Cancer Imaging (2007) **7,** 195–201
DOI: 10.1102/1470-7330.2007.0028

CI

e-med
www.e-med.org.uk

ARTICLE

Spectrum of findings and usefulness of integrated PET/CT in patients with known or suspected neuroendocrine tumors of the lung

Semin Chong[a] and Kyung Soo Lee[b]

[a]Department of Radiology, Chung-Ang University Medical Center, Chung-Ang University College of Medicine, Seoul 156-755, Korea; [b]Department of Radiology and Center for Imaging Science, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul 135-710, Korea

Corresponding address: Kyung Soo Lee, MD, Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50, Ilwon-dong, Kangnam-gu, Seoul 135-710, Korea.
Email: kyungs.lee@samsung.com

Data accepted for publication 17 October 2007

Abstract

Positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose (FDG) has been known to increase diagnostic accuracy in differentiating benign and malignant lung lesions and to improve identification of lymph node and extrathoracic metastasis in pulmonary neoplasms. In this review, the authors describe the spectrum of integrated PET/CT findings on neuroendocrine (NE) tumors of the lung. We also demonstrate the usefulness of this imaging modality in patients with known or suspected NE tumors of the lung.

Keywords: *Chest; CT; lung; oncologic imaging; PET/CT.*

Introduction

Neuroendocrine (NE) tumors of the lung, arising from Kulchitzky cells of the bronchial mucosa, can be categorized into typical carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma (LCNEC), and small cell lung carcinoma (SCLC)[1]. The prognosis and behavioral features of these NE tumors worsen as the grade of malignancy increases[2].

It is reported that positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose (FDG) increases diagnostic accuracy when differentiating benign and malignant lesions. In addition, it is shown to improve identification of lymph node and extrathoracic metastasis in pulmonary neoplasms. Pulmonary carcinoid tumors have been known to exhibit little activity on PET scans and usually have less FDG uptake than expected for malignant tumors[3,4]. Recently, it was reported that most LCNECs have homogeneously high FDG uptake[5]. As much as it is used to evaluate non-small cell carcinoma of the lung, FDG PET has also been studied for the evaluation of SCLC. FDG PET was found to be highly sensitive in detecting SCLC and useful for evaluating prognosis and tumor stage[6,7]. In this review, we describe the spectrum of integrated PET/CT findings on NE tumors of the lung. We also describe the usefulness of this imaging modality in patients with known or suspected NE tumors of the lung.

Tumor histology

Neuroendocrine tumors of the lung share NE morphologic features such as organoid nesting, palisading, rosettes, and a trabecular growth pattern. In 1991, Travis *et al.*[1] proposed the following classification of pulmonary NE tumors: low-grade malignancy, namely, typical carcinoid tumors; medium-grade malignancy, which includes atypical carcinoid tumors; and high-grade malignancy, such as LCNEC and SCLC (Fig. 1).

These tumors represent a broad clinicopathologic spectrum with variable morphologic features and biologic behaviors. In terms of histologic features predictive of prognosis, typical carcinoid tumors show no evidence

This paper is available online at http://www.cancerimaging.org. In the event of a change in the URL address, please use the DOI provided to locate the paper.

