PET Scan in Lung Cancer: Current Recommendations and Innovation

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Abstract: In the past 10 years, positron emission tomography (PET), usually with ^{18}F-fluoro-2-deoxy-D-glucose (FDG), has become an important imaging modality in patients with lung cancer. FDG-PET is recommended for the diagnosis of indeterminate pulmonary nodules, for which it is significantly more accurate than computed tomography (CT) in the distinction between benign and malignant lesions. A large body of evidence convincingly demonstrates that loco-regional lymph node staging by FDG-PET (in correlation with CT images) is significantly superior to CT alone, with a negative predictive value equal or even superior to mediastinoscopy. FDG-PET also improves extrathoracic staging through detection of lesions missed at conventional imaging or characterization of lesions that remain equivocal on conventional imaging. Ongoing studies now concentrate on more advanced clinical applications, such as the planning of radiotherapy, the response evaluation after the induction of therapy, the early detection of recurrence, and the use in lung cancer screening. Technical innovations, such as PET cameras with better spatial resolution, or new radiopharmaceutical probes to study applications of PET in molecular biology hold promise for future refinements in this field.

Key Words: Tomography, Emission computed, Lung neoplasms, Diagnosis, Staging, Treatment outcome.

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The use of positron emission tomography (PET) with ^{18}F-fluoro-2-deoxy-D-glucose (FDG) in oncology is based on its ability to visualize the differences among the glucose metabolism of tissues. Neoplastic cells have a much higher rate of glycolysis compared with non-neoplastic cells and an increased cellular uptake of glucose, because of an increased expression of glucose transport proteins. FDG undergoes the same cellular uptake as glucose but is metabolically trapped and accumulated in the neoplastic cell after phosphorylation by hexokinase. The preferential accumulation of FDG in neoplastic cells permits differentiation between benign and malignant tissue. In this way, FDG-PET complements the anatomic information on standard imaging with "metabolic" information.

FDG-PET has become an important lung cancer imaging tool. Current recommendations include the diagnosis of lung cancer as well as loco-regional and distant staging of non–small-cell lung cancer (NSCLC). Several innovative techniques and clinical applications are being studied.

Diagnosis of Lung Cancer

PET has been studied extensively in the diagnosis of indeterminate lung lesions. The technique has been proven to be significantly more accurate than computed tomography (CT) in differentiating benign from malignant lesions as small as 1 cm. An overall sensitivity of 96% (range, 83–100%), specificity of 79% (range, 52–100%), and accuracy of 91% (range, 86–100%) can be expected.[1,2] False-negative results can occur in subcentimetric lesions because a critical mass of metabolically active malignant cells is required for PET diagnosis. Even when they are larger than 1 cm, bronchoalveolar cell carcinomas, which often have a distinct pattern on CT (ground-glass opacity), may exhibit little or no FDG uptake. False-positive FDG uptake is seen in inflammatory conditions and granulomatous diseases. Because of its high negative predictive value, PET excludes malignancy correctly in the vast majority of cases. Thoracotomy can be avoided in such patients, and follow-up with radiographic or CT scan at 3, 6, 12, and 24 months can be advised.[3] As the specificity is only 79%, the positive predictive value will be lower. In clinically suspicious cases, further investigations for detection of infectious or granulomatous disorders are indicated. If there is doubt, solitary nodules with high FDG uptake require resection.

Loco-regional and Extrathoracic Staging

A large number of accuracy studies previously summarized in six meta-analyses,[2,4–8] have convincingly demonstrated that PET is a superior imaging technique for mediastinal lymph node staging in potentially operable NSCLC. For the distinction between N0-1 and N2-3 patients, the review yielded an overall sensitivity of 89% (range, 67–100%) with a specificity of 92% (range, 79–100%) and an accuracy of 90% (range, 78–100%). For CT, the sensitivity was 65% (range, 20–86%), specificity was 80% (range, 43–90%), and accuracy was 75% (range, 52–79%).[1] Interpretation of PET images is improved by visual correlation with CT through

