The role of positron emission tomography in the management of non–small cell lung cancer

Abdollah Behzadi, MD, MBA[*†]
Yee Ung, MD[‡]
Val Lowe, MD[§]
Claude Deschamps, MD[¶]

From the *Department of Surgery, The Scarborough Hospital, the †Department of Surgery, Sunnybrook Health Sciences Centre, the ‡Odette Regional Cancer Centre, Department of Radiation Oncology, University of Toronto, Sunnybrook Health Sciences Centre, Toronto, Ont., and the Departments of §Radiology and of ¶General Thoracic Surgery, Mayo Clinic, Rochester, Minn.

Accepted for publication
Feb. 5, 2008

Correspondence to:
Dr. A. Behzadi
3030 Lawrence Ave. E, Ste. 204
Toronto ON M1P 2T7
fax 416 431-0836
abehzadi@tsh.to

The potential use of positron emission tomography (PET) imaging in patients with non–small cell lung cancer (NSCLC) is broadly divided into 5 categories: management of solitary pulmonary nodule, mediastinal lymph node evaluation, detection of metastases, evaluation of response to chemoradiation and detection of recurrence. The purpose of this review is to discuss the current clinical applications of ^{18}F-fluorodeoxyglucose PET in patients with NSCLC and to discuss future applications and developments of this technology.

Les indications possibles de la tomographie à émission de positrons chez les patients atteints de cancer du poumon non à petites cellules se divisent *grosso modo* en 5 catégories : prise en charge des nodules pulmonaires solitaires, évaluation des ganglions lymphatiques médiastinaux, dépistage des métastases, évaluation de la réponse à la chimioradiothérapie et dépistage des récidives. La présente synthèse a pour but de décrire les applications cliniques actuelles de la tomographie à émission de positrons au ^{18}F-fluorodésoxyglucose chez des patients atteints d'un cancer du poumon non à petites cellules et d'aborder les applications et développements futurs de cette technologie.

Despite many advances in the diagnosis, staging and treatment of non–small cell lung cancer (NSCLC), the overall 5-year survival rate of patients with resectable NSCLC is less than 50%.[1] This suboptimal survival rate is likely due to many factors, including the aggressiveness of the specific phenotype, locally advanced disease at presentation and inaccurate pretreatment staging. It is plausible that undetected locoregional and distant micrometastatic disease at the time of presentation results in suboptimal or at times inappropriate treatment and, therefore, decreased stage-specific survival. Accurate clinical staging at the time of diagnosis has many important advantages, of which the following 3 have particular importance:

- it allows for appropriate patient selection for potentially curative surgical and/or nonsurgical therapies,
- it identifies patients who would benefit from neoadjuvant therapy, and
- it allows for more accurate follow-up assessment and detection of locoregional recurrences that might still be amenable to salvage treatment.

In the management of NSCLC, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is an imaging technology with evolving potential. The advantage of FDG-PET lies in its ability to detect metabolic changes in cancer cells even before the manifestation of the anatomic changes commonly identified by conventional imaging modalities such as computed tomography (CT), ultrasonography, magnetic resonance imaging (MRI) and bone scintigraphy. This advantage may help with more accurate staging than is possible with conventional imaging. It may also identify tumours at an earlier stage, assess their response to neoadjuvant therapy and help with follow-up surveillance. The potential capability of PET in assessing the tumour responsiveness to chemotherapy can be used as a prognostic factor, thereby influencing the direction of further management.

The optimal use of FDG-PET in the management of lung cancer continues to evolve. The overall poor prognosis of lung cancer and lack of optimal

treatment for advanced stages of the disease have facilitated rapid integration of this imaging technology in the management of NSCLC. However, its financial burden on health care systems and individual payers has brought its widespread use into question. The purpose of this review is to discuss the current practical applications of FDG-PET in patients with NSCLC, summarizing clinically applicable data. A systematic review of the role FDG-PET in the diagnosis and staging of lung cancer has already been published by one of us (Y.U.).[2]

Basic principles of FDG-PET

^{18}F-fluorodeoxyglucose is a radiolabelled glucose analogue taken up by metabolically active cells that have increased glycolysis capability. This capability is largely related to upregulation of glucose membrane transporters and increased activity of enzymes involved in the glycolytic pathway.[3] Once injected intravenously, FDG diffuses into the extracellular space and subsequently is taken up by cells. In the intracellular space, FDG is phosphorylated to FDG-6-phosphate by hexokinase, the first enzyme of the glycolytic pathway. Since FDG-6-phosphate is not a substrate for the second enzyme, glucose-6-phosphate isomerase, it is not catabolized further and remains trapped in the cells of uptake.[4,5]

The trapped FDG decays by positron emission. The collision of a positron with an electron produces energy in the form of 2 511-KeV photons that travel in opposite directions. The PET scan detects these annihilation photons and is able to construct an image based on the concentration and distribution of the radioisotope emitted from various point sources. This creates PET scan images that can be displayed in coronal, sagittal or transverse manners.

Normal physiologic uptake of FDG takes place in various organs such as the brain, heart, kidneys, bladder and, to a lesser extent, the liver, stomach, colon, spleen and bone marrow (Fig. 1). The cellular concentration of FDG is characterized by a semiquantitative measurement called standardized uptake value (SUV). ^{18}F-fluorodeoxyglucose uptake in a nonphysiologic region with an SUV greater than 2.5 is considered to be suspicious for the presence of cancer.

Non–small cell lung cancer

In dealing with primary NSCLC, pathological diagnosis and clinical staging form the basis for further management and treatment. Pathological diagnosis, which is commonly initiated on discovery of a solitary pulmonary nodule (SPN) or mass, is followed by clinical staging that involves the assessment of mediastinal nodal status and search for distant metastatic disease. The PET scan appears to play a role in assessing an SPN, evaluating mediastinal lymph node involvement and detecting distant metastasis (Fig. 2).

