Cancer Imaging (2011) **11,** 237–246
DOI: 10.1102/1470-7330.2011.0033

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REVIEW

Small peripheral lung adenocarcinoma: CT and histopathologic characteristics and prognostic implications

Zhi-gang Chu[a], Zhi-gang Yang[ab], Heng Shao[a], Zhi-yu Zhu[c], Wen Deng[a], Shi-si Tang[a], Jing Chen[a] and Yuan Li[a]

[a]Department of Radiology, West China Hospital, Sichuan University, 37# Guo Xue Xiang, Chengdu, Sichuan 610041, China; [b]State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, 37# Guo Xue Xiang, Chengdu, Sichuan 610041, China; [c]Department of Pathology, West China College of Stomatology, Sichuan University, No. 14, Section 3, People's South Road, Chengdu, Sichuan 610041, China

Corresponding address: Zhi-gang Yang. Department of Radiology, West China Hospital, Sichuan University, 37# Guo Xue Xiang, Chengdu, Sichuan 610041, China.
Email: yangzg1117@yahoo.com.cn

Date accepted for publication 3 October 2011

Abstract

Since the introduction of computed tomography (CT), detection of small lung cancer, especially small peripheral adenocarcinoma, is common. Recently, the morphological characteristics, including thin-section CT and pathologic findings, and prognosis of small peripheral lung adenocarcinomas have been studied extensively. The radiologic and microscopic findings correlate well with each other and are closely associated with tumour prognosis. Most importantly, some subtypes of small lung adenocarcinomas with specific CT or pathologic features are curable. Therefore, all defining characteristics (CT, pathologic and prognostic) of this kind of tumour should be integrated to improve our understanding, provide guidelines for management and accurately assess its prognosis.

Keywords: *Lung neoplasms; adenocarcinoma; CT; histopathology; prognosis.*

Introduction

Lung cancer is one of the most common malignancies and is a worldwide public health problem that often presents at an advanced stage at diagnosis, progresses rapidly and has a dismal clinical outcome. These characteristics are particularly true for the peripheral tumours that lack common signs and other sentinel symptoms of lung cancer in their curative stages. In light of this, early screening for lung cancer was suggested with the hope of decreasing mortality. Chest radiography (CXR) was initially used for screening, but was not proven to be efficacious because of its limitations in detecting smaller tumours[1,2]. In recent years, low-dose computed tomography (CT) has been widely used for lung cancer screening and confirmed to be sensitive for small pulmonary nodules[3–12]. Furthermore, annual CT screening detects curable lung cancers and substantially improves 10-year survival of patients with lung cancer[13,14].

Among peripheral lung cancers, the most common histological type is adenocarcinoma, the incidence of which has replaced that of squamous cell carcinoma in recent years[15–17]. In CT screening, most peripheral lung cancers detected were adenocarcinomas measuring 2 cm or less in diameter (also known as small peripheral lung adenocarcinomas)[4,18–22]. The rate of lymph node metastasis in these small adenocarcinomas was significantly lower than the rate in those measuring 2.1 to 3 cm[20]. In addition, some were cured by early intervention[7,23]. For these reasons, diagnosis and evaluation of these tumours are very valuable. In recent studies, CT and histopathologic findings, as well as prognosis of small peripheral lung adenocarcinomas, have been well investigated[15,16,21–32]. As a result, a range of radiologic and pathologic characteristics have been identified, which are more valuable than TNM staging for assessing tumour prognosis.