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better localization of PET abnormalities with the help of the anatomical detail of CT. Of major clinical importance is the good negative predictive value of PET in lymph node staging. Patients with mediastinal PET-negative results may be adequately staged without invasive procedures and can proceed directly to thoracotomy,[9,10] provided that some conditions are respected: (1) sufficient FDG uptake in the primary tumor; (2) absence of a central tumor or important hilar lymph node disease that may obscure coexisting N2 disease on PET (Figure 1); and (3) use of a dedicated PET camera.[11] Although the positive predictive value is reasonable, false-positive results can be obtained in the case of anthracosilicosis, infection, or granulomatous disorders. In these patients, confirmation of N2 or N3 disease by mediastinoscopy is mandatory to ensure that no patient with resectable N0 or N1 disease is denied the chance of curative surgery.

As for extrathoracic staging, PET is a useful adjunct to conventional imaging. PET offers an additional value in the detection of distant metastases in potentially operable NSCLC by two means.[12] First, there is the detection of unexpected metastatic spread. After a negative conventional staging, unknown metastases were found on PET in 5 to 29% of patients. The incidence of occult metastatic lesions increases with increasing pre-PET stage from 8% in stage I, to 18% in stage II, to 24% in stage III.[13] Second, PET is able to determine the nature of equivocal lesions on conventional imaging, present in 7 to 19% of patients. Exclusion of malignancy by PET requires caution in the case of a small lesion (<1 cm).

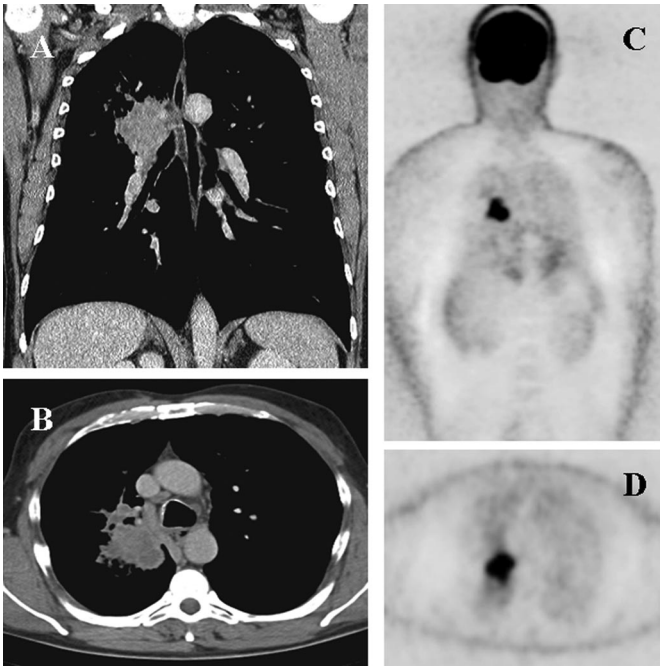

FIGURE 1. Patient with centrally located squamous cell carcinoma originating from the right upper lobe (**A** and **B**). Although PET shows only one area of increased FDG uptake without the suggestion of mediastinal lymph node metastases (**C** and **D**), a mediastinoscopy is indicated to rule out adjacent lymph nodes.

As a whole, PET has a positive impact on overall staging and patient management.[14] The use of PET imaging for clinical staging results in a stage different from that determined by conventional methods in 27 to 62% of patients with NSCLC. Up-staging is more frequent than down-staging and is related mainly to the detection of unexpected distant lesions by PET. Across series, this leads to a change in patient management for 25 to 52% of patients (mainly changes in treatment intent from curative to palliative).[12] In one study, an intramodality change was reported in 26% of the patients.[15] There is also randomized evidence that PET reduces the need for invasive procedures and futile surgery.[16] Whether it seemingly improves survival because of stage migration or whether it truly improves survival because of better therapeutic strategies remains to be determined.

Innovation

Different innovative clinical applications of PET in the field of lung cancer are studied intensively.

In a recent systematic review on the use of PET for prognostic and therapeutic assessment,[17] we summarized that there is good evidence that FDG uptake on PET has independent prognostic value in patients with newly diagnosed NSCLC.