Management of an SPN

An SPN, or coin lesion, is defined as a nonspiculated round lesion smaller than 3 cm in diameter without associated atelectasis or adenopathy.[6] Larger lesions are likely to be cancerous and prompt pathological diagnosis; subsequent resection is usually indicated. However, 70%–75% of nodules that are labelled as indeterminate based on initial history and standard radiological studies may ultimately be cancerous.[7] In view of the primary objectives of managing SPN — namely early detection of lung cancer, avoidance of surgery on benign lesions and efficient use of resources — PET imaging has been shown to help differentiate benign from cancerous lesions as small as 1 cm.[8] The sensitivity, specificity and accuracy of PET in differentiating benign from cancerous SPNs are more than 95%, 75% and 90%, respectively.[9–12] The false-negative rate of PET for SPN was reported to be less than 5% in one study.[13] However, 8 of 20 PET-negative SPNs smaller than 1 cm were proven to be cancerous in another study.[14] The cost-effectiveness of adding PET to standard radiological modalities used in the management of SPN is suggested for those larger than 1 cm,[15,16] when pretest probability of cancer and CT scan findings is discordant, or in patients with intermediate pretest probability who are at high risk for surgical complications.[17] Preliminary analysis of a multicentre cooperative study to determine the accuracy of PET in SPNs larger than 1 cm also suggests higher specificity and the same sensitivity rates as CT scanning.[18]

Positron emission tomography can be an effective tool in managing SPNs larger than 1 cm, especially if more invasive diagnostic modalities such as transthoracic needle aspiration and bronchoscopy fail to provide tissue for definitive diagnosis. For SPNs smaller than 1 cm, only strong uptake of FDG may be of diagnostic value. Despite the information provided by PET that can influence management, no data exist to support improved overall survival when PET is used in the management of SPNs, as is true with other diagnostic procedures and imaging.

Positron emission tomography has some inherent limitations that should be considered when it is used in the clinical setting. Although FDG has high sensitivity for cancerous conditions, there are benign processes that result in abnormal accumulation of FDG and false-positive images.[19–21] These false-positive results are due to conditions where FDG accumulation occurs in metabolically active tissue that is not cancerous. These conditions include infection; chronic or acute granulomatous disease such as sarcoidosis; autoimmune disease such as Grave disease; inflammatory conditions such as postoperative surgical field or radiated field; atherosclerotic plaque; and certain benign tumours such as giant-cell tumour, bony fibrous dysplasia and colonic adenomatous polyps.[22–26] False-negative PET images can also occur for low-metabolism tumours such as bronchioloalveolar carcinomas (up to 60%)[27] and carcinoid tumours (up to 85%).[28,29]

The use of PET in diabetic patients may pose a unique

challenge because the rate of FDG accumulation in tumours is decreased and tumour targeting with FDG is impaired among these patients; therefore, diabetes may reduce the sensitivity of FDG-PET for lung cancer detection.[30] However, it is shown that FDG uptake in lung tumours is not substantially influenced by blood glucose levels in diabetic patients if blood glucose levels are well controlled.[31] The accuracy of PET in diabetic patients, as long as the blood glucose levels are under control, is considered to be the same as in the general population.

Positron emission tomography is a valuable tool to evaluate SPNs; however, one must be aware of the causes of false-positive and false-negative results when interpreting SUV. As a recent study suggests, there is a 24% chance that a suspicious nodule with an SUV of 0–2.5 is cancerous.[32]

Mediastinal lymph node evaluation

Mediastinal lymph node metastasis has a clinically important impact on the course of therapy and prognosis of NSCLC.[33] Anatomic lung resection is the standard treatment for resectable NSCLC without evidence of mediastinal and distant metastasis. In the case of ipsilateral lymph node metastasis (N2), neoadjuvant therapy followed by surgery or chemoradiation therapy with curative intent are the accepted treatments.[34,35]

Traditional mediastinal node assessment is done using a CT scan of the chest and/or mediastinoscopy. A mediastinal node is considered to be abnormal on a CT scan if its shortest axis is greater than 1 cm. In this situation, mediastinoscopy is warranted. The American College of Surgeons Oncology Group Z0050 trial evaluated the addition of PET to routine staging in 303 patients with documented or suspected NSCLC who were found to be surgical candidates.[36] Positron emission tomography was significantly better than CT for the detection of N1 and N2/N3 disease (42% v. 13%, $p = 0.018$ for N1 disease and 58% v. 32%, $p = 0.004$ for N2/N3 disease), with the negative predictive value close to 90%. This advantage was also supported by a meta-analysis that showed that the median sensitivity and specificity for CT were 61% and 79%, respectively, compared with a sensitivity and specificity of 85% and 90%, respectively, for PET.[37] However, the cost-effectiveness of this superiority can only be demonstrated if PET can convincingly replace invasive pathologic evaluation of lymph nodes by transbronchial bronchoscopy, mediastinoscopy or thoracotomy, thereby rendering pathological evaluation of lymph nodes unnecessary (Fig. 3).