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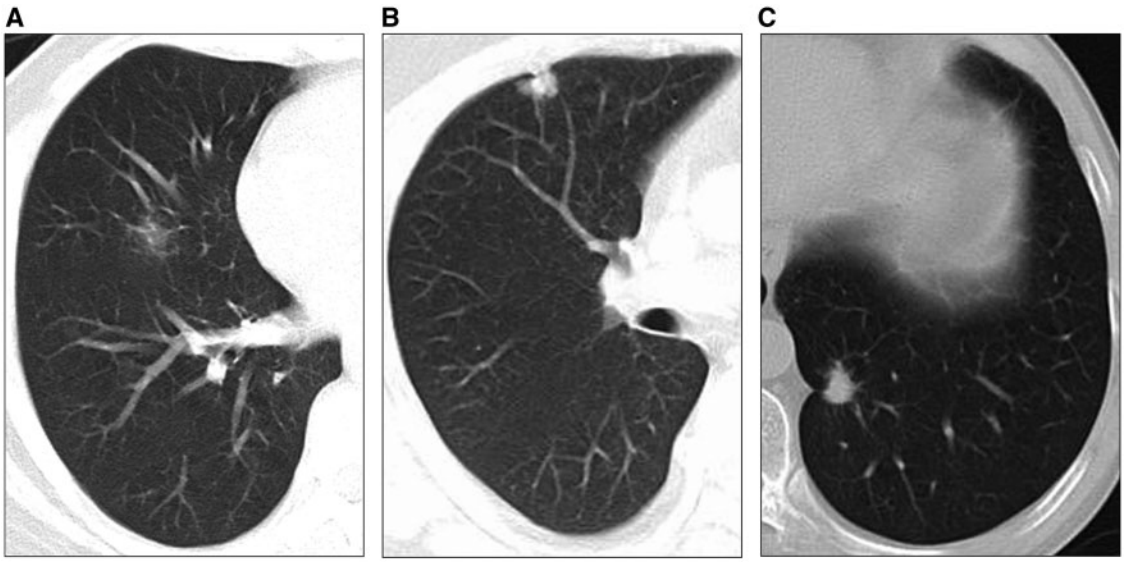

Figure 1 **Different types of nodules frequently detected by low-dose CT in screening for lung cancers. (a) A GGO nodule does not obscure lung parenchyma. (b) A part-solid nodule partly obscures lung parenchyma. (c) A solid nodule with short spiculations completely obscures lung parenchyma.**

Findings from previous studies indicated that understanding the imaging features and corresponding histopathologic basis of small peripheral lung adenocarcinomas may be highly beneficial for early diagnosis, intervention and prediction of postoperative prognosis. In addition, such findings provided a basis for adequate surgical management of such tumours. Thus, all defining characteristics (CT, pathologic and prognostic) of this kind of tumour should be integrated to improve our understanding, provide guidelines for management and accurately assess its prognosis.

Low-dose CT as a preferred tool for detecting small peripheral lung cancers

The key to reducing mortality in patients with lung cancer is early detection, diagnosis and resection. However, early lung cancers (stage I or II) are usually asymptomatic and are detected incidentally on chest imaging studies performed for other reasons[33], after which effective screening for tumours is conceivable and performed. During the 1980s, 3 major medical centres in the United States conducted a large population-based randomized controlled trial with the aim of screening for lung cancers by CXR. Although some lung cancers were detected and the patients underwent aggressive treatment, CXR failed to improve the 5-year survival rate[1,2]. In addition, subsequent studies supported this conclusion and identified the limitations of CXR in screening[34–36]. The substantial drawbacks of CXR including limited visualization of lesions and structure superposition made it impossible to improve the detection rate of small peripheral lung cancer[37]. Therefore, it is necessary to establish another more sensitive screening method.

Low-dose CT with a reduced tube current has been developed and used recently. This substantially decreases the radiation dose without significant loss of image quality. It has a relatively high clinical value for widespread application with the greatest advantage of detecting small lung nodules. Nodules frequently detected by low-dose CT were divided into 2 types: calcified and non-calcified. Calcified nodules were regarded as benign, whereas non-calcified nodules including ground glass opacities (GGO), as well as part-solid and solid nodules (Fig. 1) were recommended for further investigation according to the size because their nature could not be determined[7]. Several studies have indicated that low-dose CT is the most effective method for detecting early lung cancer[4,5,7–9,18,19,38–40]. The detection rate achieved using low-dose CT was significantly higher than that using conventional CXR, ranging from 0.43% to 2.7% in the screening populations and most of the tumours detected were in stage I[4,5,7,18,39,41]. The number of studies of small peripheral lung adenocarcinomas has increased presumably because of the increase in the lung cancer detection rate using low-dose CT, and we have obtained an in-depth understanding of their radiologic and pathologic features, as well as the associated prognosis.