1470-7330/07/000001 + 07

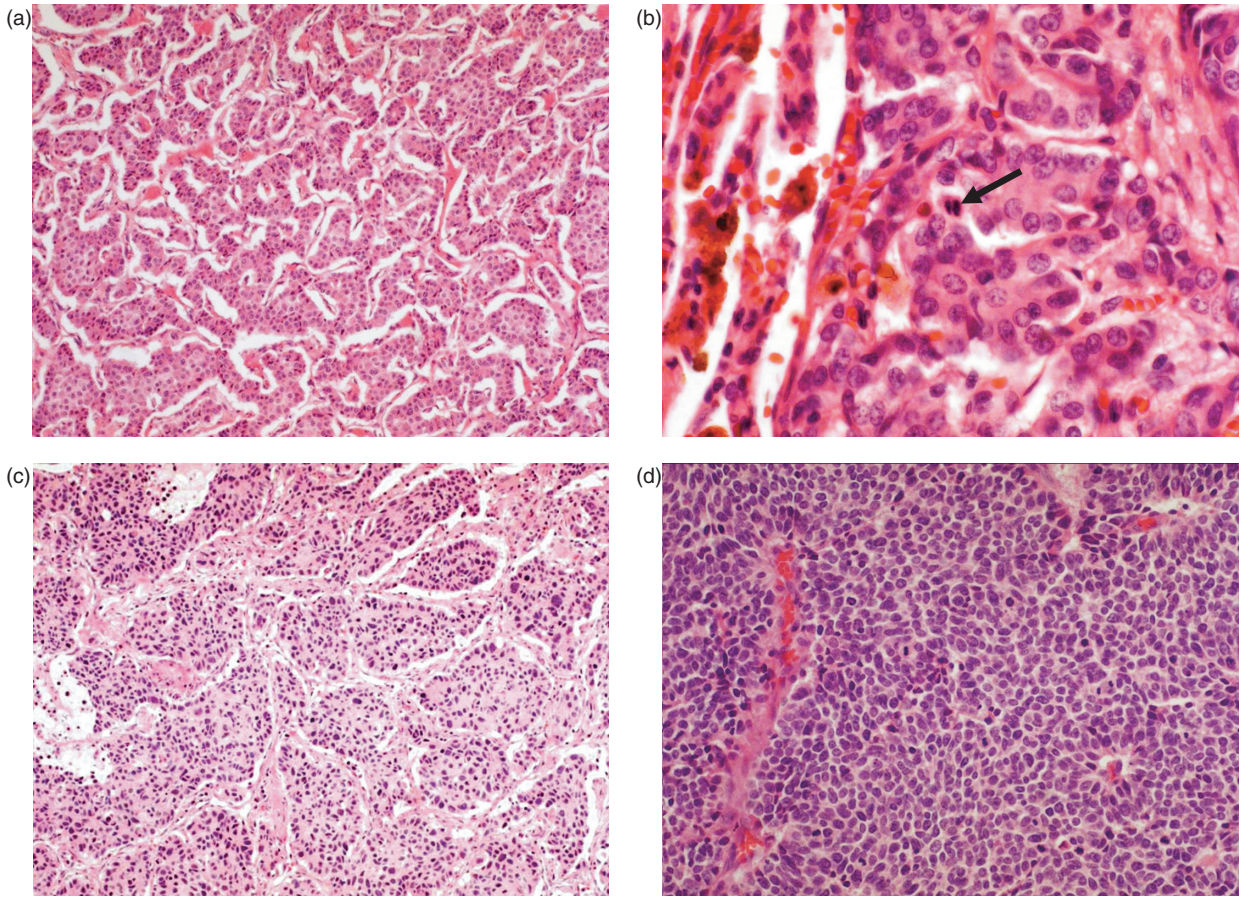

Figure 1 **Histopathologic features of pulmonary neuroendocrine tumor of the lungs. (a) Typical carcinoid. Photomicrograph shows small nests of uniform cells without mitotic or necrotic features (H&E, ×40). (b) Atypical carcinoid. Photomicrograph shows nuclear pleomorphism and mitosis (arrow) (H&E, ×400). (c) Large cell neuroendocrine carcinoma. Photomicrograph shows a neuroendocrine appearance with peripheral palisading and rosettes (H&E, ×40). (d) Small cell lung carcinoma. Photomicrograph shows high cellularity; the small round cells have scanty cytoplasm and coarse chromatin. Also note frequent mitoses (H&E, ×200).**

of necrosis and less than 2 mitoses per 10 high power fields (HPFs) (or 2 mm^2) of viable tumor (Fig. 1a), whereas atypical carcinoid tumors have areas of necrosis or 2–10 mitoses per 10 HPFs (Fig. 1b)[2]. The histopathologic diagnostic criteria for LCNEC proposed by the World Health Organization (WHO) in 1999 is as follows: (1) NE morphologic features (organoid nesting, palisading, rosettes, or trabecular growth pattern); (2) high mitotic rate (>10 per 10 HPFs); (3) necrosis (often large zones); (4) cytologic features different from SCLC (large cell size, polygonal, low nuclear/cytoplasmatic ratio, finely granular eosinophilic cytoplasm, coarse nuclear chromatin, and frequent nucleoli); (5) positive immunohistochemical staining for one or more NE markers including chromogranin A, synaptophysin and neural cell adhesion molecule (NCAM/CD56) (Fig. 1c)[8]. The cells in SCLCs are usually small and round or fusiform in shape. Also, SCLSs have high cellularity with a very high mitotic rate. Therefore, the prognosis and tumor biology of these NE tumors worsen as the grade of malignancy increases (Fig. 1d)[2].

