Recent Progress in Positron Emission Tomography Concerning Diagnosis and Treatment of Lung Cancer

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Introduction

A fused image from radio-labeled 18F-fluoro-2-deoxy-D-glucose positron emission tomography and chest computed tomography (FDG-PET/CT) is now used widely for lung cancer diagnosis. Major indications include differential diagnosis between benign and malignant lung nodules, evaluation of regional lymph node involvement, and screening for extrathoracic distant metastases. Additional recent clinical applications of this new imaging method have received considerable attention.

Early Studies of PET in Lung Cancer

Studies in the early 1990s have found that PET frequently identifies unsuspected malignant lesions, leading to changes in preoperative assessment of lung cancer patients. Using the criterion of standardized uptake value (SUV) 2.5 or greater to indicate malignancy, accuracy of PET was 92%. Further, SUV correlated significantly with a doubling time in the rate of lung cancer growth. PET was also adopted as an effective tool in the clinical workup of lung cancer patients and proved to be particularly superior to CT alone in the assessment of hilar and mediastinal nodal metastases. These early findings led us to integrate scanning of whole-body PET with brain MRI (magnetic resonance imaging) so that we could more accurately determine the clinical stage of lung cancer. In 2001, the first integrated PET/CT scanner was installed; use of this modality has expanded rapidly as a way to overcome the lack of anatomic detail with PET alone. However, over subsequent years, we have learned that false positive and false negative results are obtained more often by FDG-PET/CT, for both primary lesions and intrathoracic lymph nodes than we had previously thought. Recent efforts to increase PET/CT accuracy or compensate for limitations of PET/CT diagnosis have produced encouraging results.

Evaluation of Regional Lymph Nodes

Many studies have evaluated the efficacy of PET in diagnosis of hilar or mediastinal lymph node metastases. In an early study, sensitivity, specificity, and accuracy of CT for detecting metastatic lymphadenopathy were reported as 68%, 61%, and 63% respectively; for PET, these values were 87%, 91%, and 82%. In that study, false-positive findings of FDG-PET affected treatment selection in 83% of patients. FDG-PET/CT is considered significantly better than stand-alone CT for staging of lung cancer, improving accuracy and specificity in nodal staging. However, PET/CT staging of the mediastinum may be less sensitive in elderly patients with non-small cell lung cancer (NSCLC), who have shown a lower positive predictive value. Thus, elderly patients showing mediastinal uptake should not be refused surgical resection with curative intent on the basis of such uptake alone. For Pathologic confirmation, endobronchial ultrasonography-fine needle aspiration (EBUS-FNA) is superior to PET/CT alone in predicting absence of nodal metastasis, although mediastinoscopy is still considered the “gold standard” for nodal staging irrespective patient age in Western countries. Aiming to avoid invasive methods when possible, I consider PET/CT followed by EBUS-FNA for PET-positive nodes...
to be the most effective minimally invasive approach for hilar and mediastinal lymph node assessment.

Individualization of Surgical Methods

If the potential of lung cancer cells to metastasize to regional lymph nodes can be estimated based on SUV, the necessity of lymph node dissection and extent of lung resection could be determined, individually, from SUV measurements. Casiraghi et al. analyzed 219 patients with pathologic T1 NSCLC, finding a low probability of lymph node involvement in NSCLC, when the longest dimension of the tumor was less than 1 cm, or when the SUV was less than 2; thus, lymphadenectomy might then be avoided.8 Veronesi et al. studied 97 patients with early-stage clinical N0 lung cancers, obtaining similar results.9 If we would reconfirm these results in larger studies, we could select limited resection and omit lymphadenectomy for certain patients according to the preoperative FDG-PET/CT.

Evaluation of Therapeutic Effects

Since SUV is considered to semi-quantitatively represent growth activity of tumors, changes between pre- and post-treatment SUV may be used as an indicator of therapeutic effect. Although SUV was difficult to use for this purpose in radiotherapy because of radiation-related inflammation,10 chemotherapeutic response was evaluated successfully by comparing SUV from such serial PET/CT scans.11,12 However, a conflicting report concluded that PET evaluation was not a good marker of efficacy for neoadjuvant chemotherapy.13 In that study, metabolic activity by PET was associated with no significant difference in survival, while response determined by CT using Response Evaluation Criteria in Solid Tumors (RECIST) was associated with survival. The conflicting results need to be resolved by future studies.