Factors affecting visibility of small lung cancers by conventional CXR

Conventional CXR is not suitable for screening for lung cancers because of its inability to detect smaller or lower

density nodules. This defect is closely related to tumour characteristics[3,42–44]. Detection of the small peripheral lung cancers on CXR is directly influenced by tumour size, optical contrast and gradient, and density[3,44]. Generally, visible tumours are larger than invisible tumours. Only a small proportion of nodules ($\leq$20 mm) were visible on CXR[3]. Visibility of nodules on CXR also requires an optical density of 0.1–0.3 OD and a gradient of 0.03–0.11 OD mm^{-1}[44]. The density and difference in density between a nodule and its periphery measured on CT were higher for visible tumours than for invisible tumours[44]. Pathologically, the contrast, gradient and CT density of tumours are influenced by the tumour type. Tumours with a higher extent of localized bronchioloalveolar carcinoma (BAC), manifested as GGO on CT, were less visible on CXR[45]; this was because residual gas in BAC decreased the density of tumours. In addition, tumours with poorly defined margins and those located in the upper lobe or concealed lung zones with overlapping thoracic components were more difficult to detect[3,46].

Histopathologic features of small peripheral lung adenocarcinoma

Along with an increase in the incidence of small peripheral lung adenocarcinoma by CT, a study of its histopathologic and biological characteristics that may be related to tumour prognosis was performed and some very useful prognostic indicators were identified. Based on the growth characteristics, the growth pattern of small peripheral lung adenocarcinomas was divided into lepidic (replacement) growth and hilic (non-replacement) growth[38]. Noguchi et al.[47] reviewed the histology of small peripheral adenocarcinomas and grouped them into 6 distinctive subtypes: type A, well-differentiated localized BAC; type B, localized BAC with foci of structural alveolar collapse; type C, localized BAC with foci of active fibroblastic proliferation; type D, poorly differentiated adenocarcinoma showing largely solid growth and minor papillary or tubular growth patterns; type E, tubular adenocarcinoma; and type F, papillary adenocarcinoma with expansive and destructive growth patterns. Types A, B and C show a replacement tumour growth pattern; types D, E and F show a non-replacement tumour growth pattern[48]. Areas with a lepidic and hilic growth pattern were seen with non-solid and solid components, respectively. Besides the BAC component, collapsed alveoli, collapsed alveoli with BAC, tumour cells, proliferated fibroblasts and mucus were the main components of adenocarcinomas[49].

In peripheral lung adenocarcinomas, central fibrosis is very common. Stromal elastosis had 2 histomorphological patterns: a preserved framework composed of a uniformly thick stroma due to contraction and thickening of the alveolar walls and a disrupted framework indicating stromal invasion in central fibrosis[29]. The different stromal elastosis patterns were related to varying growth rates and the clinical outcome.

Thin-section CT features of small peripheral lung adenocarcinomas

Because the histologic features of small peripheral lung adenocarcinomas vary, it is understandable that the CT characteristics they reflect also differ. Generally, non-calcified nodules on CT have 3 main appearances: a solid type completely obscuring the entire lung parenchyma within it; a non-solid type without obscuring involved lung parenchyma; and a part-solid type consisting of both solid and non-solid areas. In CT screening for lung cancer, non-solid or part-solid nodules with GGO were commonly detected and were more likely to be malignant than solid nodules[50]. Besides lung carcinomas, GGO is also seen in focal interstitial fibrosis, inflammation and haemorrhage. However, the persistence of GGO over time, especially when the nodule or included solid component increased in size, may be strongly suggestive of an early-stage malignancy[51].

Yang et al.[42,43] classified small peripheral lung adenocarcinomas into four types on thin-section CT images based on the density distribution in nodules and tumour growth patterns. Type I was the well-defined pure GGO nodule showing lepidic growth without alveolar collapse (Fig. 2)[52,53]. Type II was the heterogeneous low-attenuation nodule showing lepidic growth accompanied by proliferation of elastic fibres and scattered foci of alveolar collapse (Fig. 3). Type III was the ill-defined nodule with high-density central zone in GGO showing lepidic growth in the periphery and collapsed alveoli with disrupted elastic fibres at the centre (Fig. 4). It indicated that the higher the proportion of GGO in tumours, the greater the extent of BAC. Type IV was the homogeneous soft tissue density nodule exhibiting hilic growth without residual gas but with proliferation of elastic fibres (Fig. 5). Stromal framework in type I and II tumours was preserved, but that in type IV tumours and in the center of type III tumours was disrupted. Similarly, another new classification based on the presence of solid and GGO on thin-section CT divided small peripheral lung adenocarcinomas into the following 6 subtypes: type 1, a simple GGO; type 2, an intermediate homogeneous increase in density; type 3, a halo; type 4, a mixed area of GGO and a solid tumour; type 5, a solid tumour with GGO (Fig. 6), and type 6, a purely solid tumour[54]. Types I and 1, types II and 4, Types III and 3, and Types IV and 6 had similar appearances.