Typical imaging findings

The majority of carcinoid tumors are centrally located and thus related to airways. Therefore, imaging studies show a well-defined hilar or perihilar mass as an isolated finding or with associated distal parenchymal changes of atelectasis or obstructive pneumonia (Fig. 2). About 16–40% of these tumors occur in the peripheral lung[9,10]. The tumors appear at CT as a spherical or ovoid nodule or mass with well-defined and slightly lobulated border. They are typically located close to central bronchi, often near the bifurcation area. On CT scans, calcification or ossification can be seen in up to 30% of tumors, and manifests as punctate or diffuse. Moreover, calcification is more frequent in central carcinoids than in peripheral carcinoids. Therefore, observation of a central tumor that causes a bronchus to be narrowed,

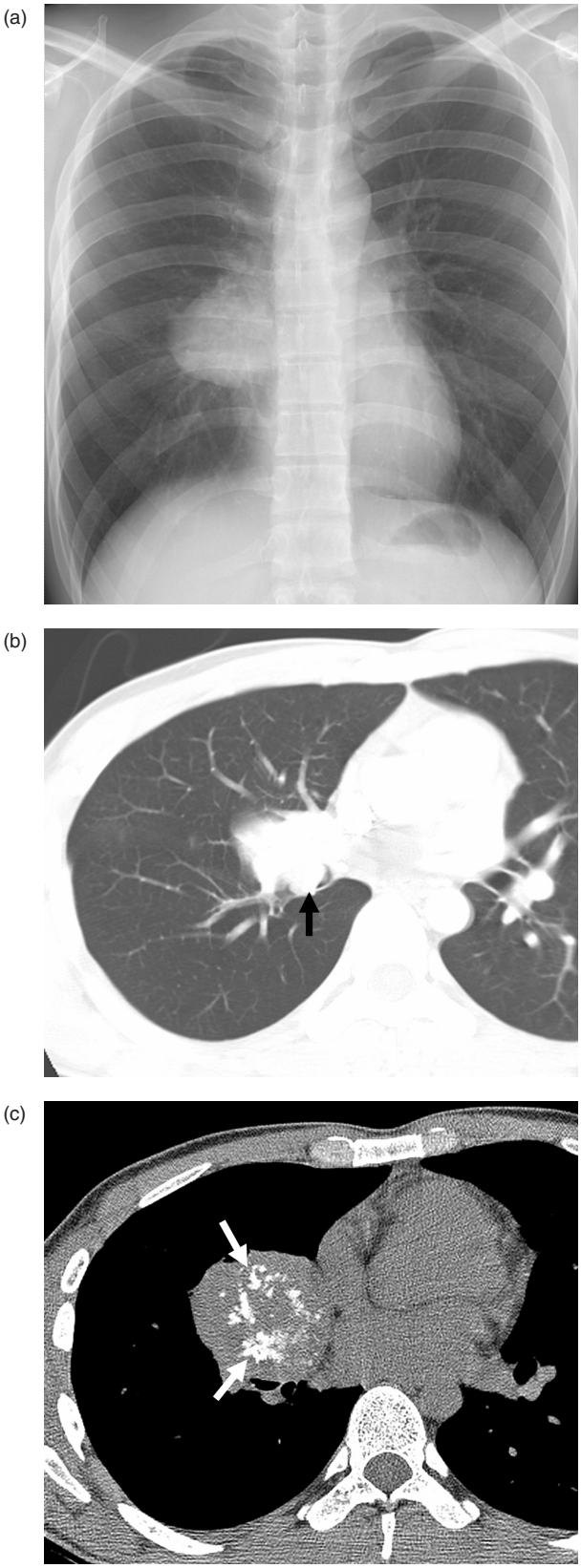

Figure 2 **A 24-year-old man with typical carcinoid. (a) Chest radiograph shows a large mass in the right infrahilar area. (b) Transverse unenhanced CT scan (5-mm section thickness, 130 mAs) obtained at the level of the left lower lobar bronchus demonstrates the upper portion of the tumor involving the distal bronchus intermedius with an intrabronchial component of the tumor (arrow). (c) Mediastinal window image of a transverse CT scan (1.0-mm section thickness, 120 mAs) obtained at the level of the inferior pulmonary vein shows a large mass containing nodular calcifications (arrows) within the lesion in the right middle lobe. (a) and (c) are reproduced with permission from Chong *et al*.[10].**

