Surgically Curable Peripheral Lung Carcinoma∗

Correlation of Thin-Section CT Findings With Histologic Prognostic Factors and Survival

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Study objectives: To define characteristics of surgically curable, early cancers of the lung, we retrospectively studied relationships between thin-section CT (TS-CT) scans, pathologic features, and outcome data in 287 patients with resected small-diameter (<20 mm) peripheral lung carcinoma. Cases included 260 adenocarcinomas, 16 squamous cell carcinomas, 6 small cell carcinomas, 3 large cell carcinomas, and 2 others.

Measurements and results: All tumors were classified by tumor shadow disappearance rate (TDR) on TS-CT as having either an “air-containing” or “solid-density” pattern. Adenocarcinomas are typically classified into these patterns. Air-containing patterns (n=136) showed 1% pleural involvement and 2% vascular invasion, with no lymphatic permeation by pathology. Solid-density patterns (n=124) showed 34% pleural involvement, 42% vascular invasion, and 29% lymphatic permeation. No cases of relapse or death were observed in cases with the air-containing pattern, in contrast to the high relapse and death rate in solid-density cases (p<0.0001). All non-adenocarcinoma cases (n=25) had a solid-density pattern, with 4% pleural involvement, 52% vascular invasion, and 44% lymphatic permeation. The overall 5-year survival rate for non-adenocarcinoma was 60%, similar to that for solid-density adenocarcinoma.

Conclusions: When peripheral lung cancers <20 mm in diameter show air-containing patterns on TS-CT images, surgical outcomes may be favorable with curable disease.

(CHEST 2005; 127:871–878)

Key words: adenocarcinoma; air-containing pattern; early peripheral lung cancers; histopathologic classification; prognosis; solid-density pattern; thin-section CT

Abbreviations: BAC = bronchioloalveolar carcinoma; CR = chest radiography; GGO = ground-glass opacity; HU = Hounsfield unit; kVp = kilovolt peak; mDmax = maximum dimension of tumor using mediastinal window level setting; mDperp = largest dimension of the perpendicular axis on mediastinal window level setting; MWLS = mediastinal window level setting; pDmax = maximum dimension of tumor using pulmonary window level setting; pDperp = largest dimension of the perpendicular axis using pulmonary window level setting; PWLS = pulmonary window level setting; TDR = tumor shadow disappearance rate; TS-CT = thin-section CT

Recently, the number of patients with small peripheral lung cancers detected by CT scanning has been increasing.1–3 In these reports, most cases have been adenocarcinoma and, more rarely, non-adenocarcinoma. Early detection of lung cancer, which can be achieved through recent advances in CT scan technology, may improve the survival rate of patients with this disease. However, the prognosis of resected lung cancer remains poor, and <80% of stage I patients are cured by surgical resection alone.4 Because regional lymph node involvement is found in approximately 20% of primary lung adeno-

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This work was supported in part by Grant for Scientific Research Expenses for Health Labour and Welfare Programs and the Foundation for the Promotion of Cancer Research, and by Second-Term Comprehensive 10-year Strategy for Cancer Control.

Manuscript received December 8, 2003; revision accepted September 29, 2004. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (e-mail: permissions@chestnet.org).

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carcinomas of ≤2.0 cm in size, major lung resection and locoregional lymph node resection or sampling have been recommended even for small tumors. Yet, tumor size is not a reliable prognostic indicator for small peripheral lung adenocarcinomas.

Histologically and biologically, adenocarcinoma of the lung constitutes a heterogeneous group of tumors; it is difficult to predict the prognosis of surgically treated patients with this disease. Recently, the size of central collapse/fibrosis and the percentage of the bronchioalveolar carcinoma (BAC) component have been proposed as prognostic indicators for small lung adenocarcinomas. Although many reports on the radiologic-pathologic correlations of small lung adenocarcinoma have been published, there is little clinical information on prognostic factors during the pretreatment state. Furthermore, in cases of non-adenocarcinoma, there are no comparable definitions for early cancers. Thus, the concept of peripherally located, surgically curable, “early lung cancer” remains controversial. This study retrospectively analyzed findings obtained by thin-section CT (TS-CT) and correlated them with histologic features and outcome in patients with small-size lung cancers.