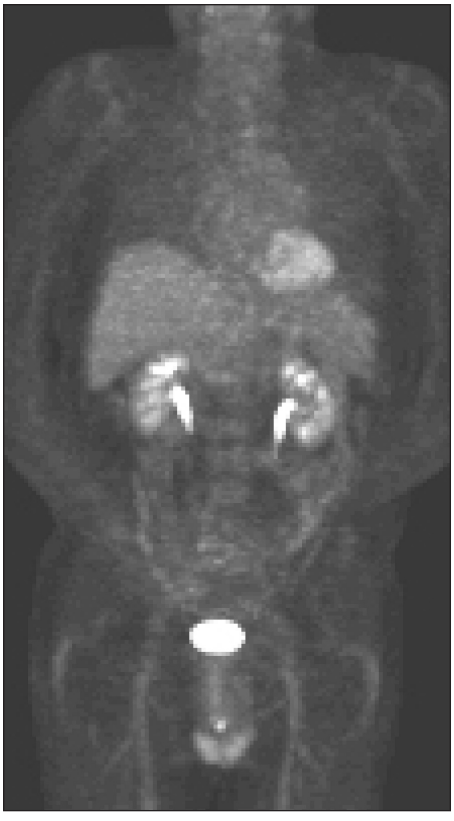

Fig. 1. Coronal maximum intensity projection image of a normal positron emission tomography scan showing the physiologic uptake of ^{18}F-fluorodeoxyglucose in the heart, kidneys and bladder.

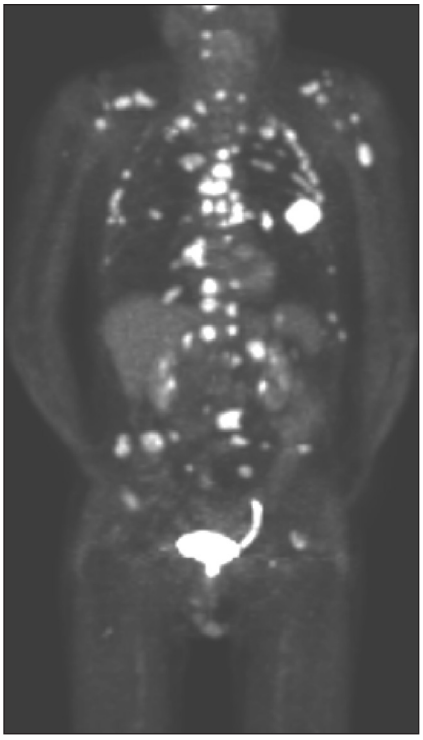

Fig. 2. Images of an abnormal positron emission tomography scan showing cancer in the left lung with extensive mediastinal disease and bone metastasis not detected on bone scan, bone radiographs or computed tomography (CT) scans. Only the lung mass was seen on a CT scan. The patient died 1 month later.

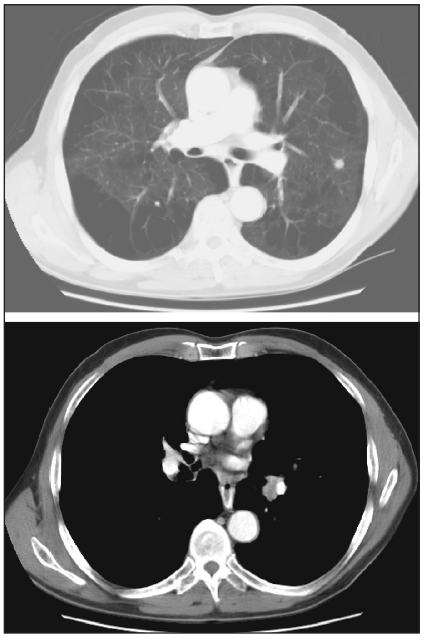

Fig. 3. Computed tomography scans of a calcified nodule in the left lung and borderline mediastinal adenopathy in a symptomatic patient. Bronchoscopy and mediastinoscopy were nondiagnostic. A coronal maximal intensity projection positron emission tomography image showing abnormal ^{18}F-fluorodeoxyglucose uptake only in the left hilum. On thoracotomy, hilar nodes were positive for mixed small- and large-cell lung cancer. The left nodule was a necrotizing granuloma.

When compared with mediastinoscopy, the sensitivity, specificity, positive and negative predictive values and accuracy for PET scan for N2/N3 disease were 64.4%, 77.1%, 44.6%, 88.3% and 74.3%, respectively.[38] Therefore, a positive PET scan result for mediastinal nodes requires pathological confirmation.[39] However, the result of a negative PET scan may negate the requirement of mediastinoscopy for mediastinal nodes that were negative on CT scan.[40] This conclusion is supported by a recent meta-analysis reporting a post-test probability for N2 disease of 5% for lymph nodes measuring 10–15 mm on CT scans in patients with negative PET scan results.[41]

Detection of distant metastases

Metastases from NSCLC occur mostly in the brain, bones, liver and adrenal glands in decreasing order.[42] As discussed in the section on PET limitations, this imaging modality has low sensitivity for detecting brain metastases because of the high rate of glucose uptake by brain cells, and therefore it is not recommended for this purpose. Up to 10% of patients with NSCLC have unilateral adrenal mass at presentation,[43] of which about 60% are benign.[44] Therefore, a number of patients with localized NSCLC and an asymptomatic unilateral adrenal mass require percutaneous biopsy. Positron emission tomography can further decrease the need for biopsy for PET-negative adrenal lesions as its sensitivity and specificity for detecting metastatic adrenal disease are 93%–100%, and 80%–96%, respectively.[45,46] The overall accuracy of PET for adrenal lesions identified on CT scans or MRIs is reported to be 92%.[47] A PET-positive adrenal lesion, however, should still undergo biopsy to confirm metastatic disease if this is the sole site of metastases.

Bone involvement is usually assessed by ^{99}Tc radionuclide technetium isotope medronate methylene diphosphonate bone scintigraphy, which has a sensitivity, specificity and accuracy of around 90%, 60% and 66%, respectively. Positron emission tomography is reported to have similar sensitivity as bone scintigraphy (90%), but a higher specificity (98%) and accuracy (96%).[48] In another study, the accuracy of PET and bone scintigraphy were 94% and 85%, respectively ($p < 0.05$), sensitivity values were 91% and 75%, respectively, and specificity values were 96% and 95%, respectively.[49] Therefore, the findings of bone scintigraphy may, at best, replicate information that can be obtained using PET.