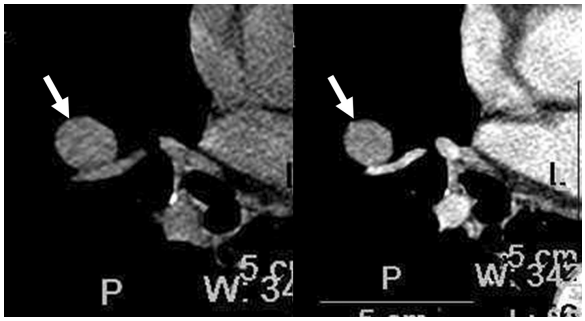

Figure 3 **A 58-year-old man with typical carcinoid. Mediastinal window images of transverse CT scans before (left) and 60 s after (right) contrast medium injection show enhancing nodules (arrows; 37 HU on unenhanced scan and 76 HU on enhanced scan) in the right middle lobe.**

deformed or obstructed and that displays punctate or diffuse calcification should suggest the diagnosis of bronchial carcinoids (Fig. 2)[10]. They occasionally present with a small nodule entirely located within the lumen of a bronchus. Even a small nodule, located beyond the origin of a subsegmental bronchus, may be noticed abutting a subsegmental bronchus or displaying a small endoluminal component of tumor at thin-section CT. Peripheral carcinoids may manifest as a well-defined, lobulated nodule or mass without CT evidence of a bronchial relationship. Carcinoids tend to be vascular and may demonstrate intense enhancement (Fig. 3). In a dynamic enhanced CT study, typical and atypical carcinoid tumors show high enhancement, more than 30 HU of net enhancement[10].

Imaging findings of LCNECs are similar to those of other common non-small cell lung cancers. Approximately 80% of LCNECs appear as a peripheral mass or nodule, whereas 20% of the tumors present with a central mass and attendant atelectasis or distal mucus plugging. Intratumoral calcifications are seen in 9% of patients with LCNEC[10].

Most SCLCs are located centrally and appear with mediastinal (92%) or hilar (84%) lymphadenopathy with displacement or narrowing of the tracheobronchial trees (68%) or major vessels (68%). Other intrathoracic CT findings are major (at least lobar) atelectasis (30%), a non-contiguous parenchymal mass (41%), and pleural effusion (38%). In 5–10% of cases, SCLC manifests as