The CT patterns of small peripheral adenocarcinomas on thin-section CT were consistent to some extent with the pathologic classifications raised by Noguchi (50% for type C; 100% for types D–F)[42]. Because the CT characteristics of some pathologic subtypes are not exclusive, other aspects should also be considered in differentiating them. The extent of GGO could be used to differentiate

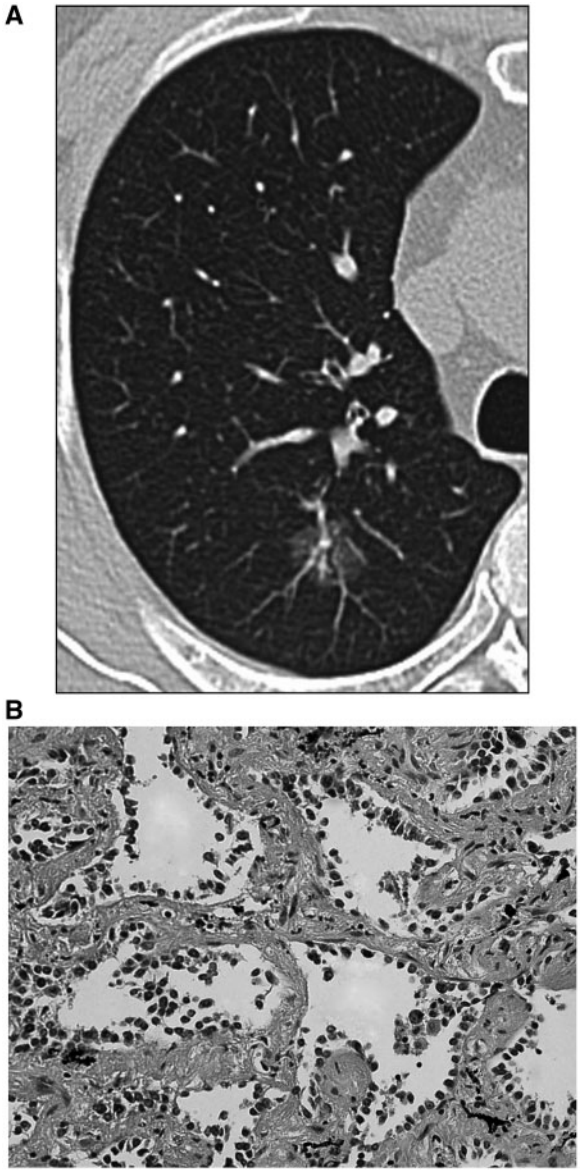

Figure 2 **Thin-section CT scan depicts a pure GGO nodule (1.4 × 1.8 cm) that proved to be well-differentiated adenocarcinoma in a 56-year-old man. No solid components other than blood vessels are seen. The photomicrograph of the histology specimen shows growth of tumour cells in the alveolar lining without alveolar collapse (haematoxylin and eosin (H and E), × 40).**

