Fluorodeoxyglucose positron emission tomography (FDG-PET) has entered routine use in the management of lung cancer, at least in countries and health systems that can afford it. FDG-PET has better sensitivity than computed tomography (CT) scanning in the detection of distant metastases in patients with non–small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). However, the relatively low specificity of FDG-PET and the difficulty in localizing the “hot spots” identified by FDG-PET imaging have elicited efforts to integrate FDG-PET with other radiologic imaging techniques, such as CT scans.

In this issue of the Journal, Ung et al. (1) present an extensive systematic review of the published literature on the accuracy and utility of FDG-PET in the diagnosis and staging of lung cancer. The authors focus on three areas: 1) use of FDG-PET in differentiating lung nodules; 2) preoperative staging of NSCLC—in particular, preoperative mediastinal staging; and 3) use of FDG-PET in staging SCLC.

Although the systematic review by Ung et al. (1) includes recent reports, it also takes into consideration studies performed over 10 years ago. The improvement in imaging technology that occurred in recent years needs to be considered to be able to formulate guidelines and recommendations.

Solitary Pulmonary Nodules
Numerous benign conditions, such as granuloma, hamartoma, round pneumonia, round atelectasis, hematoma, and arteriovenous malformation, can appear as lung nodules. FDG-PET has high sensitivity (96%) but relatively low specificity (78%) in differentiating benign from malignant nodules as small as 1 cm (1). Furthermore, in patients with prior malignancies, histologic confirmation of the nature of the nodule is usually necessary, regardless of PET findings (2), especially in geographic areas where benign lung lesions are common (e.g., tuberculosis in Korea).

The difficulties in assessing small pulmonary nodules are becoming more important in view of the increasing use of helical low-dose CT scans in screening people at risk of lung cancer. FDG-PET could have a role in helping to indicate which pulmonary nodules detected by such scans should be assessed surgically. In particular, FDG-PET may be helpful in evaluating nodules larger than 5 mm in diameter, which are detected in 10%–15% of heavy smokers who undergo screening CT scans (3). It should be noted, however, that there are differences in FDG uptake among the different histologic types of lung tumors, and these should be taken into consideration when assessing relatively small pulmonary nodules. In fact, FDG-PET scans are usually strongly positive in NSCLC and SCLC but weaker in more slowly growing bronchial tumors, such as carcinoids and bronchioloalveolar carcinomas.

Preoperative Staging of Non–Small Cell Lung Cancer
Randomized studies have reported conflicting results in terms of the relative reduction in the number of noncurative (futile) thoracotomies with FDG-PET staging (4,5). These conflicting results are due in part to differences in the patient populations that were studied (4,5), but they may also be due to differences among studies in the preoperative staging. In particular, the study by Viney et al. (5) allowed individuals with stage IIIA disease that was deemed completely resectable to proceed directly to thoracotomy, whereas in the study by van Tinteren et al. (4) such patients underwent mediastinoscopy. A major role of FDG-PET in the preoperative staging of NSCLC is in excluding patients who have distant metastases, i.e., in whom thoracotomy would not be curative. Approximately 10% of distant metastases identified at staging with FDG-PET are in locations usually not investigated by routine CT scanning. However, patients with stage I and II disease are less often excluded from surgery based on distant metastases detected by FDG-PET than patients who present with stage IIIA disease. In general, sites that appear by FDG-PET...
scanning to harbor metastatic disease should be confirmed by histologic diagnosis, especially in the case of single potential metastatic sites.

A major area of research of FDG-PET scanning has been the staging of mediastinal nodes. Several guidelines or recommendations have been published. For example, the American Society of Clinical Oncology issued recommendations regarding the staging and treatment of lung cancer in 2003 (6). FDG-PET scanning was recommended to complement findings on CT scans.

FDG-PET appears to be superior to CT for mediastinal staging of NSCLC (7). In the case of enlarged mediastinal lymph nodes seen on a CT scan but a negative PET scan of the mediastinum, mediastinoscopy would be required in many institutions and patients with negative FDG-PET would proceed directly to thoracotomy. A negative FDG-PET scan of the mediastinum has been reported to have a predictive value of more than 95% (8). However, some recent findings have questioned the high negative predictive value of PET scanning (9), and mediastinoscopy still plays an important role in nonenlarged and FDG-PET-negative mediastinal nodes.

Because of the relatively high rate of false positivity of both CT and FDG-PET, mediastinoscopy is required to exclude from surgery patients with enlarged mediastinal nodes on CT scans (i.e., >1 cm in the short axis) and positive FDG-PET scans of the mediastinum. Mediastinoscopy is superior to FDG-PET in predicting the mediastinal node status (9). The high rate of false-positive results by FDG-PET—caused, for example, by inflammation resulting from postobstruction pneumonia or silicosis—means that positive results require histologic or cytologic verification. The sensitivity of mediastinoscopy is over 80%, and its negative predictive value is approximately 90% (10). The staging of the mediastinal nodes has, however, witnessed some changes in recent years due to the introduction of less invasive endoscopic techniques, such as esophageal ultrasound with fine needle aspiration and endobronchial ultrasound with transbronchial needle aspiration. Which of these techniques is used depends mainly on the localization of the presumed mediastinal lymph node metastasis. However, mediastinoscopy has a lower rate of false negatives than the fine needle aspiration techniques, and mediastinoscopy is still preferred when feasible (10).

Integrated FDG-PET/CT images are superior to FDG-PET or CT images alone for assessing tumor stage (7). FDG-PET/CT also showed improvement of N staging compared with FDG-PET alone (7). However, comparisons of FDG-PET/CT to FDG-PET alone or CT alone are no longer realistic, because most developed countries now use integrated FDG-PET/CT machines, and therefore results produced by these examinations should be compared with side-by-side evaluation of both conventional FDG-PET and CT scans. Although software can be used to fuse separately obtained FDG-PET and CT scans, these reconstructions are only successful in about two-thirds of cases (7) due to the influence of breathing and to variable use of intravenous contrast agents. These results can be improved with specific protocols of contrast injection and breathing instructions. In general, however, integrated machines so far appear to give better results than those obtained by software that attempts to fuse results obtained by separate examinations.

Staging of Small Cell Lung Cancer

Although FDG-PET has not been studied extensively in SCLC, it appears to have good accuracy in classifying extensive versus limited disease, as reported in the review by Ung et al. (1). In a recent study of 63 patients with otherwise limited disease, stage was changed to extensive disease in 8% of patients, based on FDG-PET findings (11).

There are other uses of FDG-PET scans that were not addressed in the overview in this issue (1), such as the monitoring of responses to systemic therapy and to radiotherapy, especially in the presence of atelectasis, and of postradiation effects. In addition, the use of other radionuclides such as 18-fluoroethionamide and the prognostic value of FDG-PET standardized uptake value merit investigation. Moreover, the use of other imaging techniques is being investigated in place of or possibly as a complement to FDG-PET scanning. For example, whole-body magnetic resonance imaging was recently shown to be as accurate as FDG-PET for the detection of metastatic sites in lung cancer patients (12).

In conclusion, FDG-PET is being increasingly used in lung cancer and has acquired a relevant role in staging patients, assessing treatment strategies, and monitoring treatment effects. Although FDG-PET has not replaced more accurate and invasive procedures, such as mediastinoscopy, improvements in the integration of FDG-PET with other imaging modalities are promising and likely to affect the management of patients with lung cancer in the future.

References