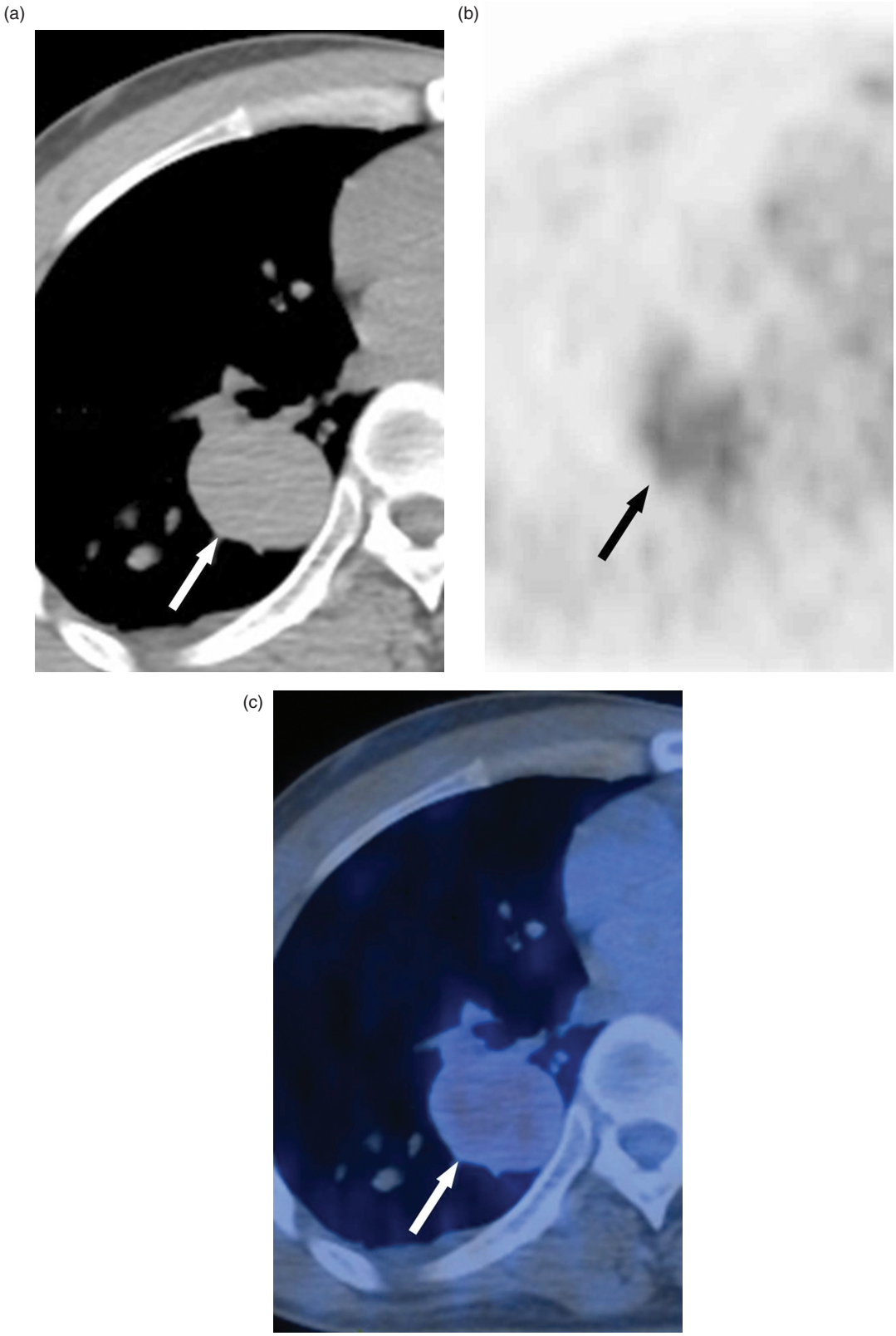

Figure 4 **A 56-year-old man with typical carcinoid (T2N0M0, IB). (a) Transverse unenhanced CT scan (5-mm section thickness, 40 mAs) obtained at the level of the right inferior pulmonary vein shows a 42-mm-sized mass (arrow) in the right lower lobe. (b),(c) FDG PET (b) and integrated PET/CT (c) scans show little FDG uptake (arrow) within the tumor (SUV_{max}, 3.4).**

a peripheral nodule without associated lymphadenopathy. Intratumoral calcification may be seen in up to 23% of SCLCs[10].

Tumor staging

In carcinoids and LCNECs, tumor stages are determined by the TNM and American Joint Committee on Cancer staging systems as in non-small cell lung cancers[11,12]. However, SCLC is usually classified using a two-stage system, i.e., limited (LD) or extensive disease (ED). LD is defined as a tumor confined to one hemithorax including regional mediastinal and supraclavicular lymph nodes, whereas ED is defined as disease beyond these boundaries. The criteria for these two categories remain controversial. However, the Veterans Administration Lung Study Group (VALG) definition of LD, primary tumor and nodal involvement limited to one hemithorax, is widely used[13].

FDG uptake of tumors

In a few studies about the PET findings of carcinoid tumors[3–5], it has been initially reported that typical carcinoid tumors do not exhibit increased activity during PET and usually have less FDG uptake than expected for malignant tumors (Fig. 4). However, subsequent reports described that typical carcinoid tumors show variable uptake according to mitotic figures and tumor proliferation[5,14]. Atypical carcinoid tumors also show variable FDG uptake (Fig. 5). According to a report, three (60%) of five atypical carcinoids had higher than mediastinal uptake (maximum SUV, 4.0–7.1)[5]. Therefore, both typical and atypical carcinoid tumors show variable FDG uptake according to mitotic figure and tumor proliferation.

In the PET/CT analysis study of LCNECs[5], all tumors had homogeneously high FDG uptake with their maximum SUVs ranging from 3.9 to 25.6 (mean 12.0, median 10.7) (Fig. 6). In cases of SCLCs, the tumors showed high FDG uptake with their SUVs ranging from 6.1 to 17.3 (mean 11.6, median 11.7) (Fig. 7). Therefore, the maximum SUVs of NE tumors are significantly different, listed in increasing order, in carcinoids, LCNECs and SCLCs.