SUV for the Primary Lesion as a Prognostic Factor

Since SUV reflects the proliferation potential of tumor cells, SUV might serve as a prognostic indicator. Vansteenkiste et al.14 reported that in 125 NSCLC patients, poor performance status, advanced stage, and SUV of 7 or greater correlated significantly with poor survival in a multivariate analysis. In the group with resection, patients with a tumor smaller than 3 cm and SUV below 7 had an expected 2-year survival of 86%, which declined to 60% if SUV was 7 or more. Those authors concluded that FDG uptake in primary NSCLC shown by PET has an important prognostic value and could complement other well-known factors in decision-making concerning adjuvant treatment protocols. Analyzing 100 consecutive post-resection patients, Downey et al.15 found that 2-year survival for patients with SUV of 9 or more was 68%, but when SUV was below 9 survival was 96%. In a multivariate analysis, tumor size exceeding 3 cm and SUV of 9 or more showed an interaction and were significant predictors of poor survival. In addition to overall survival, lower FDG uptake appeared to be predictive of disease-free survival in patients with stage I lung adenocarcinoma in another study.16 Results of all these studies indicated that SUV could serve as a useful prognostic marker for resected NSCLC.

Factors Affecting SUV

Differences in FDG uptake related to histologic type of lung cancer should be kept in mind.17 Spatial distributions of cancer cells within the lesion and tumor size both also influence SUV, in addition to cellular glucose uptake capability. In general, SUV of a squamous cell carcinoma is greater than that of adenocarcinoma of the same size, probably depending on differences in histologic structure between these types. SUV for poorly differentiated adenocarcinoma is greater than that for well–differentiated bronchioloalveolar carcinoma.18,19 Thus, malignant potential or prognostic effects of SUV should be analyzed within the same histologic type and disease stage.

Randomized Clinical Trials

Several randomized clinical trials (RCTs) have been performed to determine whether PET/CT is more informative in preoperative evaluation of lung cancer than conventional CT. In the initial Dutch study,20 188 patients were assigned randomly to either conventional workup (CWU) or CWU plus PET. While 39 patients had a thoracotomy without curative possibility in the CWU group, only 19 patients in the CWU plus PET group underwent such a futile thoracotomy, representing 51% relative reduction in unnecessary surgery. In a later Dutch study21 involving 465 patients (233 CWU, 232 PET), agreement between clinical and final stages did not differ between the 2 arms, but PET maintained reliability of TNM staging with less invasive surgery, because mediastinoscopies.
were performed significantly less often in the PET arm. Similar results were obtained in a Danish study, although overall mortality after surgical treatment was similar between groups.\textsuperscript{22} In a Canadian study, more incorrectly upstaged patients were found in the PET group,\textsuperscript{23} but a more recent Canadian study\textsuperscript{24} reported that PET improved discrimination between N0-1 and N2-3 in patients without enlarged lymph nodes. All of these RCTs suggested that FDG-PET/CT is useful in avoiding unnecessary surgery; nonetheless, cytologic or histologic confirmation is necessary when mediastinal lymph nodes are PET-positive, in order to exclude false positive cases.

**Meta-Analysis**

Several meta-analyses reviewing different aspects of PET concerning lung cancer have been reported. With respect to nodal metastases, PET was significantly more accurate than CT, but was less specific when CT shows enlarged mediastinal lymph nodes. This suggests that we cannot determine therapeutic strategy based on results of PET/CT alone.\textsuperscript{25-27} When analysis is limited to T1N0 NSCLCs, PET/CT provides a favorable negative predictive value for mediastinal metastases, suggesting a low yield from routine invasive staging procedures performed for this subgroup of patients.\textsuperscript{28} Concerning extrathoracic lesions, FDG-PET/CT has higher diagnostic value for diagnosing bone metastasis from lung cancer in terms of sensitivity, specificity, and diagnostic odds ratios than any other imaging method including MRI and bone scintigraphy.\textsuperscript{29} Prognostic value of SUV was confirmed in a meta-analysis including a total of 1474 patients with NSCLC.\textsuperscript{30} Generally, results of these meta-analyses agreed with those of previous RCTs.

FDG-PET/CT is a unique imaging analysis that reflects physiologic characteristics of cancer cell metabolism. We can obtain useful information using FDG-PET/CT to guide diagnosis and treatment of lung cancer, when we take into account both the power and limitations of this new diagnostic modality.

**References**