Unsuspected liver metastases occur in 3%–6% of patients with lung cancer who have normal hepatic function.[50] The conventional methods for detecting liver metastases are ultrasonography, CT and/or MRI. Although there are no specific series on the use of PET in detecting liver metastases in patients with NSCLC, PET is reported to detect liver metastases in up to 2% of patients who were thought to be free of liver metastases based on conventional imaging.[51] Overall, the sensitivity of the liver metastasis detection in patients with other cancers is reported to be higher with PET than other modalities.[52] Therefore, by inference, one may conclude that information provided by PET can help characterize indeterminate hepatic lesions suspected of metastases and, in a small number of patients, detect a missed hepatic lesion.

In the American College of Surgeons Oncology Group Z0050 trial,[36] 6.3% of patients with documented or suspected NSCLC who were found to be surgical candidates based on routine staging procedures had unsuspected metastatic disease or a second primary cancer. Distant metastatic disease found in 6.6% of patients was subsequently shown to be benign. By correctly identifying advanced disease (stages IIIA, IIIB and IV) or benign lesions, it was concluded that the use of PET helped to potentially avoid unnecessary thoracotomy in 20% of patients. This conclusion, however, is challenged by a recent prospective randomized controlled trial involving patients with stage I and II NSCLC.[53] In this trial, 92 patients were assigned to the no PET group and 91 were assigned to the PET group. Compared with conventional staging, PET upstaged 22 patients, confirmed staging in 61 and staged 2 patients as benign. Stage IV disease was detected in only 2 patients. This modality led to further investigation or a change in clinical management in 13% of patients and provided information that could have affected management in a further 13% of patients. There was no significant difference between the trial arms in the number of thoracotomies avoided ($p = 0.2$). Although PET was useful in the clinical management of patients with NSCLC in this group of patients with predominantly stage I disease, its addition did not result in fewer thoracotomies in patients who had careful conventional staging.

Determination of response to chemoradiation

Neoadjuvant chemoradiation therapy followed by curative resection is emerging as an acceptable treatment for resectable NSCLC with pathologically proven nonbulky ipsilateral paratracheal and/or subcarinal mediastinal nodal metastasis (stage IIIa).[54] Assessment of response to neoadjuvant therapy may in fact result in the alteration of the course of management and provide prognostic information. This information can also contribute to the management of patients who are offered definitive chemoradiation (stage IIIb and unresectable stage IIIa) (Fig. 4).

Weber and colleagues[55] prospectively evaluated the role of PET in predicting response to chemotherapy in 57 patients with advanced NSCLC who were scheduled to undergo platinum-based chemotherapy. Patients were studied using FDG-PET before and after the first cycle of therapy. A reduction of tumour FDG uptake by more than 20%, as assessed by SUV, was used as a criterion for a metabolic response. The median times to progression and overall survival were significantly longer for metabolic

responders than for metabolic nonresponders (163 v. 54 d, $p < 0.001$ and 252 v. 151 d, $p = 0.005$, respectively). Cerfolio and colleagues[56] also suggested that when the SUV decreased by 80% or more, a complete pathologic response could be predicted with a sensitivity of 90%, specificity of 100% and accuracy of 96%, irrespective of cell type or neoadjuvant treatment.

The Leuven Lung Cancer Group[57] examined the value of PET in predicting long-term oncologic outcomes. They analyzed SUV and survival in 91 patients who underwent complete surgical resection. Patients with a resected tumour smaller than 3 cm had an expected 2-year survival of 86% if the SUV was below 7 and 60% if it was greater than 7. Nearly all resected tumours larger than 3 cm had SUVs greater than 7 and an expected 2-year survival of 43%. An SUV of 7 was found to have the best discriminative value for survival. These survival differences are also observed when SUV of primary NSCLC was taken into account in more recent studies.[58,59]

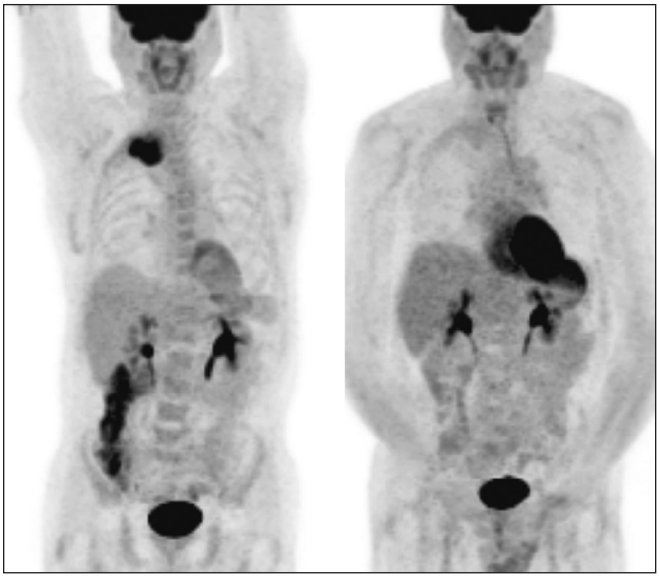

Fig. 4. Positron emission tomography scan showing the coronal maximum intensity projection view of locally advanced non–small cell lung cancer (left) before and (right) after completion of neoadjuvant therapy. Decreased ^{18}F-fluorodeoxyglucose uptake suggests tumour response to therapy.

