INVITED COMMENTARY

Can ^{11}C-Methionine Play a Role in Lung Cancer Staging?

Up to 30% of patients who have thoracotomies for lung cancer have unexpected regional extension or distant metastases at the time of surgery. Few situations are more devastating to a thoracic surgeon when attempting to do a lobectomy with intent to cure, than to realize that he/she is dealing with a nonresectable lung cancer. Which diagnostic imaging methods could prevent patients with stage IIIb and stage IV from undergoing surgery?

CT, the standard preoperative staging procedure for non–small cell lung cancer (NSCLC), has a sensitivity of 55%–65% and a specificity of 65%–75%. The other recommended procedure for preoperative staging is PET using FDG. The superiority of FDG PET, especially in diagnosing hilar and mediastinal lymph node metastases, has been sufficiently demonstrated (*1–3*).

In this issue of the *Journal of Nuclear Medicine*, Yasukawa et al. (*4*) report on "The usefulness of PET with ^{11}C-methionine for the detection of hilar and mediastinal lymph node metastasis in lung cancer." Their article deserves a closer look, considering that CT and FDG PET are far from being perfect. Any improvement in noninvasive preoperative staging might help to avoid mediastinoscopies and—most important—unnecessary thoracotomies.

CT shows invasive disease effectively, but it is less sensitive in detecting lymph node metastases. The survey of McLoud et al. (*5*) of CT for staging lung cancer found 64% true-positive cases compared with only 44% true-positive mediastinal lymph nodes. The CT criterion for positive lymph nodes is based on size, using a 1-cm dimension in the short axis as cutoff. This makes CT less sensitive than surgical lymph node sampling, which includes nonpalpable lymph nodes and nodes <1 cm and has the benefit of histologic examination.

According to Lewis et al. (*6*) and Valk et al. (*7*), whole-body PET frequently detects occult metastases and alters treatment in up to 40% of cases. FDG PET can reduce the number of mediastinoscopies and at the same time not deny the chance for curative resection (*8*). One problem with FDG PET is false-positive results that are mostly the result of inflammatory and infectious processes such as active tuberculosis, fungal infections, sarcoidosis, histoplasmosis, granulomas, etc. (*2,9–12*). This nonspecific nature of FDG accumulation needs to be further investigated.

In 1983 Kubota et al. (*13*) suggested ^{11}C-methionine as a radiotracer for lung cancer and mediastinal lymph nodes, and now Yasukawa et al. propose ^{11}C-methionine in conjunction with newer PET technology. The basis for considering ^{11}C-methionine for staging lung cancer is the tumor affinity of this amino acid reflecting "the metabolic demand for amino acids in cancer cells." The study of Yasukawa et al. (*4*) certainly has scientific merit but suffers from some methodologic problems, such as possible bias in image interpretation (CT and PET images interpreted by 1 radiologist), somewhat vague criteria for positive lymph nodes by PET, and a nonvalidated coregistration method. There is also some concern regarding the slice thickness of the PET and CT scanners, image resolution, and partial-volume effect problems that are not addressed in great depth. Also, the kinetics of ^{11}C-methionine, the rate of uptake, washout, residence time, and catabolism are not discussed in any detail. Nevertheless, amino acid PET data acquisition 22 min after injection and using tumor-to-muscle ratios (TMRs) as an indicator of "uptake" constitute an acceptable approach. For positive lymph nodes, the TMR was 5.15 ± 1.69, compared with 2.91 ± 0.76 for nonmetastatic lymph nodes ($P < 0.0001$). It is not clear how the regions of interest over negative lymph nodes were chosen or how lymph nodes without methionine activity could be removed. Yet, according to the authors, CT and PET detected all removed lymph nodes. It would also be of interest to know the TMR for the primary lesions.

The results of this comparative study show a remarkable difference between CT, with a positive predictive value (PPV) for lymph node metastases of 57.6%, a negative predictive value (NPV) of 81.7%, a sensitivity of 52.8%, a specificity of 84%, and an accuracy of 75.4%, compared with PET, which has a PPV of 79.5%, NPV of 94.3%, sensitivity of 86.9%, specificity of 91.1%, and accuracy of 89.7%. The receiver operating characteristic analysis for the TMRs resulted in an optimal cutoff of 4.1. One of the main findings in this study is the high negative predictive value (10/14) of ^{11}C-methionine. There were 4 of 25 false-positive results in medium-sized lymph nodes and 4 of 14 in large lymph nodes. Interestingly, there were no "specific histologic findings" in false-positive lymph nodes.

