PET/CT Fusion Scan in Lung Cancer: Current Recommendations and Innovations

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Abstract: Combined fluorodeoxyglucose-positron emission tomography (PET)/ computed tomography (CT) imaging has the potential to become the new standard imaging modality for the staging and restaging of patients with lung cancer. PET/CT is superior to PET alone, CT alone, and visual correlation of both techniques separately. In particular, it improves T3 and T4 staging and delineation of tumors associated with atelectasis. CT contrast media enhancement is probably only still needed when a substantial mediastinal tumor component is present and delineation of tumor from vascular structures is relevant. PET/CT is very accurate in detecting mediastinal nodal disease, but false-positive results are sufficiently frequent to require sampling in some positive cases. Whole-body PET/CT is the most sensitive technique for detecting extracranial metastatic disease, unexpected additional primary malignancies, and recurrence. Innovations include therapy monitoring, prognostic information, evaluation of small-cell lung cancer, its use for radiotherapy planning, and four-dimensional respiratory gating acquisition.

Key Words: Lung cancer, PET/CT, Staging, Restaging

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All relevant imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), are used for imaging lung cancer. A multidisciplinary approach contributes to a correct staging and restaging, and therapy becomes more successful. In lung cancer, both CT and PET using fluorodeoxyglucose (FDG) play an important role in the diagnosis and staging of patients with lung cancer. CT provides excellent morphologic information but has significant limitations in differentiating between benign and malignant lesions either in an organ or in lymph nodes. As the previous revision has brilliantly explained, PET using FDG provides excellent metabolic information of the tumoral lesions in a whole-body study and improves the rate of detection of mediastinal lymph node metastases as well as extrathoracic metastases when compared with CT. Limitations of PET are that the technique provides little information on the exact anatomic localization of lesions and that FDG is not specific for malignant tissue. Fusing the morphologic and functional datasets may provide further diagnostic confidence. Faulty co-registration as a result of motion-induced misalignment in the abdomen and chest has, so far, limited all software-based image fusion tools. This limitation can be overcome by an integrated PET/CT system that provides co-registered morphologic and functional datasets as part of a single examination.

The first prototype of a PET/CT scanner was developed at the University of Pittsburg in 1998, and a combined PET/CT system became commercially available in the United States in the spring of 2001.[1] In Europe, the first clinical PET/CT was set up in the University Hospital of Zurich in 2001. Our institution in Barcelona, Spain, started in 2003; since then, more than 1500 scans have been performed in patients with suspected or diagnosed lung cancer. Within 3 years, more than 450 PET/CT scanners had been sold worldwide, with the majority being in the United States, and PET/CT scanners comprise more than 80% of total PET scanner sales since 2003.[2]

The PET/CT scanners combine a multidetector helical CT (located proximally in the gantry) to provide the anatomical information with a dedicated PET ring (located distally in the gantry) to provide metabolic information. Automatic and exact fusion of both modalities is performed by a dedicated workstation. In our institution, all scans are obtained in a Discovery ST scanner (General Electric Healthcare, Milwakee, WI).

Compared with PET, using integrated PET/CT for patients with lung cancer presents three important advantages: (1) increases the accuracy and certainty of locating lesions; (2) reduces time of acquisition (more rapid scans than PET alone) and final diagnosis (CT and PET in a single scanning session); and (3) improves staging and restaging accuracy (differentiating physiological from pathological foci).[3,4] PET/CT results can therefore change the patient's management. In overall staging of non–small-cell lung cancer, PET/CT provides more information than PET alone, CT

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alone, and probably more than the visual correlation of PET and CT performed separately.[5–10]

Current Recommendations

Current recommendations for the use of PET/CT in lung cancer are obviously the same as for PET, with some important advantages in certain indications. As previously reported for FDG-PET in lung cancer, PET/CT is also widely accepted for imaging lung nodules and staging and restaging non–small-cell lung cancer.[11]

Integrated PET/CT imaging from the head to the upper legs is performed in all remitted patients with proven or suspected non–small-cell lung cancer, which allows a complete tumor node metastases staging.