**Materials and Methods**

We retrospectively reviewed the records and CT images of 287 patients with peripheral lung cancers <20 mm in diameter between 1992 and 2002. The majority of patients were found by screening for lung cancer. Those found by chance during follow-up of other diseases were the second most common. The patients who visited our hospital with complaints suggestive of lung cancer ranked third. Informed consent was obtained from each patient before operation. Chest CT images were obtained by an X-Vigor/Real CT scanner (Toshiba Medical Systems; Tokyo, Japan). Conventional CT images were obtained serially from the thoracic inlet to the lung bases at 120 kilovolt peak (kVp) and 200 mA, with 10-mm section thickness, 10-mm section spacing, 512×512 pixel resolution, and 1-s scanning time. High-resolution images targeted to the tumor were obtained serially at 120 kVp and 200 mA, with 2-mm section thickness, pitch 1, 1- to 2-mm section spacing, 512×512 pixel resolution, and 1-s scanning time, using a high-spatial-reconstruction algorithm with a 20-cm field of view. These images were printed as photographs on each sheet of film using a mediastinal window level setting (MWLS; level, 40 Hounsfield units [HU]; width, 400 HU) and a pulmonary window level setting (PWLS; level, −600 HU; width, 1,600 HU).

While contrast medium (60 mL) was infused IV during imaging, lesion sites were translocated in a helical scan mode with a CT table speed of 2 mm/s; TS-CT images were obtained at 1 breath-holding (120 kVp, 200 mA). The time interval between CT examination and subsequent surgery was <2 weeks in all patients. All CT images were reviewed by four thoracic oncologists who were not informed of the pathologic findings. They obtained the following information from the TS-CT images: the maximum dimension of tumor using PWLS (pDmax), the largest dimension of the perpendicular axis using PWLS (pDperp), the maximum dimension of tumor using MWLS (mDmax), and the largest dimension of the perpendicular axis on MWLS (mDperp).

We defined the tumor shadow disappearance rate (TDR) using the following formula (Fig 1): TDR = 1 - (mDmax × mDperp/pDmax × pDperp). TDRs of ≥50% vs <50% were considered to represent air-containing and solid-density patterns, respectively. Ground glass opacity (GGO) was defined as a hazy increase in lung attenuation without obscuring the underlying bronchial or vascular structures. Examples of CT images of the two groups are shown in Figures 2–4.
Each pattern based on TS-CT images was evaluated in terms of pathologic findings and survival outcome. We evaluated pathologic TNM (pathologic stage), pleural involvement, vascular invasion, and lymphatic permeation. In addition, the pathologic subtypes according to the classification of Noguchi et al. of small adenocarcinoma of the lung were evaluated. The length of survival was defined as the interval in months between the date of surgical resection and the date of last follow-up or death due to any cause.

Statistical analyses were carried out using the generalized Wilcoxon test and log-rank test. Statistical significance was accepted at a $p < 0.05$. Relapse-free and overall survival rates were estimated by the Kaplan-Meier method.

**RESULTS**

Patient characteristics are summarized in Table 1. A total of 287 patients (128 men and 159 women; age range, 26 to 86 years; mean age, 65 years) were included in the study, and consisted of 260 cases of adenocarcinoma and 27 cases of non-adenocarcinoma (16 squamous cell, 6 small cell, 3 large cell, and 2 of other histology). Among the adenocarcinoma cases, there were 62 cases with the largest diameter of the lesion < 10 mm, 88 cases were 10 to 15 mm, and 110 cases were 16 to 20 mm.

Chest radiography (CR) and CT detected 155 cases and 132 cases, respectively, of chest lesions < 20 mm in diameter. With respect to the chance of detection and initial size, 11 cases and 51 cases of lesions < 10 mm in diameter were detected by CR and CT, respectively. Correspondingly, 42 cases and 46 cases of lesions 10 to 15 mm in diameter and 82 cases and 28 cases of lesions 16 to 20 mm in diameter.
were detected, respectively. Among non-adenocarcinoma cases, seven were initially detected by CT; however, these tumors were also detected by CR.

Table 2 shows the relationship between classification according to TS-CT images and pathologic findings of the adenocarcinoma cases. The number of cases with an air-containing pattern was 136, and the number of cases with a solid-density pattern was

Figure 3. Solid-density type of adenocarcinoma (19 × 8 mm) in the right upper lobe. Top left and top right: The value of TDR in this adenocarcinoma was 90%. Bottom left: Histologic section shows a poorly differentiated adenocarcinoma (hematoxylin = eosin, original × 6). Bottom right: Same as previous image (bottom left) but with higher magnification (hematoxylin = eosin, original × 200).