Correlation with tumor staging and prognosis

As for the relationship between the maximum SUVs of pulmonary NE tumors and tumor stages, Chong *et al.*[5] reported that there is no significant positive correlation between the maximum SUV of primary tumors and tumor stage of carcinoids and LCNECs. In addition,

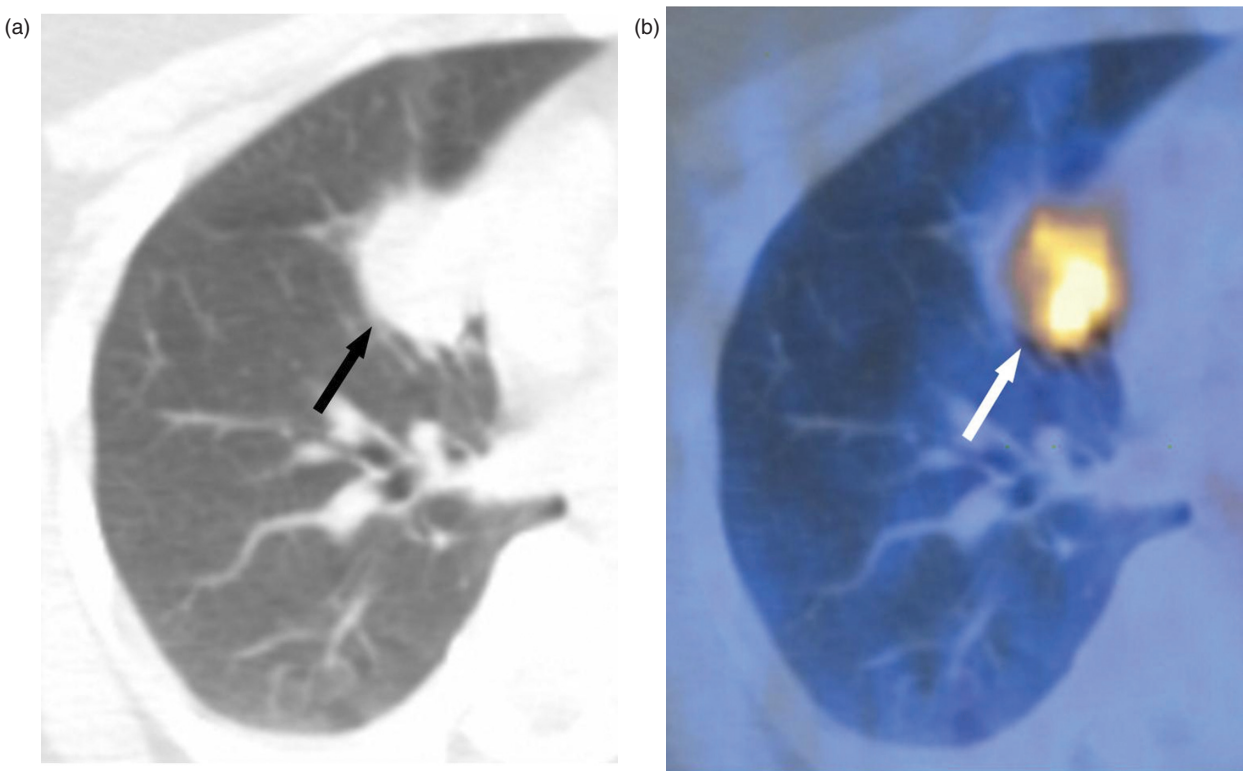

Figure 5 **A 44-year-old woman with atypical carcinoid (T1N0M0, IA). (a) Lung window image of a transverse unenhanced CT scan (5-mm section thickness, 40 mAs) obtained at the level of the right inferior pulmonary vein shows a 25-mm-sized nodule (arrow) in the right middle lobe. (b) Integrated PET/CT scan shows high FDG uptake (arrow) within the tumor (SUV_{max}, 7.1).**