The primary tumor can be resectable depending on its extension (T stage), which is usually assessed by CT. However, the low accuracy of chest CT in the evaluation of invasion of the chest wall or involvement of the mediastinum and the correct differentiation between tumor and peritumoral atelectasis often limits precise T staging with CT. A disadvantage of PET is the limited anatomic resolution, which makes the assessment of tumor extension unreliable, particularly if the tumor infiltrates the chest wall or the mediastinum. Integrated PET/CT provides important information on the exact demarcation of the tumor and improves T3 and T4 stage assessment. A fundamental, but easily overlooked, premise when discussing the use of imaging for T staging is that the primary tumor can be clearly defined. In fact, it may be difficult to distinguish the tumor from distal collapsed or consolidated lung on CT, and this can result in overestimation of tumor size and extent of parietal pleural contact. It has been shown that PET/CT is a useful tool for the differentiation between tumor, which is hypermetabolic, and peritumoral atelectasis, which is usually normometabolic, although it also can be invaded by the tumor (pattern of replacement atelectasis).[12] (Figure 1). This may be particularly important for the planning of radiotherapy, in which the information provided contributes to a change in the radiation field in approximately 30 to 40% of patients.[13]

CT, MRI, and PET (and obviously PET/CT) can clearly show the presence of extensive tumor within the mediastinum, but lesser degrees of invasion cannot be reliably diagnosed or excluded by either modality. Although CT is accurate in predicting non-invasion of the chest wall and mediastinum, it is less accurate in positively diagnosing invasion of these structures. Glazer et al.[14] correlated three features of the tumor observed in CT with resectability: (1) less than 3 cm of mediastinal contact, (2) maintained fat plane of separation form mediastinum, and (3) less than 90 degrees of circumferential aortic contact. These criteria are useful in predicting resectability but are unreliable evidence for irresectability: inflammatory changes adjacent to the tumor can show identical patterns of extensive contact and loss of the fat plane. Further research is needed to evaluate the potential additional diagnostic impact of intravascular contrast agents when performing a PET/CT.[15]

A peripheral lung tumor may transgress the parietal pleural and invade the ribs and intercostal muscles. Both CT and MRI can clearly show these findings of chest wall invasion. Lesser degrees of invasion, such as limited pleural thickening, are produced not only in invasion but also in inflammation-fibrosis and adherences adjacent to the tumor. PET/CT can provide additional information in these cases.

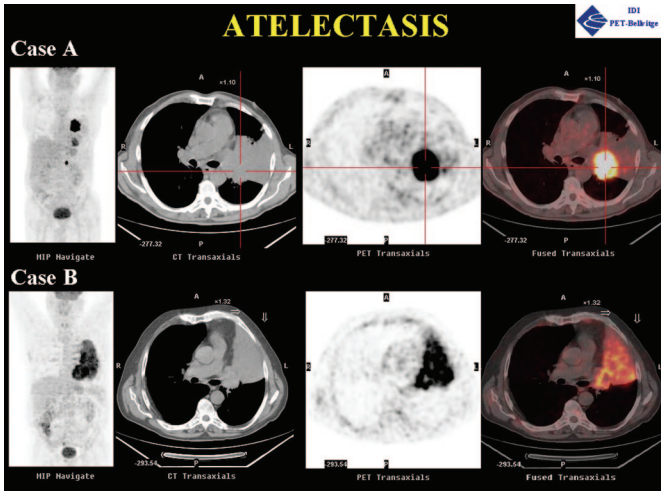

FIGURE 1. Representative positron emission tomography/computed tomography images from two patients with lung cancer associated with atelectasis in which computed tomography cannot delineate the exact localization of the tumor. (A) A 60-year-old man with left lung adenocarcinoma limited to the perihilar region causing distal normometabolic atelectasis. Unsuspected left adrenal hypermetabolic lesion is observed consistent with metastases. (B) A 67-year-old man with squamous cell carcinoma in the upper lobe of left lung where tumor has replaced the lobe showing extensive hypermetabolism (replacement atelectasis).

PET is very effective for staging of mediastinal nodes, without the limitation of the CT in nodes that are less than 1 cm. PET/CT provides exact localization and classification of affected lymph nodes. Although PET/CT is the most accurate technique, false-positive results are sufficiently frequent to require sampling in some cases.[16–18]

Although FDG-PET is the most sensitive technique for detecting extracraneal metastatic disease, PET/CT allows its exact localization so that further therapies can be suitably managed. In a number of patients diagnosed with primary lung cancer, second metachronous tumors are sometimes discovered with PET/CT, mainly localized in the gastrointestinal tract.[11,19–21]

For patients with a suspected recurrence of non–small-cell lung cancer, as the group of Haifa has recently published, PET/CT provides a better anatomic localization of suspicious lesions compared with PET interpreted with side-by-side CT data. This improved diagnostic performance of PET/CT has a further impact of the clinical management of and treatment planning for the patients.[22]