Figure 4. Solid-density squamous cell carcinoma (18 × 16 mm) in the right upper lobe. Top left and top right: The value of TDR in this carcinoma was 95%. Bottom left: Histologic section reveals moderately differentiated squamous carcinoma (hematoxylin = eosin, original × 6). Bottom right: Same as previous image (bottom left) but with higher magnification (hematoxylin = eosin, original × 200).
Among air-containing cases, 1% had pleural invasion, 2% had vascular invasion, and 0% had lymphatic permeation. Among solid-density cases, 42 cases (34%) had pleural involvement, 53 cases (42%) had vascular invasion, and 36 cases (29%) had lymphatic permeation. All cases with an air-containing pattern were pathologic stage IA, in contrast to only 71% of cases with a solid-density pattern.

Table 3 shows the relationship between TS-CT classification and the Noguchi pathologic classification. In the air-containing pattern, almost all of types A and B, and 40% of type C cases were included, and no cases of type D and E and F were included. In contrast, all of types D and E and F and 60% of type C were included in the solid-density pattern. Two cases of type A were also included in this pattern, and these proved to be mucocellular adenocarcinomas, which explains their high density on TS-CT images. Of the 260 adenocarcinoma patients, 169 underwent lobectomy and 2 underwent pneumonectomy, while 89 patients underwent segmental and wedge resections combined with systematic hilar and mediastinal node dissection. In the 89 patients who did not have complete resection, 60 showed air-containing patterns and 29 were solid-density patterns. The 60 patients with an air-containing pattern had intentional limited resection because of their small size, while the 29 patients with a solid-density underwent compromised limited resection because of age or pulmonary hypofunction.

The overall and relapse-free survival of patients with adenocarcinoma from the time of surgery are shown in Figures 5 and 6, respectively. The air-containing pattern had a 100% 5-year survival rate, and relapse-free survival was significantly better than that of solid-density cases (p < 0.0001, generalized Wilcoxon test and log-rank test). There were no included. In contrast, all of types D and E and F and 60% of type C were included in the solid-density pattern. Two cases of type A were also included in this pattern, and these proved to be mucocellular adenocarcinomas, which explains their high density on TS-CT images. Of the 260 adenocarcinoma patients, 169 underwent lobectomy and 2 underwent pneumonectomy, while 89 patients underwent segmental and wedge resections combined with systematic hilar and mediastinal node dissection. In the 89 patients who did not have complete resection, 60 showed air-containing patterns and 29 were solid-density patterns. The 60 patients with an air-containing pattern had intentional limited resection because of their small size, while the 29 patients with a solid-density underwent compromised limited resection because of age or pulmonary hypofunction.

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recurrences in patients with air-containing lesions. Intentional limited resection is therefore considered to be adequate for type A and B lesions, which were air containing and consisted mainly of GGO.

For non-adenocarcinomas, pathologic findings included 4% pleural involvement, 56% vascular invasion, and 48% lymphatic permeation, with 81% of patients in pathologic stage IA (Table 2). The 5-year survival rate for patients with non-adenocarcinoma was 60% (Fig 7).

**Discussion**

Tumor size in lung adenocarcinoma cancer is not as good a prognostic factor as it is for squamous cell carcinoma, we often encounter small lung adenocarcinomas that have mediastinal lymph node involvement or even distant metastasis. Peripheral lung adenocarcinomas smaller than 3 cm frequently recur, resulting in cancer deaths (5-year disease-free survival for T1N0 disease of approximately 70%).

It is important to established reliable prognostic factors for small peripheral lung adenocarcinoma. Consequently, qualitative analysis of tumors is required to establish prognostic criteria in addition to size.

In 1995, Noguchi et al proposed a histologic classification of small lung adenocarcinomas based on the presence or absence of a bronchioloalveolar carcinoma (BAC) component. Tumors with a BAC component were further subclassified into three groups: type A, BAC without collapse or fibrosis; type B, BAC with foci of collapse; and type C, BAC with foci of active fibroblastic proliferation. Invasive carcinomas without a BAC component were subdivided into types D to F. In their report, patients with type A or type B have shown no lymph node spread and have excellent outcomes (100% 5-year survival). Therefore, prompt detection, diagnosis, and treatment of type A or type B are thought to greatly improve outcome.

However, these criteria were based on postoperative pathologic findings after resection; therefore, these cannot have an impact on the choice of treatment. Because noninvasiveness can be identified only by postoperative microscopic study, type A or type B must be selected by preoperative TS-CT images. We have analyzed TS-CT images of lung adenocarcinoma using TDR. We found most of types A and B and 40% of type C have the air-containing pattern, whereas all of types D, E, and F and 60% of type C are included in the solid-density pattern. The air-containing pattern has a 100% 5-year survival rate, and relapse-free survival was significantly better than that of solid-density cases.