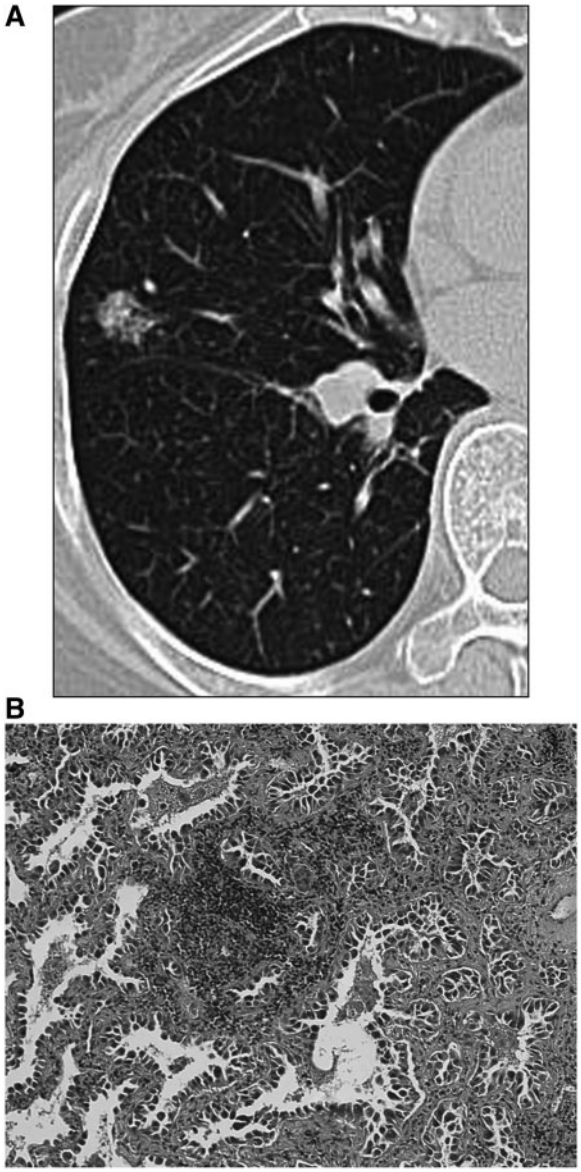

Figure 3 **Thin-section CT scan depicts a heterogeneous low attenuation nodule (1.3 × 1.6 cm) with clear margins that proved to be an adenocarcinoma in a 58-year-old woman. The photomicrograph of the histology specimen shows growth of tumour cells in the alveolar lining with scattered areas of alveolar collapse (H and E, × 40).**

local BAC from small adenocarcinomas exhibiting a non-lepidic growth pattern[53], which was seen as the only significant factor for discriminating type C from types A and B (Noguchi's classification)[55]. In addition, air bronchogram and bubble-like areas were seen more frequently in type C than in type D–F tumours[48]. Type A tumours should also be differentiated from atypical adenomatous hyperplasia (AAH), which also manifest as a GGO nodule on CT and are considered as a precursor of peripheral lung adenocarcinomas[42,56–62]. AAH is most likely to be found in cases of adenocarcinoma, especially in the BAC subtype. However, AAH cannot be differentiated from small peripheral adenocarcinomas based only on CT images.

Except for the above classifications, small lung adenocarcinomas have also been divided into air-containing and solid-density types on CT according to whether areas of tumour opacity on mediastinal window images were half the size or less or more than half the size of those noted on lung window images[21,63]. Pathologically, areas of tumour opacity on mediastinal window images in air-containing type adenocarcinomas predominantly demonstrated collapse of alveolar structures and/or collapse with BAC; solid-density type areas predominantly

