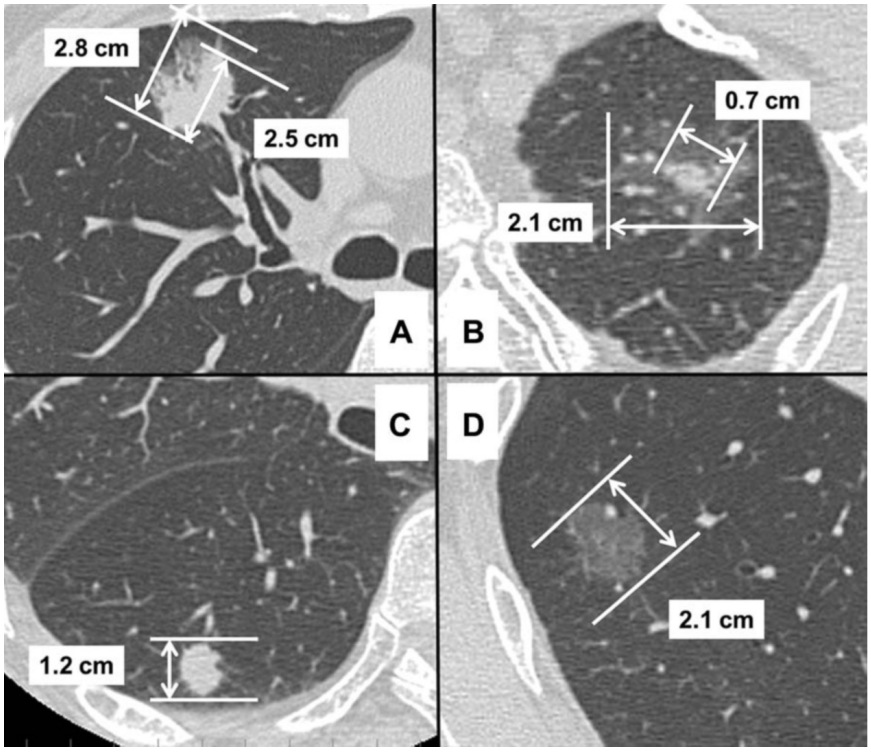

FIGURE 1. Examples of whole tumor sizes and tumor sizes calculated eliminating the areas of GGO (solid tumor size) on high-resolution computed tomography. *A*, Whole tumor size: 2.8 cm (T1b) and solid tumor size: 2.5 cm (mT1b). *B*, Whole and solid tumor sizes: 2.1 cm (T1b) and 0.7 cm (mT1a). *C*, Whole and solid tumor sizes: 1.2 cm (T1a) and 1.2 cm (mT1a). *D*, Whole and solid tumor sizes: 2.1 cm (T1b) and 0.0 cm (mTis). GGO, ground glass opacity.