As for the air-containing pattern, type A and B lesions have shown mostly GGO in TS-CT images and have lacked solid components. Pathologic analyses have revealed a replacing growth pattern of tumor cells along the alveolar septa, with a subsequent BAC pattern. Kuriyama et al quantitatively evaluated the extent of GGO in pulmonary adenocarcinoma with types A, B, and C and found that it was significantly greater in types A and B than in type C adenocarcinoma. However, it has been difficult to distinguish types A and B from type C using TS-CT images, specially since the presence of fibroblastic proliferation was the only differentiating factor. Although the Noguchi classification defines a surgically curable subset of peripheral lung adenocarcinomas (types A and B), the criteria for active fibroblasts remains undefined. In addition, type C tumors account for the majority of small lung adenocarcinomas, suggesting that these tumors may represent a heterogeneous group with a spectrum ranging from minimally invasive to overtly invasive cancer.

If patients who have favorable prognoses are chosen from the whole population of those with type C cancers and selectively treated, the overall prog-

![Figure 6. Relapse-free survival curve shows a significant difference between the two groups described in Figure 6.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22023/)

![Figure 7. Overall survival curve of all patients with small non-adenocarcinomas. The 5-year survival rate for patients with non-adenocarcinoma was 60%.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22023/)
nosis of patients with small pulmonary adenocarcinoma would improve. Suzuki et al. found a subgroup of type C cancers associated with a good prognosis. In our study, we found that type C cases present with both air-containing and solid-density patterns. It was conceived that the BAC component in the peripheral region was predominant in type C cancers with an air-containing pattern, whereas fibrotic scar in the central region was predominant in those classified as solid density. We might have isolated those cases with a good prognosis by classifying type C lesions according to the air-containing pattern; however, we would then have been unable to distinguish types A, B, and C according to pathologic type.

Types D, E, and F have images that characteristically show a sharp margin and lobular structures without GGO components on TS-CT images. These findings are consistent with the solid-density pattern. The values of TDR in types D, E, and F were 0%, which reflects that the images consisted only of solid components. The relationship between the CT image pattern of lung cancer and pathologic stage revealed that all air-containing cases belonged to stage IA, while >20% of solid-density cases belonged to stage IB or a more advanced stage.

Ichinose et al. examined surgically treated cases of non-small cell lung cancer with diameters <10 mm and reported that even patients with pathologic stage IA have high rates of lymphatic invasion. However, we found that adenocarcinoma cases with an air-containing pattern have no lymphatic permeation, and pleura or vascular invasion occurred in as few as 1 to 2% of patients. However, 20 to 30% of adenocarcinoma cases with solid-density patterns show pleural involvement, lymphatic permeation, or vascular invasion. We conclude that patients with adenocarcinoma with a solid-density pattern have an unfavorable prognosis for postoperative survival; their 5-year survival rate is 60% compared with 100% of cases with an air-containing pattern.

Among patients with stage IA adenocarcinoma, 136 cases exhibited an air-containing pattern and 89 were solid density. All of 136 patients with IA air-containing lesions survived, and recurrence was not found any of them. In contrast, cancer recurred in 14 of 89 patients with IA solid-density lesions, and 10 of the 14 patients died. Patients with IA solid-density lesions therefore should benefit from adjuvant therapy.

Among patients with non-adenocarcinoma, no cases with air-containing patterns were shown on TS-CT imaging (Fig 4). Patients with non-adenocarcinoma have various types of histology and are too few in number to accurately evaluate their prognosis. The non-adenocarcinoma cases had low rates of pleural involvement, but high rates of vascular invasion, and lymphatic permeation. Survival curves of patients with non-adenocarcinoma resemble those of patients with adenocarcinoma of a solid-density pattern. We could not identify any subset of patients with non-adenocarcinoma who showed favorable outcomes using TS-CT images.

According to recent reports of serial changes in the appearance of BAC on CT, localized GGO can change into mixed areas of GGO and solid components, and solid components can increase over time. We suspect that adenocarcinoma with a larger GGO area is at an early and curable stage; TS-CT findings may predict this outcome.

Conclusion

Air-containing adenocarcinoma patterns may correspond to an early stage of disease when they occur in the periphery of the lung and are <20 mm in diameter.

References