Detection of recurrence

One of the most important objectives during follow-up after curative treatment of NSCLC is detection of recurrence. Most of the current imaging techniques are sensitive for structural changes but have limited ability to distinguish scars from viable tumours. The sensitivity and specificity of PET for detecting recurrence of primary NSCLC are shown to be 93%–100% and 89%–92%, respectively.[60–62] These data suggest that PET is superior to CT, with a sensitivity of 71% and specificity of 95% for detecting recurrence. A recent study has also suggested that SUV in recurrent tumours is an independent prognostic factor in patients with recurrent NSCLC.[59]

It should be emphasized that the apparent superiority of PET over standard imaging modalities in detecting recurrence is based on retrospective pilot studies with small numbers of patients. Therefore, the clinical significance of this potential superiority is still unknown, as early detection of local recurrence is of value only if there is a salvage therapy available and if there would be potentially no advantage to the early detection of distant recurrence.

Future applications and developments

Role of integrated PET/CT in the management of NSCLC

Integrated PET/CT technology has the advantage of combining the metabolic and anatomic images obtained form PET and CT scans and providing the clinicians with fusion images (Fig. 5). Whether integrated PET/CT scans substantially improve the accuracy of imaging in patients with lung cancer is the subject of many investigations.

The accuracy of clinical staging in patients with stage I, II and III NSCLC, when compared with pathologic stage, is shown to be 68%, 84% and 74%, respectively.[63] A recent study retrospectively evaluated the accuracy of integrated PET/CT scans in the staging of a suggestive lung lesion and compared the results with the accuracy of CT alone, PET alone and visually correlated PET/CT. Integrated

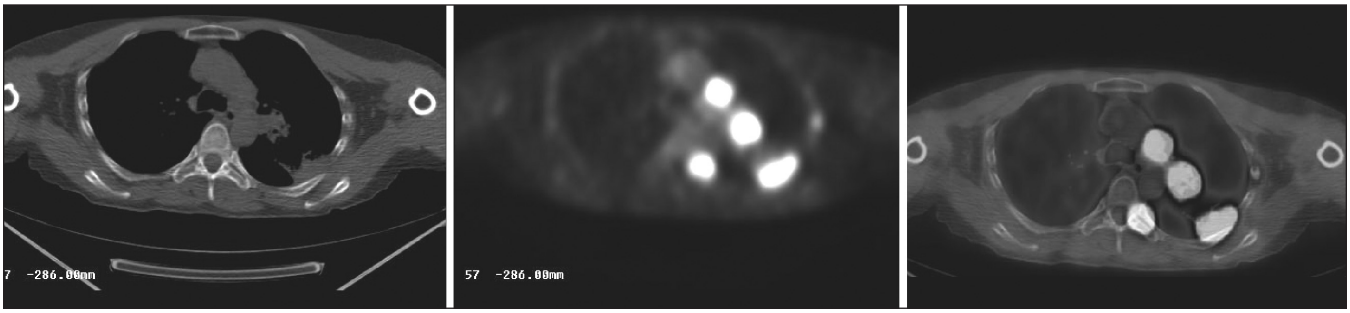

Fig. 5. Integrated positron emission tomography/computed tomography scan demonstrating cancer in the left lung with chest wall involvement and metastasis to left hilar and medistinal nodes and the left thoracic spine and ribs.

PET/CT correctly predicted the tumour, node, metastasis (TNM) status and the stage in 86%, 80%, 98% and 70% of patients, respectively. The TNM status and the stage were correctly predicted in 68%, 66%, 88% and 46% of patients, respectively, with CT alone; 46%, 70%, 96% and 30% of patients, respectively, with PET alone; and 72%, 68%, 96% and 54% of patients, respectively with visually correlated PET/CT.[64] Other studies have also reported similar findings, concluding that integrated PET/CT is more accurate than PET alone, CT alone or visually correlated PET/CT in tumour staging, node staging and detection of metastases.[65–67]

In evaluating the recurrence of NSCLC, one study reported that the sensitivity, specificity and positive and negative predictive values of integrated PET/CT for diagnosis of recurrence were 96%, 82%, 89% and 93%, respectively, compared with 96%, 53%, 75% and 90%, respectively, for PET alone.[68]

Integrated PET/CT, therefore, has the potential to become the new standard approach to imaging in the diagnosis and management of patients with NSCLC. Whether this technology will replace current imaging modalities (i.e., CT scan alone, mediastinoscopy) is debatable.

Novel traces for PET

The accuracy of PET is a function of FDG, its radiolabelled molecular marker, whose specificity is less than ideal. In an attempt to increase this specificity, other markers are being investigated.[69–72] New tracers that have shown promise in early clinical studies include ^{18}F-fluorothymidine, a proliferation marker that might give better specificity in the assessment of SPNs or better accuracy in the evaluation of early response; 11C-Choline, a marker that looks at cell membrane synthesis; (99m)Tc-Annexin V, or Apomate, an apoptosis imaging agent that could be correlated with overall and progression-free survival in phase I data; and ^{18}F-fluoromisonidazole, which can be used to quantify regional hypoxia in human tumours using PET.[73,74] However, to date, none of these tracers under development has proved superior to FDG in published data and no tumour-specific radiotracer for NSCLC has been identified. The development of such a marker would greatly improve the accuracy of PET imaging in the management of NSCLC.

Radiation treatment planning

The potential functional enhancement by PET combined with future advances in integrated PET/CT scans may also play an important role in radiotherapy treatment planning[75] and in targeted molecular therapy of NSCLC.[73] Another development that has shown a potential role in the management of NSCLC is virtual bronchoscopy using data sets from PET/CT. Data with this technology have been limited but are encouraging.[76]

The use of PET in radiation treatment planning may lead to further changes in patient management owing to upstaging the extent of disease, changing treatment intent from radical radiation to palliative treatment, increasing the radiation field size owing to the finding of unsuspected mediastinal node involvement not seen on CT scans, decreasing the treatment field size owing to better localization of the tumour in areas of associated atelectasis or postobstructive pneumonitis[77,78] and decreasing interobserver variation in target definition.[79,80]

Canadian clinical trials involving FDG-PET

In the United States, the Centers for Medicare and Medicaid Services have approved reimbursement for PET use in staging and restaging of NSCLC. In Canada, no national policy has been adopted with regard to health care coverage of the cost of PET in the management of NSCLC. The Ontario PET scan trials, ELPET and PET START, are prospective randomized clinical trials currently underway. These trials collectively are designed to assess the application of PET in the staging of NSCLC, its effect on overall survival, the prognostic factor of SUV of the index lesion before treatment, accuracy of mediastinal staging and cost-effectiveness of PET use. It is hoped that the outcomes of these trials would further define the role of PET in the management of NSCLC and facilitate the determination of optimal therapy for this prevalent cancer.