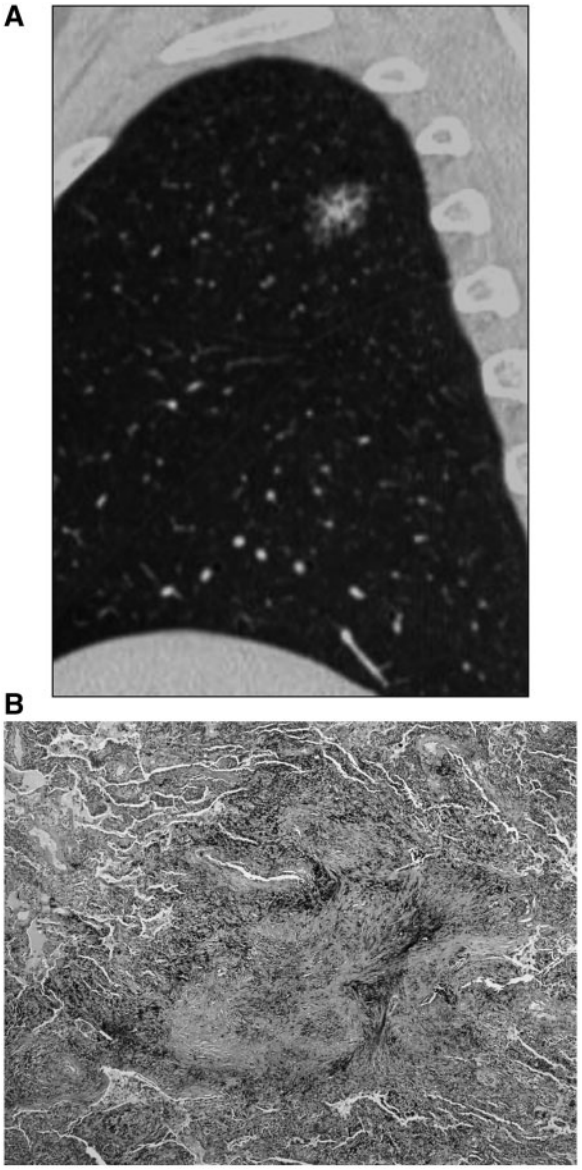

Figure 4 **Thin-section CT scan depicts an ill-defined part-solid nodule (1.9 × 1.8 cm) with higher-density central zone that proved to be an adenocarcinoma in a 56-year-old man. The photomicrograph of the histology specimen shows irregular fibrotic tissue surrounded by thickened alveolar septa and collapsed alveoli in central zone. (H and E, × 10).**

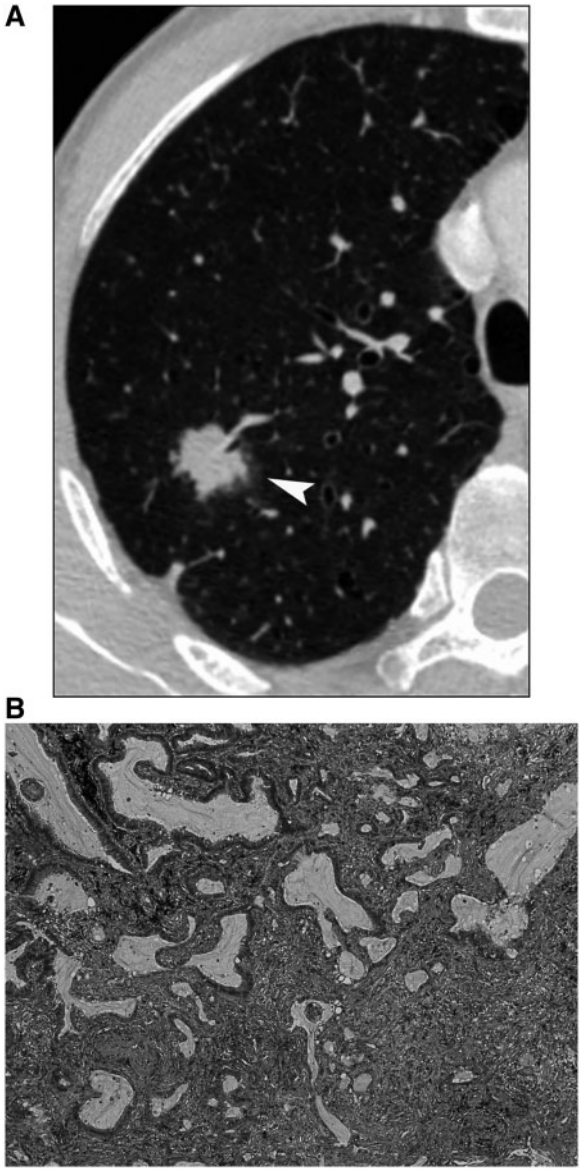

Figure 5 **Thin-section CT scan depicts an irregular solid nodule (1.8 × 1.6 cm) partly surrounded by GGO (arrowhead) with short spiculations that proved to be an adenocarcinoma in a 65-year-old man. The photomicrograph of the histology specimen shows solid tumour growth surrounded by growth of tumour cells in the alveolar lining without alveolar collapse (H and E, × 10).**

demonstrated tumour cells and/or fibroblasts[49]. The proportion of tumour opacity on mediastinal window images in nodules has the potential to evaluate tumour prognosis.