PET is more sensitive than CT in measuring the biological effects of anticancer therapy, and it can be used for additional early response assessment in clinical trials. Different studies have also used PET to evaluate response in clinical practice (Figure 2), but better standardization of the technique and response criteria is needed before taking this to large-scale use.

An increasing number of studies have examined the role of PET in restaging after induction therapy in multimodality approaches for locally advanced lung cancer. The assessment of mediastinal lymph nodes is better than that with CT but not as good as in untreated patients, especially after chemoradiotherapy induction. Lack of clearance of mediastinal lymph nodes or unchanged FDG uptake in the primary tumor usually denotes a poor outcome after multimodality treatment.

Good prospective evidence documents the superiority of PET over CT in the correct identification of recurrent lung cancer.

The additional value of PET has also been explored in lung cancer screening studies. One of the problems associated with screening is the potential need for invasive procedures in patients with benign nodules. One screening study examined the selective use of PET in screen-detected nodules larger than or equal to 7 mm.[18] PET was correctly positive in eight of nine prevalence cancers (an 8-mm adenocarcinoma was missed), and in 10 of 11 incidence cancers (with one predominantly bronchoalveolar tumor of 11 mm missed).

More fields of innovation, discussed in other contributions to this series, are the use of PET/CT fusion cameras, the use of PET/CT for radiotherapy planning, and the integration of new imaging techniques such as PET with biomarkers, another rapidly evolving field in lung cancer research.

Finally, a large number of new tracers attempt to examine the biological behavior of lung cancer in more detail

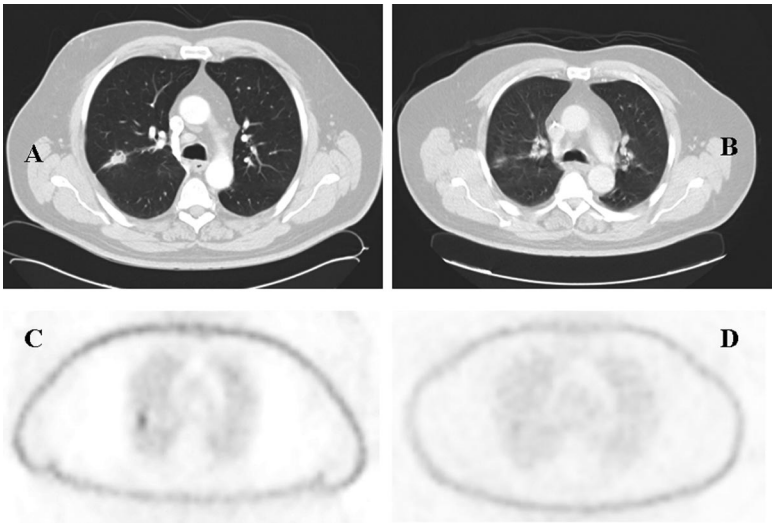

FIGURE 2. Patient with stage IIIA-N2 adenocarcinoma (peripheral lesion in the right upper lobe and right paratracheal lymph node involvement). Good tumor response after cisplatin-based induction chemotherapy, both on CT (**A** and **B**) and on FDG-PET (**C** and **D**). In the resection specimen, lymph node down-staging and only a few viable cells in the primary tumor were found.

than FDG, with promising findings. For example, for lung cancer proliferation, ^{11}C-thymidine was the first radiotracer for non-invasive in vivo imaging. The short half-life of ^{11}C and the rapid metabolism of ^{11}C-thymidine in vivo made the radiotracer less suitable for use. Recently, clinical experience was gained with the thymidine analogue 3′-deoxy-3′-^{18}fluorothymidine (FLT), a more stable proliferation marker. FLT is phosphorylated by thymidine kinase 1, which is present in large quantity in proliferating lung cancer cells. The good relationship between FLT uptake and tumor proliferation can be exploited to improve the specificity of PET imaging in solitary pulmonary nodules[19] and may be useful to improve the results with FDG when restaging patients who have undergone induction chemo(radio)therapy for NSCLC.

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