CONCLUSION

We have shown the potential applications of FDG-PET in patients with NSCLC. Positron emission tomography is a potentially powerful imaging technology, and clinicians need to determine how best to integrate this tool in the management of NSCLC to improve patient outcomes while maintaining the financial integrity of health care systems.

Competing interests: None declared.

Contributors: Drs. Behzadi, Ung and Deschamps designed the review. Drs. Behzadi and Lowe acquired data, which Dr. Deschamps analyzed. Drs. Behzadi and Ung wrote the article, which Drs. Lowe and Deschamps reviewed. All authors gave final approval for publication.

References

1. Yang P, Allen MS, Aubry MC, et al. Clinical features of 5,628 primary lung cancer patients: experience at Mayo Clinic from 1997 to 2003. *Chest* 2005;128:452-62.
2. Ung YC, Maziak DE, Vanderveen JA, et al.; Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care. 18Fluorodeoxyglucose positron emission tomography in the diagnosis and staging of lung cancer: a systematic review. *J Natl Cancer Inst* 2007;99:1753-67.

3. Hatanaka M. Transport of sugar in tumor cell membranes. *Biochim Biophys Acta* 1974;355:77-104.
4. Nolop KB, Rhodes CG, Brudin LH, et al. Glucose utilization in vivo by human pulmonary neoplasms. *Cancer* 1987;60:2682-9.
5. Rigo P, Paulus P, Kaschten BJ, et al. Oncological applications of positron emission tomography with fluorine-18 fluorodeoxyglucose. *Eur J Nucl Med* 1996;23:1641-74.
6. Zerhouni EA, Stitik FP, Siegelman SS, et al. CT of the pulmonary nodule: a cooperative study. *Radiology* 1986;160:319-27.
7. Ost D, Fein A. Evaluation and management of the solitary pulmonary nodule. *Am J Respir Crit Care Med* 2000;162:782-7.
8. Marom EM, Sarvis S, Herndon JE II, et al. T1 lung cancers: sensitivity of diagnosis with fluorodeoxyglucose PET. *Radiology* 2002;223: 453-9.
9. Gould MK, Maclean CC, Kuschner WG, et al. Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. *JAMA* 2001;285:914-24.
10. Fischer BM, Mortensen J, Hojgaard L. Positron emission tomography in the diagnosis and staging of lung cancer: a systematic, quantitative review. *Lancet Oncol* 2001;2:659-66.
11. Coleman RE. PET in lung cancer. *J Nucl Med* 1999;40:814-20.
12. Prauer HW, Weber WA, Romer W, et al. Controlled prospective study of positron emission tomography using the glucose analogue [18f]fluorodeoxyglucose in the evaluation of pulmonary nodules. *Br J Surg* 1998;85:1506-11.
13. Gupta NC, Maloof J, Gunel E. Probability of malignancy in solitary pulmonary nodules using fluorine-18-FDG and PET. *J Nucl Med* 1996;37:943-8.
14. Nomori H, Watanabe K, Ohtsuka T, et al. Evaluation of F-18 fluorodeoxyglucose (FDG) PET scanning for pulmonary nodules less than 3 cm in diameter, with special reference to the CT images. *Lung Cancer* 2004;45:19-27.
15. Lejeune C, Al Zahouri K, Woronoff-Lemsi MC, et al. Use of a decision analysis model to assess the medicoeconomic implications of FDG PET imaging in diagnosing a solitary pulmonary nodule. *Eur J Health Econ* 2005;6:203-14.
16. Detterbeck FC, Falen S, Rivera MP, et al. Seeking a home for a PET, part 1: defining the appropriate place for positron emission tomography imaging in the diagnosis of pulmonary nodules or masses. *Chest* 2004;125:2294-9.
17. Gould MK, Sanders GD, Barnett PG, et al. Cost-effectiveness of alternative management strategies for patients with solitary pulmonary nodules. *Ann Intern Med* 2003;138:724-35.
18. Fletcher JW; for the VA SNAP Cooperative Studies Group. PET for the evaluation of solitary pulmonary nodules. *J Nucl Med* 2009 Jan. 21 [Epub ahead of print].
19. Stumpe KD, Dazzi H, Schaffner A, et al. Infection imaging using whole-body FDG-PET. *Eur J Nucl Med* 2000;27:822-32.
20. Bicik I, Bauerfeind P, Breitbach T, et al. Inflammatory bowel disease activity measured by positron-emission tomography. *Lancet* 1997; 350:262.
21. Lewis PJ, Salama A. Uptake of fluorine-18-deoxyglucose in sarcoidosis. *J Nucl Med* 1994;35:1647-9.
22. Yasuda S, Shothsu A, Ide M, et al. High fluorine-18-deoxyglucose uptake in sarcoidosis. *Clin Nucl Med* 1996;21:983-4.
23. Chen YK, Chen YL. Elevated F-18 FDG uptake in the thymus in Graves' disease. *Clin Nucl Med* 2003;28:142-3.