In 1992 Kubota et al. (*14*) suggested considering other agents such as amino acids to distinguish between reactive inflammatory changes and neoplastic activity. Miyazawa et al. (*15*) showed a relationship between ^{11}C-methionine uptake and tumor growth rate and showed a high NPV of ^{11}C-methionine

Received Aug. 10, 1999; revision accepted Aug. 18, 1999.

For correspondence or reprints contact: Karl F. Hubner, MD, UTMC Knoxville, Department of Radiology, 1924 Alcoa Hwy., Knoxville, TN 37920-6999.

PET. There were only 2 of 106 false-positive lymph nodes in 1 of 24 patients, but the sensitivity was only 3 of 13, compared with 31 of 35 in the study by Yasukawa et al. This discrepancy needs to be resolved through further research.

Using ^{11}C-methionine PET, Lindholm et al. (*16*) detected lymph node metastases in 4 of 10 patients with malignant melanoma but also cautioned: "inflammatory processes may limit its use since methionine has been found to be taken up in lung granulomas, breast and brain abscesses" (*17–19*). Those findings would suggest that ^{11}C-methionine is not likely to help solve the problem of false-positive results with FDG PET in the evaluation of lymph nodes for metastatic involvement.

For the detection of hilar and mediastinal lymph node metastases, the sensitivity and specificity of ^{11}C-methionine (86.9% and 91.1%, respectively) are not appreciably different from values generated with FDG PET (averages from the published figures, 86% and 96.5%). CT is still the accepted standard of care in staging NSCLC. If CT was interpreted in light of the FDG PET, information from PET and CT combined would improve the overall accuracy and come close to, if not surpass, the accuracy of ^{11}C-methionine PET.

The question comes to this: How useful is ^{11}C-methionine PET in detecting hilar and mediastinal nodal involvement in NSCLC? Do we need it and when would we need it? FDG PET does as well as ^{11}C-methionine PET in assessing nodal involvement in NSCLC. FDG PET, widely used and based on broad experience, does not have the disadvantages of the 20-min half-life of ^{11}C and the need for an on-site cyclotron.

Yasukawa et al. did not provide much clinically relevant information or patient outcome data. Did methionine PET change the tumor, necrosis, metastasis status? All patients had surgery. Although 28.9% of the patients in this study had positive mediastinal nodes, 39 had lobectomies and 2 had partial resections. This almost "100% resectability" is in contrast with the generally expected probability of nonresectable NSCLC. Did ^{11}C-methionine PET results modify therapeutic actions? Did patients have better outcomes as a result of the ^{11}C-methionine PET study, and was that result obtained cost-effectively? These questions, of course, cannot be answered with the results of this study that involved only a small number of patients and a short follow-up period.

CT and FDG PET, or the combination of results from these modalities, probably will—for some time—remain the accepted methods for preoperative staging of NSCLC. However, additional, more specific radiotracers, such as ^{11}C-methionine or other amino acids such as ^{11}C-α-aminoisobutyric acid (*20,21*), ^{18}F-fluoro-α-methyl-thyrosine (*22*), or 1-[^{11}C]-aminocyclobutanecarboxylic acid (*23*), that have tumor affinity but less affinity to infectious processes, need to be explored for their potential as special differential diagnostic PET tools. Perhaps 1 of these amino acids might have some utility in further characterizing lesions positive on FDG PET, or for evaluation of lesions difficult to biopsy, or in patients with high risk for complications from a biopsy. Certainly, it is premature to recommend ^{11}C-methionine for routine preoperative screening for metastases in lung cancer at this time.

Karl F. Hubner
University of Tennessee Medical College Knoxville
Knoxville, Tennessee