Correlation between imaging–pathologic characteristics and prognosis of small peripheral lung adenocarcinoma

CT screening may have the potential to detect lung cancer with good prognostic factors not limited to early detection[64]. Tumour size in lung cancer was proven to be an unreliable prognostic indicator[65,66]. In recent studies on small peripheral lung adenocarcinomas, the correlations between CT or pathologic characteristics and clinical prognosis were explored. GGO and solid components noted on thin-section CT and the relevant postoperative outcome of small peripheral adenocarcinomas have been the foci of research. The proportion of BAC (GGO) or solid components in small lung adenocarcinomas and lymphovascular invasion were seen as reliable predictive factors for tumour prognosis[67]. In addition,

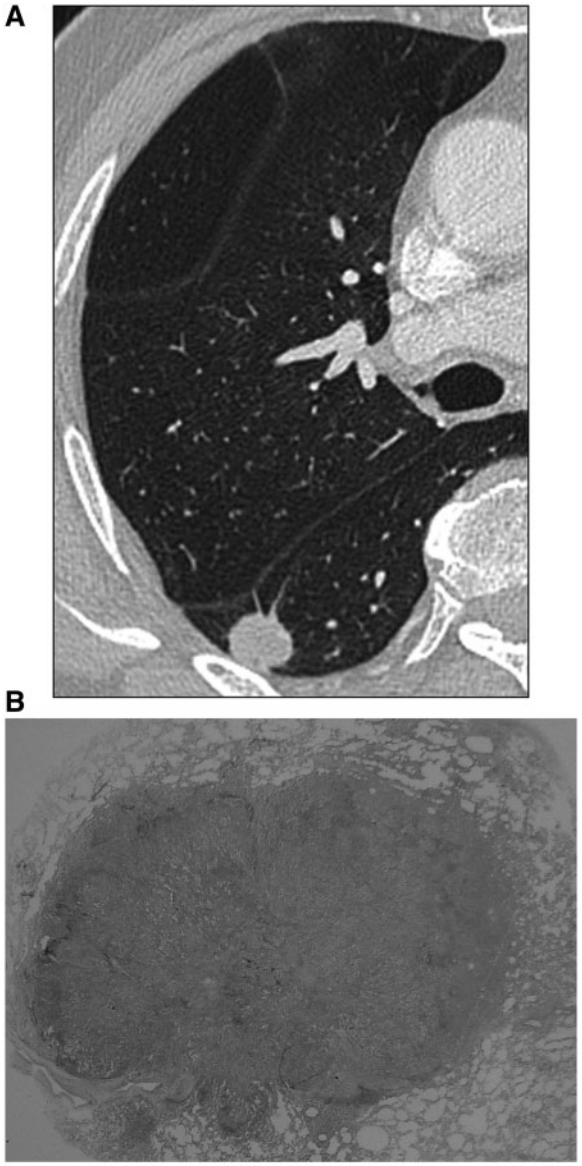

Figure 6 **Thin-section CT scan depicts a regular homogeneous solid nodule (1.1 × 1.5 cm) with spiculations that proved to be an adenocarcinoma in a 76-year-old man. The photomicrograph of the histology specimen shows tumour cells and accompanied desmoplastic response comprising a solid tumour (H and E, × 1).**

microscopic necrosis, the Ki-67 labelling index and serum carcinoembryonic antigen level were also predictors of postoperative prognosis[68].

Correlation between GGO/BAC in nodules and tumour prognosis

The extent of tumour cells growing along alveolar walls negatively correlated with lymph node metastasis[31], which indicated that the proportion of GGO (or BAC) in nodules was closely related to tumour staging and prognosis[54,66,69,70]. The GGO ratios varied among different pathologic subtypes of small peripheral adenocarcinomas, highest in type A and B but lowest in type D–F tumours (Noguchi's classification)[42,48]. Accordingly, type A and B tumours did not show lymphatic metastasis and had better prognosis; type C had an occasional lymphatic metastasis and a relatively poor prognosis; types D, E and F with the least GGO were progressive with the worst clinical outcome. In mixed adenocarcinomas with a BAC component, the BAC proportion was a more reliable prognostic factor than lymph node metastasis[71]. In addition, the air-containing type of adenocarcinomas seldom had microscopic metastasis and relapses, whereas the solid-density type often revealed microscopic metastasis and relapsed frequently[49,63,72]. Another study also indicated that there were no lymph node metastases or postoperative recurrence in tumours with a proportion of GGO above 50%[23]. Thus, the extent of GGO (or BAC) in nodules may be seen as a useful independent indicator for predicting risk of relapse in patients with small peripheral lung adenocarcinomas[72–74].