24. Rudd JH, Warburton EA, Fryer TD, et al. Imaging atherosclerotic plaque inflammation with [^{18}F]-fluorodeoxyglucose positron emission tomography. *Circulation* 2002;105:2708-11.
25. Aoki J, Watanabe H, Shinozaki T, et al. FDG PET of primary benign and malignant bone tumors: standardized uptake value in 52 lesions. *Radiology* 2001;219:774-7.
26. Kamel EM, Thumshirn M, Truninger K, et al. Significance of incidental ^{18}F-FDG accumulations in the gastrointestinal tract in PET/CT: correlation with endoscopic and histopathologic results. *J Nucl Med* 2004;45:1804-10.
27. Heyneman LE, Patz EF. PET imaging in patients with bronchioloalveolar cell carcinoma. *Lung Cancer* 2002;38:261-6.
28. Daniels CE, Lowe VJ, Aubry MC, et al. The utility of FDG-PET in the evaluation of carcinoid tumors presenting as pulmonary nodules. *Chest* 2007;131:255-60.
29. Erasmus JJ, McAdams HP, Patz EF Jr, et al. Evaluation of primary pulmonary carcinoid tumors using FDG PET. *AJR Am J Roentgenol* 1998;170:1369-73.
30. Torizuka T, Zasadny KR, Wahl RL. Diabetes decreases FDG accumulation in primary lung cancer. *Clin Positron Imaging* 1999;2:281-7.
31. Gorenberg M, Hallett WA, O'Doherty MJ. Does diabetes affect [(18)F]FDG standardised uptake values in lung cancer? *Eur J Nucl Med Mol Imaging* 2002;29:1324-7.
32. Bryant AS, Cerfolio RJ. The maximum standardized uptake values on integrated FDG-PET/CT is useful in differentiating benign from malignant pulmonary nodules. *Ann Thorac Surg* 2006;82:1016-20.
33. Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. *Chest* 1997;111:1718-23.
34. Martini N, Kris MG, Ginsberg RJ. The role of multimodality therapy in locoregional non-small cell lung cancer. *Surg Oncol Clin N Am* 1997;6:769-91.
35. Vansteenkiste J, De Leyn P, Deneffe G, et al. Present status of induction treatment in stage IIIA-N2 non-small cell lung cancer: a review. The Leuven Lung Cancer Group. *Eur J Cardiothorac Surg* 1998;13:1-12.
36. Reed CE, Harpole DH, Posther KE, et al. Results of the American College of Surgeons Oncology Group Z0050 trial: the utility of positron emission tomography in staging potentially operable non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2003;126:1943-51.
37. Gould MK, Kuschner WG, Rydzak CE, et al. Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non-small-cell lung cancer: a meta-analysis. *Ann Intern Med* 2003;139:879-92.
38. Gonzalez-Stawinski GV, Lemaire A, Merchant F, et al. A comparative analysis of positron emission tomography and mediastinoscopy in staging non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2003; 126:1900-5.
39. Cerfolio RJ, Ojha B, Bryant AS, et al. The role of FDG-PET scan in staging patients with nonsmall cell carcinoma. *Ann Thorac Surg* 2003; 76:861-6.
40. Detterbeck FC, Falen S, Rivera MP, et al. Seeking a home for a PET, part 2: defining the appropriate place for positron emission tomography imaging in the staging of patients with suspected lung cancer. *Chest* 2004;125:2300-8.
41. de Langen AJ, Raijmakers P, Riphagen I, et al. The size of mediastinal lymph nodes and its relation with metastatic involvement: a meta-analysis. *Eur J Cardiothorac Surg* 2006;29:26-9.
42. Quint LE, Tummala S, Brisson LJ, et al. Distribution of distant metastases from newly diagnosed non-small cell lung cancer. *Ann Thorac Surg* 1996;62:246-50.
43. Klein JS, Webb WR. The radiologic staging of lung cancer. The radiologic staging of lung cancer. *J Thorac Imaging* 1991;7:29-47.
44. Ettinghausen SE, Burt ME. Prospective evaluation of unilateral adrenal masses in patients with operable non-small-cell lung cancer. *J Clin Oncol* 1991;9:1462-6.
45. Erasmus JJ, Patz EF Jr, McAdams HP, et al. Evaluation of adrenal masses in patients with bronchogenic carcinoma using 18F-fluorodeoxyglucose positron emission tomography. *AJR Am J Roentgenol* 1997;168:1357-60.
46. Jana S, Zhang T, Milstein DM, et al. FDG-PET and CT characterization of adrenal lesions in cancer patients. *Eur J Nucl Med Mol Imaging* 2006;33:29-35.
47. Kumar R, Xiu Y, Yu JQ, et al. 18F-FDG PET in evaluation of adrenal lesions in patients with lung cancer. *J Nucl Med* 2004;45: 2058-62.