Innovations

The most important innovations in PET/CT in its lung cancer application include (1) the assessment of response and prediction of outcome, (2) the evaluation of small-cell lung

cancer, (3) the radiotherapy planning, and (4) the four-dimensional respiratory gating PET/CT acquisition.[23]

PET/CT is increasingly used to monitor tumor response in patients undergoing chemotherapy and chemoradiotherapy for two reasons. First, because it can assess changes in all the characteristics of tumor lesions, such as the localization, the size, the number of lesions, and the metabolic activity, in a single examination. Second, there is a correlation between FDG uptake and the prediction of tumor response and patient outcome very early in the course of therapy. Treatment may be adjusted according to the chemosensitivity and radiosensitivity of the tumor tissue in an individual patient. Thus, FDG-PET has an enormous potential to reduce the side effects and costs of ineffective therapy. (Figure 2).[24]

It seems likely that PET/CT will play an increasing role in the management of patients with small-cell lung cancer; in staging, radiation therapy planning in limited stage disease, and the assessment of treatment response. Overall, in various studies, PET upgraded limited disease to extensive disease in 8% to 11% and changed treatment planning for patients with presumed limited-stage disease.[25–28] Patients with negative scans after therapy had better long-term survival compared with those who had PET-positive results.[29] (Figure 3).

Integrated PET/CT for radiotherapy planning improves the standardization of volume delineation compared with that of CT alone and may reduce the risk for geographic misses, minimizing the dose radiation applied to non-target organs and changing gross tumor volume and, indeed, planning tumor volume.[30–32]

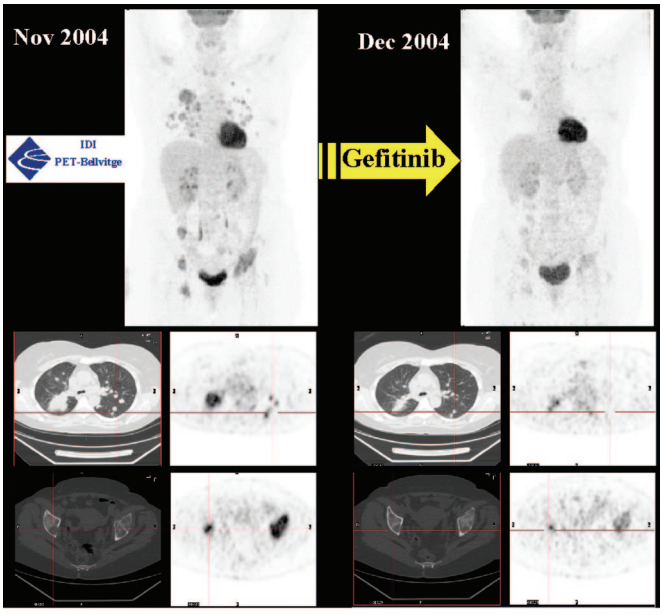

FIGURE 2. This is a baseline positron emission tomography/computed tomography scan of a 51 year-old woman diagnosed with non–small-cell lung cancer showing a mass in the right lung, lymph nodes adenopathies, and multiple pulmonary and bone metastases. After only 1 month of treatment with gefitinib, the positron emission tomography/computed tomography scan revealed an important metabolic response.

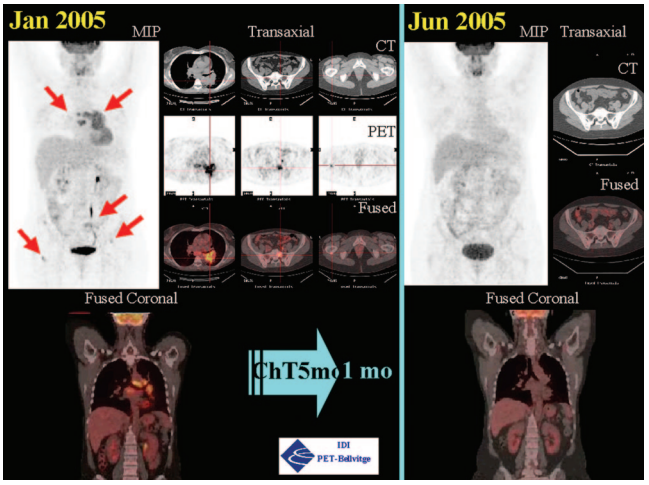

FIGURE 3. A 42-year-old woman with small-cell lung cancer referred for primary staging. Positron emission tomography/computed tomography imaging shows extensive disease involving the left lung, mediastinum, and bone, as shown in the left sacrum and the right femur. She received chemotherapy for 5 months, and restaging with a PET/CT 1 month after the completion of treatment showed a complete remission.