Correlation between the solid component and fibrosis in nodules and tumour prognosis

The solid component in nodules shown on CT was also related to outcome in small peripheral lung adenocarcinomas. Solid type (GGO% <10%) on CT was seen as an important prognostic factor in stage IA peripheral adenocarcinoma, which was closely associated with lymph node involvement and poor postoperative outcome[75]. It indicated that patients with solid adenocarcinomas should adopt a new strategy for therapy even though it was at an early stage. In addition, Sakao et al.[76] confirmed that the bigger the maximum dimension of tumours on the mediastinal window, the lower the 5-year disease-free survival. Thus, the ratio of tumour dimension on the mediastinal window to that on the lung window could also be considered a useful predictive factor for prognosis. Except for the extent of the solid component in nodules, central fibrosis that developed in tumours was also confirmed to be an important prognostic factor for lung adenocarcinomas chiefly because of its association with angiogenesis and lymphangiogenesis[77,78]. Because fibrotic foci increased with tumour progression, it seemed reasonable that the high attenuation area in tumours on CT was a negative prognostic factor[73].

Correlation between tumour growth rate and prognosis

Prognosis of lung cancer also correlated well with tumour volume doubling time (TVDT), which in turn correlated with the histopathologic type[79–81]. The TVDT of lung adenocarcinomas was much longer than that of squamous carcinomas and small cell carcinomas[82]. Among

the different types of lung cancers on CT, the mean TVDT was significantly longer for non-solid tumours than solid tumours[14,78,82,83]. It indicated that the proportion of GGO in nodules had some correlation with the rate of tumour growth, and that the most rapidly growing tumours exhibited a solid growth pattern[82,84]. Thus, the radiologic classification provided information not only for identifying tumours but also for determining proper intervals between follow-up examinations. In addition, changes in the stromal elastotic framework in nodules also influenced the rate of growth of peripheral lung adenocarcinomas. Tumours with a preserved framework usually showed a gradual increase in density but no significant change in size and had better prognosis, whereas those with a disrupted framework in central fibrosis often enlarged within a short period and recurred frequently[29].

There are distinct prognostic indicators of small peripheral lung carcinomas revealed by CT and pathologic examinations. Tumours with a large proportion of GGO on thin-section CT or the BAC component without local invasion and with a low growth rate usually have a better clinical outcome after surgery.

Management of small peripheral lung adenocarcinoma

Immediate biopsy of lung nodules detected by CT is justified if the likelihood of cancer is high, although a period of observation by CT is appropriate if the likelihood is low or intermediate[85]. Once a diagnosis of small peripheral lung cancer is confirmed, appropriate surgical treatment aimed directly at different subtypes of tumours should be performed. Depending on the findings on preoperative CT, video-assisted thoracoscopic limited surgery may be feasible and appropriate for early lung cancers at the present time[86]. Lobectomy and segmental, wedge or sublobar resection are treatment options for small peripheral lung adenocarcinomas. Lobectomy was viewed as appropriate for clinical stage IA non-small cell lung cancer[87], but whether it is appropriate for all types of small adenocarcinomas is still a controversial topic[88]. Segmentectomy may be acceptable for tumours 2.0 cm or less in diameter, and a wedge resection may be acceptable for those measuring 1 cm or less[89–91]. For Noguchi's type A and B tumours, especially type A pure GGO, segmental or wedge resection may be sufficient and could be safely performed because of their minimally invasive nature[32,47,54,91–95]. After surgery, the 5-year survival rates are very good for small BACs and mixed-type adenocarcinomas with a predominant BAC pattern. With regard to sublobar resection, initial evidence showed that it might be acceptable for management of small air-containing type lung adenocarcinomas[96]. As for pure BACs less than 2 cm in diameter, sublobar resection seems equivalent to lobectomy; systematic nodal dissection may be unnecessary if there are no lymph node metastases[21,23,97]. Although several studies suggested the suitability of limited resection without nodal dissection for small lung adenocarcinomas, this procedure should be validated in future clinical trials.

Conclusion

The application of low-dose CT as a screening tool for small peripheral lung cancers prompted a series of studies on early-stage tumours. CT and pathologic characteristics of frequently detected small peripheral lung adenocarcinomas were distinct and mirrored each other well, and were all closely associated with tumour prognosis. Understanding these morphological and prognostic findings may be extremely helpful for early identification and diagnosis of these malignancies, to direct surgical treatment and evaluate postoperative outcome, both macroscopically and microscopically.

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