48. Bury T, Barreto A, Daenen F, et al. Fluorine-18 deoxyglucose positron emission tomography for the detection of bone metastases in patients with non-small cell lung cancer. *Eur J Nucl Med* 1998;25: 1244-7.
49. Cheran SK, Herndon JE II, Patz EF Jr. Comparison of whole-body FDG-PET to bone scan for detection of bone metastases in patients with a new diagnosis of lung cancer. *Lung Cancer* 2004;44:317-25.
50. Pagani JJ. Non-small cell lung carcinoma adrenal metastases. Computed tomography and percutaneous needle biopsy in their diagnosis. *Cancer* 1984;53:1058-60.
51. MacManus MP, Hicks RJ, Matthews JP, et al. High rate of detection of unsuspected distant metastases by pet in apparent stage III non-small-cell lung cancer: implications for radical radiation therapy. *Int J Radiat Oncol Biol Phys* 2001;50:287-93.
52. Kinkel K, Lu Y, Both M, et al. Detection of hepatic metastases from cancers of the gastrointestinal tract by using noninvasive imaging methods (US, CT, MR imaging, PET): a meta-analysis. *Radiology* 2002;224:748-56.
53. Viney RC, Boyer MJ, King MT, et al. Randomized controlled trial of the role of positron emission tomography in the management of stage I and II non-small-cell lung cancer. *J Clin Oncol* 2004;22:2357-62.
54. Lorent N, De Leyn P, Lievens Y, et al. Long-term survival of surgically staged IIIA-N2 non-small-cell lung cancer treated with surgical combined modality approach: analysis of a 7-year prospective experience. *Ann Oncol* 2004;15:1645-53.
55. Weber WA, Petersen V, Schmidt B, et al. Positron emission tomography in non-small-cell lung cancer: prediction of response to chemotherapy by quantitative assessment of glucose use. *J Clin Oncol* 2003;21:2651-7.
56. Cerfolio RJ, Bryant AS, Winokur TS, et al. Repeat FDG-PET after neoadjuvant therapy is a predictor of pathologic response in patients with non-small cell lung cancer. *Ann Thorac Surg* 2004;78:1903-9.
57. Vansteenkiste JF, Stroobants SG, Dupont PJ, et al. Prognostic importance of the standardized uptake value on (18)F-fluoro-2-deoxy-glucose-positron emission tomography scan in non-small-cell lung cancer: an analysis of 125 cases. Leuven Lung Cancer Group. *J Clin Oncol* 1999;17:3201-6.
58. Downey RJ, Akhurst T, Gonen M, et al. Preoperative F-18 fluorodeoxyglucose positron emission tomography maximal standardized uptake value predicts survival after lung cancer resection. *J Clin Oncol* 2004;22:3255-60.
59. Higashi K, Ueda Y, Arisaka Y, et al. 18F-FDG uptake as a biologic prognostic factor for recurrence in patients with surgically resected non-small cell lung cancer. *J Nucl Med* 2002;43:39-45.
60. Bury T, Corhay JL, Duysinx B, et al. Value of FDG-PET in detecting residual or recurrent nonsmall cell lung cancer. *Eur Respir J* 1999; 14:1376-80.
61. Hellwig D, Groschel A, Graeter TP, et al. Diagnostic performance and prognostic impact of FDG-PET in suspected recurrence of surgically treated non-small cell lung cancer. *Eur J Nucl Med Mol Imaging* 2006;33:13-21.
62. Hicks RJ, Kalff V, MacManus MP, et al. The utility of (18)F-FDG PET for suspected recurrent non-small cell lung cancer after potentially curative therapy: impact on management and prognostic stratification. *J Nucl Med* 2001;42:1605-13.
63. Cerfolio RJ, Bryant AS, Ojha B, et al. Improving the inaccuracies of clinical staging of patients with NSCLC: a prospective trial. *Ann Thorac Surg* 2005;80:1207-13.
64. De Wever W, Ceyssens S, Mortelmans L, et al. Additional value of PET-CT in the staging of lung cancer: comparison with CT alone, PET alone and visual correlation of PET and CT. *Eur Radiol* 2007; 17:23-32.
65. 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;348:2500-7.
66. 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;22:4357-68.
67. 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* 2005;128:2289-97.
68. 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;45:1640-6.
69. Yap CS, Czernin J, Fishbein MC, et al. Evaluation of thoracic tumors with 18F-fluorothymidine and 18F-fluorodeoxyglucose positron emission tomography. *Chest* 2006;129:393-401.
70. Pal A, Glekas A, Doubrovin M, et al. Molecular imaging of EGFR kinase activity in tumors with 124I-labeled small molecular tracer and positron emission tomography. *Mol Imaging Biol* 2006;8:262-77.
71. Sandblom G, Sorensen J, Lundin N, et al. Positron emission tomography with C11-acetate for tumor detection and localization in patients with prostate-specific antigen relapse after radical prostatectomy. *Urology* 2006;67:996-1000.
72. Cho SY, Polster J, Engles JM, et al. In vitro evaluation of adenosine 5′-monophosphate as an imaging agent of tumor metabolism. *J Nucl Med* 2006;47:837-45.
73. Vansteenkiste JF, Stroobants SG. Positron emission tomography in the management of non-small cell lung cancer. *Hematol Oncol Clin North Am* 2004;18:269-88.
74. Tian M, Zhang H, Oriuchi N, et al. Comparison of 11C-choline PET and FDG PET for the differential diagnosis of malignant tumors. *Eur J Nucl Med Mol Imaging* 2004;31:1064-72.
75. Lavrenkov K, Partridge M, Cook G, et al. Positron emission tomography for target volume definition in the treatment of non-small cell lung cancer. *Radiother Oncol* 2005;77:1-4.
76. Seemann MD, Schaefer JF, Englmeier KH. Virtual positron emission tomography/computed tomography-bronchoscopy: possibilities, advantages and limitations of clinical application. *Eur Radiol* 2007; 17:709-15.
77. Mah K, Caldwell CB, Ung YC, et al. The impact of 18FDG-PET on target and critical organs in CT based treatment planning of patients with poorly defined non-small cell lung carcinoma: a prospective study. *Int J Radiat Oncol Biol Phys* 2002;52:339-50.
78. Bradley J, Thorstad WL, Mutic S, et al. Impact of FDG-PET on radiation therapy volume delineation in non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2004;59:78-86.
79. Caldwell CB, Mah K, Ung YC, et al. Observer variation in contouring gross tumor volume in patients with poorly defined non-small-cell lung tumors on CT: the impact of 18FDG-hybrid PET fusion. *Int J Radiat Oncol Biol Phys* 2001;51:923-31.
80. Fox JL, Rengan R, O'Meara W, et al. Does registration of PET and planning CT images decrease interobserver and intraobserver variation in delineating tumor volumes for non-small-cell lung cancer? *Int J Radiat Oncol Biol Phys* 2005;62:70-5.