REFERENCES

1. Gupta NC, Graeber GM, Rogers JS, Bishop HA. Comparative efficacy of PET with FDG and computed tomographic scanning in preoperative staging of NSCLC. *Ann Surg.* 1999;229:286–291.
2. Steinert HC, Hauser M, Allemann F, et al. Non-small cell lung cancer: nodal staging with FDG PET versus CT with correlative lymph node mapping and sampling. *Radiology.* 1997;202:441–446.
3. Erasmus JJ, McAdams HP, Patz EP, Goodman P, Coleman RE. Thoracic FDG PET: state of the art. *RadioGraphics.* 1998;18:5–20.
4. Yasukawa T, Yoshikawa K, Aoyagi H, et al. Usefulness of PET with ^{11}C-methionine for the detection of hilar and mediastinal lymph node metastasis in lung cancer. *J Nucl Med.* 2000;41:283–290.
5. McLoud TC, Bourguoin PM, Greenberg RW, et al. Bronchogenic carcinoma: analysis of staging of the mediastinum with CT by correlative lymph node mapping and sampling. *Radiology.* 1992;182:319–323.
6. Lewis P, Griffin S, Marsden P, et al. Whole-body F-18-fluorodeoxyglucose positron emission tomography in preoperative evaluation of lung cancer. *Lancet.* 1994;344:1265–1266.
7. Valk PE, Pounds TR, Hopkins DM, et al. Staging non-small cell lung cancer by whole-body positron emission tomographic imaging. *Ann Thorac Surg.* 1995;60:1573–1582.
8. Vansteenkiste JF, Stroobants SG, De Leyn PR, et al. Mediastinal lymph node staging with FDG-PET scan in patients with potentially operable non-small cell lung cancer: a prospective analysis of 50 cases. *Chest.* 1997;112:1480–1486.
9. Wahl RL, Quint LE, Greenough RL, Meyer CR, White RI, Orringer MB. Staging of mediastinal non-small cell lung cancer with FDG PET, CT, and fusion images: preliminary prospective evaluation. *Radiology.* 1994;191:371–377.
10. Bury T, Dowlati A, Paulus P, et al. Whole body ^{18}FDG positron emission tomography in the staging of non-small cell lung cancer. *Eur Respir J.* 1997;10:2529–2534.
11. Knight SB, Delbeke D, Stewart JR, Sandler MP. Evaluation of pulmonary lesions with FDG-PET: comparison of findings in patients with and without a history of prior malignancy. *Chest.* 1996;109:982–988.
12. Schiepers C. Role of positron emission tomography in the staging of lung cancer. *Lung Cancer.* 1997;17(suppl 1):S29–S35.
13. Kubota K, Ito M, Fukuda H, et al. Cancer diagnosis with positron computed tomography and carbon-11-labeled L-methionine. *Lancet.* 1983;2:1192.
14. Kubota R, Yamada S, Kubota K, Ishiwata K, Tamahashi N, Ido T. Intratumoral distribution of fluorine-18-fluorodeoxyglucose in vivo: high accumulation in macrophages and granulation tissues studied by microautoradiography. *J Nucl Med.* 1992;33:1972–1980.
15. Miyazawa H, Arai T, Iio M, Hara T. PET imaging of non-small-cell lung carcinoma with carbon-11-methionine: relationship between radioactivity uptake and flow-cytometric parameters. *J Nucl Med.* 1993;34:1886–1891.
16. Lindholm P, Leskinen S, Nagren K, et al. Carbon-11-methionine PET imaging of malignant melanoma. *J Nucl Med.* 1995;36:1805–1810.
17. Kubota K, Matsuzawa T, Fujiwara T, et al. Differential diagnosis of lung cancer with positron emission tomography: a prospective study. *J Nucl Med.* 1990;31:1927–1932.
18. Leskinen-Kallio S, Nagren K, Lehikoinen P, Ruotsalainen U, Joensuu H. Uptake of C-11-methionine in breast cancer studied by PET: an association with the size of S-phase fraction. *Br J Cancer.* 1991;64:1121–1124.
19. Ishii K, Ogawa T, Hatazawa J, et al. High L-methyl-[C-11] methionine uptake in brain abscess: a PET study. *J Comput Assist Tomogr.* 1993;17:660–661.
20. Dimitrakopoulou-Strauss A, Strauss LG, Goldschmidt H, et al. FDG and C-11-aminoisobutyric acid (AIB) in tumors [abstract]. *J Nucl Med.* 1999;5:238.
21. Conti PS. *Synthesis of Carbon-11 Labeled Biological Molecules for the In Vivo Study of Biochemical Processes and Structure Activity Relationships in Normal and Malignant Tissue* [thesis]. New York, NY: 1985:65–82.
22. Oriuchi N, Inoue K, Tomiyoshi K, et al. F-18-fluoro-α-methyl-tyrosine (FMT) and 18-F-FDG PET in patients with sarcoidosis [abstract]. *J Nucl Med.* 1995;36:193P.
23. Washburn LC, Sun TT, Byrd BL, Hayes RL, Butler TA. 1-aminocyclobutane [C-11] carboxylic acid, a potential tumor seeking agent. *J Nucl Med.* 1979;210:1055–1061.