Respiratory motion may reduce the sensitivity of PET in detecting the pulmonary nodules, especially near the diaphragm, as motion artifacts are more frequently encountered. Respiratory motion also involves tumor motion during the respiratory cycle, which affects not only quantification of the tumor but also definition of the planning target volume in the radiotherapy planning. Four-dimensional respiratory gating consists of acquiring the same volume throughout the respiratory cycle. An infrared camera records the patient's natural breathing pattern by tracking the movement of chest sensors during inhalation and exhalation and triggering the acquisition. For lung tumors, the four-dimension respiratory gating allows a better accuracy for tumor delineation as it reduces the partial volume effects. Furthermore, as Nehmeh et al.[33] pointed out, it allows a better quantification of the radiotracer uptake within the lesions as reflected by the more consistent and reliable standardized uptake value measurements. It also improves the detection of pulmonary nodules enhancing its visualization. Four-dimensional respiratory gating also allows an investigator to follow tumor motion during the respiratory cycle. This improves definition of the planning target volume as the location in time of the tumor will be more accurately known. Moreover, the side effects of radiotherapy for the neighboring organs at risk will be reduced.

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REFERENCES

1. Beyer T, Townsend DW, Brun T, et al. A combined PET/CT scanner for clinical oncology. *J Nucl Med* 2000;41:1369–1379.
2. Towsend DW, Beyer T, Blodgett TM. PET/CT scanners: a hardware approach to image fusion. *Sem Nucl Med* 2003;193–204.
3. Truong MT, Erasmus JJ, Munden RF, et al. Focal FDG uptake in mediastinal brown fat mimicking malignancy: a potential pitfall resolved on PET/CT. *AJR Am J Roentgenol* 2004;183:1127–1132.
4. Truong MT, Erasmus JJ, Macapinlac HA, et al. Integrated positron emission tomography/computed tomography in patients with non-small cell lung cancer: normal variants and pitfalls. *J Comput Assist Tomogr* 2006;29:205–209.
5. Lardinois D, Weder W, Hany TF, et al. Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. *N Engl J Med* 2003;348:2500–2507.
6. Antoch G, Stattaus J, Nemat AT, et al. Non-small cell lung cancer: dual-modality PET/CT in preoperative staging. *Radiology* 2003;229: 526–533.
7. Cerfolio RJ, Ojha B, Bryant AS, et al. The accuracy of integrated PET-CT compared with dedicated PET alone for the staging of patients with nonsmall cell lung cancer. *Ann Thorac Surg* 2004;78:1017–1023.
8. Antoch G, Saoudi N, Kuehl H, et al. Accuracy of whole-body dual-modality fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography and computed tomography (FDG-PET/CT) for tumor staging in solid tumors: comparison with CT and PET. *J Clin Oncol* 2004;22: 4357–4368.
9. Shim SS, Lee KS, Kim BT, et al. Non-small cell lung cancer: prospective comparison of integrated FDG PET/CT and CT alone for preoperative staging. *Radiology* 2006;236:1011–1019.
10. Halpern BS, Schiepers C, Weber WA, et al. Presurgical staging of non-small cell lung cancer: positron emission tomography, integrated positron emission tomography/CT, and software image fusion. *Chest* 2006;128:2289–2297.
11. Goerres GW, von Schulthess GK, Steinert HC. Why most PET of lung and head-and-neck cancer will be PET/CT. *J Nucl Med* 2004;45(Suppl 1):66S–71S.
12. Naidich DP, Zerhouni EA, Siegelman SS, Kuhn JP. Lobar collapse. In: Naidich DP, Zerhouni EA, Siegelman SS (Eds.), Computed Tomography and Magnetic Resonance of the Thorax, 2nd ed. New York: Raven Press, 1991. Pp. 222–223.
13. Chapman JD, Bradley JD, Eary JF, et al. Molecular (functional) imaging for radiotherapy applications: an RTOG symposium. *Int J Radiat Oncol Biol Phys* 2003;55:294–301.