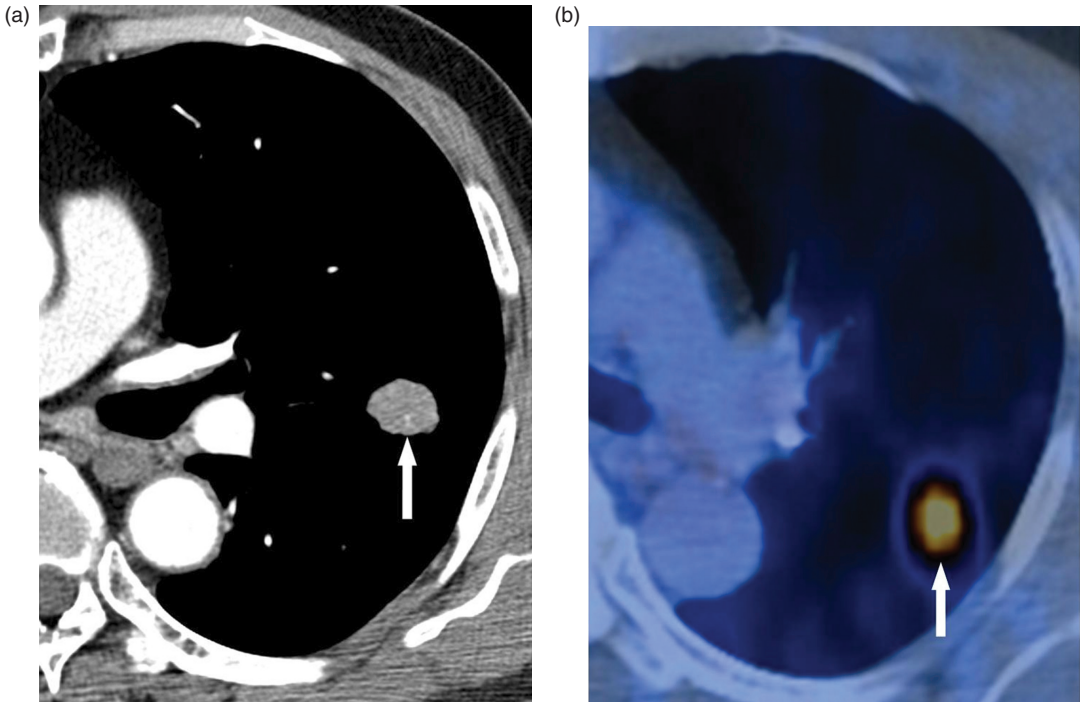

Figure 6 **A 70-year-old man with a large cell neuroendocrine cell carcinoma (T1N0M0, IA). (a) Mediastinal window image of a transverse contrast-enhanced CT scan (5-mm section thickness, 130 mAs) obtained at the level of the left upper divisional bronchus shows a 19-mm-sized peripheral nodule (arrow) in the left lower lobe. (b) Integrated PET/CT scan shows high FDG uptake (arrow) within the tumor (SUV_{max}, 10.7).**

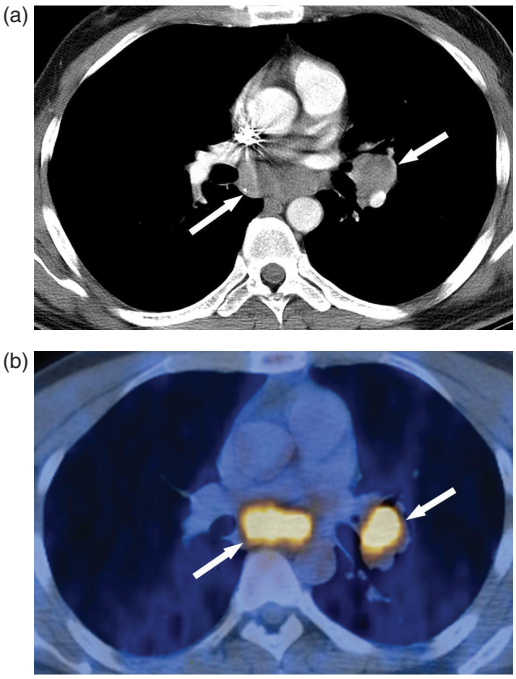

Figure 7 **A 39-year-old woman with small cell lung carcinoma (limited disease). (a) A mediastinal window image of a transverse contrast-enhanced CT scan (5-mm section thickness, 130 mAs) obtained at the subcarinal area shows an enlarged lymph node in the subcarinal and left hilar areas (arrows). (b) Integrated PET/CT scan shows high FDG uptake (arrows) within the nodes (SUV_{max}, 15.7).**

the difference in maximum SUV between limited and extensive stages of SCLCs is not statistically significant. Therefore, the estimation of maximum SUVs in pulmonary NE tumors seems to be not helpful in the initial differentiation of early from advanced stages of disease.

However, the maximum SUV appears to be related to the patients' survival. Chong *et al.*[5] found a significant negative correlation between the initial maximum SUVs of LCNECs and SCLCs and patients' survival. For example, a maximum SUV greater than 13.7 suggests relatively shorter survival time for patients with LCNEC and those with SCLC. Pandit *et al.*[7] reported that PET of patients with SCLC is useful for predicting prognosis, especially among treated patients. After-treatment survival in PET-positive cases is significantly worse than in PET-negative cases.