14. Glazer HS, Kaiser LR, Anderson DJ, et al. Indeterminate mediastinal invasion in bronchogenic carcinoma: CT evaluation. *Radiology* 1989; 173:37–42.
15. Antoch G, Freudenberg LS, Beyer T, et al. To enhance or not to enhance? 18F-FDG and CT contrast agents in dual-modality 18F-FDG PET/CT. *J Nucl Med* 2004;45(Suppl 1):56S-–65S.
16. Birim O, Kappetein AP, Stijnen T, et al. Meta-analysis of positron emission tomographic and computed tomographic imaging in detecting mediastinal lymph node metastases in nonsmall cell lung cancer. *Ann Thorac Surg* 2006;79:375–382.
17. Cerfolio RJ, Bryant AS, Ojha B, et al. Improving the inaccuracies of clinical staging of patients with NSCLC: a prospective trial. *Ann Thorac Surg* 2006;80:1207–1213.
18. Eloubeidi MA, Cerfolio RJ, Chen VK, et al. Endoscopic ultrasound-guided fine needle aspiration of mediastinal lymph node in patients with suspected lung cancer after positron emission tomography and computed tomography scans. *Ann Thorac Surg* 2006;79:263–268.
19. Ishimori T, Patel PV, Wahl RL. Detection of unexpected additional primary malignancies with PET/CT. *J Nucl Med* 2006;46:752–757.
20. Lardinois D, Weder W, Roudas M, et al. Etiology of solitary extrapulmonary positron emission tomography and computed tomography findings in patients with lung cancer. *J Clin Oncol* 2006;23:6846–6853.
21. Choi JY, Lee KS, Kwon OJ, et al. Improved detection of second primary cancer using integrated [18F] fluorodeoxyglucose positron emission tomography and computed tomography for initial tumor staging. *J Clin Oncol* 2006;23:7654–7659.
22. Keidar Z, Haim N, Guralnik L, et al. PET/CT using 18F-FDG in suspected lung cancer recurrence: diagnostic value and impact on patient management. *J Nucl Med* 2004;45:1640–1646.
23. Detterbeck FC, Vansteenkiste JF, Morris DE, et al. Seeking a home for a PET, part 3: Emerging applications of positron emission tomography imaging in the management of patients with lung cancer. *Chest* 2004; 126:1656-1666.
24. Mac Manus MP, Hicks RJ, Matthews JP, et al. Positron emission tomography is superior to computed tomography scanning for response-assessment after radical radiotherapy or chemoradiotherapy in patients with non-small-cell lung cancer. *J Clin Oncol* 2003;21:1285–1292.
25. Hauber HP, Bohuslavizki KH, Lund CH, et al. Positron emission tomography in the staging of small-cell lung cancer : a preliminary study. *Chest* 2001;119:950–954.
26. Schumacher T, Brink I, Mix M, et al. FDG-PET imaging for the staging and follow-up of small cell lung cancer. *Eur J Nucl Med* 2001;28:483-488.
27. Bradley JD, Dehdashti F, Mintun MA, et al. Positron emission tomography in limited-stage small-cell lung cancer: a prospective study. *J Clin Oncol* 2004;22:3248–3254.
28. Brink I, Schumacher T, Mix M, et al. Impact of [18F]FDG-PET on the primary staging of small-cell lung cancer. *Eur J Nucl Med Mol Imag* 2004;31:1614–1620.
29. Blum R, MacManus MP, Rischin D, et al. Impact of positron emission tomography on the management of patients with small-cell lung cancer: preliminary experience. *Am J Clin Oncol* 2004;27:164–171.
30. Ciernik IF, Dizendorf E, Baumert BG, et al. Radiation treatment planning with an integrated positron emission and computer tomography (PET/CT): a feasibility study. *Int J Radiat Oncol Biol Phys* 2003;57: 853–863.
31. Ashamalla H, Rafla S, Parikh K, et al. The contribution of integrated PET/CT to the evolving definition of treatment volumes in radiation treatment planning in lung cancer. *Int J Radiat Oncol Biol Phys* 2006; 63:1016–1023.
32. van Der Wel A, Nijsten S, Hochstenbag M, et al. Increased therapeutic ratio by 18FDG-PET CT planning in patients with clinical CT stage N2-N3M0 non-small-cell lung cancer: a modeling study. *Int J Radiat Oncol Biol Phys* 2006;61:649–655.
33. Nehmeh SA, Erdi YE, Pan T, et al. Four-dimensional (4D) PET/CT imaging of the thorax. *Med Phys* 2004;31:3179–3186.