Accuracy of tumor staging

Accurate tumor staging, particularly accurate detection of N1–N3 metastatic lesions or extrathoracic tumor involvement is a determining factor in treatment modality and patient prognoses. According to a report[5], in LCNEC, integrated PET/CT and standalone CT both showed similar and high accuracy in predicting the presence of N1 and N2 metastasis. However, PET/CT was more effective for identifying N3 (supraclavicular) disease and extrathoracic (bone) metastasis.

Accurate staging is also important for patients with a SCLC. Patients with limited disease are treated with chemoradiation therapy, whereas those with extensive disease usually receive chemotherapy alone. PET has been considered valuable for initial tumor staging and for treatment planning of SCLC. Stage evaluation using PET is accurate and it usually concurs with the final clinical stage determined by conventional methods.

Conclusion

Carcinoids show variable FDG uptake at PET depending on their mitotic figures and the extent of tumor proliferation. Most patients with a LCNEC show homogeneously high FDG uptake on PET scans. The maximum SUVs of NE tumors are significantly different for carcinoids, LCNECs and SCLCs (listed in order of increasing value). Integrated PET/CT is more accurate than standalone CT or conventional staging methods in detecting extrapulmonary metastatic lesions especially in LCNECs and SCLCs. Moreover, the maximum SUVs in LCNECs and SCLCs appear to be related to patient survival. Thus, integrated PET/CT is useful not only in characterizing and staging of pulmonary NE tumors but also in predicting patient prognoses in these tumors.

Acknowledgment

This work was supported by the Korea Research Foundation Grant funded by the Korean government (MOEHRD) (KRF-2004-E00132).

References

[1] Travis WD, Linnoila RI, Tsokos MG, *et al.* Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma. An ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. Am J Surg Pathol 1991; 15: 529–53.

[2] Travis WD, Rush W, Flieder DB, *et al.* Survival analysis of 200 pulmonary neuroendocrine tumors with clarification of criteria for atypical carcinoid and its separation from typical carcinoid. Am J Surg Pathol 1998; 22: 934–44.

[3] Erasmus JJ, McAdams HP, Patz Jr EF, Coleman RE, Ahuja V, Goodman PC. Evaluation of primary pulmonary carcinoid tumors using FDG PET. AJR Am J Roentgenol 1998; 170: 1369–73.

[4] Wartski M, Alberini JL, Leroy-Ladurie F, *et al.* Typical and atypical bronchopulmonary carcinoid tumors on FDG PET/CT imaging. Clin Nucl Med 2004; 29: 752–3.

[5] Chong S, Lee KS, Kim BT, *et al.* Integrated PET/CT of pulmonary neuroendocrine tumors: diagnostic and prognostic implications. AJR Am J Roentgenol 2007; 188: 1223–31.

[6] Blum R, MacManus MP, Rischin D, Michael M, Ball D, Hicks RJ. Impact of positron emission tomography on the management of patients with small-cell lung cancer: preliminary experience. Am J Clin Oncol 2004; 27: 164–71.

[7] Pandit N, Gonen M, Krug L, Larson SM. Prognostic value of [^{18}F]FDG-PET imaging in small cell lung cancer. Eur J Nucl Med Mol Imaging 2003; 30: 78–84.

[8] Travis WD, Colby TV, Corrin B, Shimosato Y, Brambilla E. Histological typing of lung and pleural tumors, 3rd ed. Berlin: Springer-Verlag; 1999, p. 5–98.

[9] Rosado de Christenson ML, Abbott GF, Kirejczyk WM, Galvin JR, Travis WD. Thoracic carcinoids: radiologic-pathologic correlation. Radiographics 1999; 19: 707–36.

[10] Chong S, Lee KS, Chung MJ, Han H, Kwon OJ, Kim TS. Neuroendocrine tumors of the lung: clinical, pathologic, and imaging findings. Radiographics 2006; 26: 41–57.

[11] AJCC. Cancer staging manual, 6th ed. New York: Springer; 2002, p. 65–177.

[12] Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. Chest 1997; 111: 1718–23.

[13] Zelen M. Keynote address on biostatistics and data retrieval. Cancer Chemother Rep 1973; 4: 31–42.

[14] Kruger S. Buck AK, Blumstein NM, *et al.* Use of integrated FDG PET/CT imaging in pulmonary carcinoid tumors. J Intern Med 2006; 260: 545–40.