ORIGINAL ARTICLE

Staging of Non–Small-Cell Lung Cancer with Integrated Positron-Emission Tomography and Computed Tomography

Didier Lardinois, M.D., Walter Weder, M.D., Thomas F. Hany, M.D., Ehab M. Kamel, M.D., Stephan Korom, M.D., Burkhardt Seifert, Ph.D., Gustav K. von Schulthess, M.D., Ph.D., and Hans C. Steinert, M.D.

ABSTRACT

BACKGROUND

We compared the diagnostic accuracy of integrated positron-emission tomography (PET) and computed tomography (CT) with that of CT alone, that of PET alone, and that of conventional visual correlation of PET and CT in determining the stage of disease in non–small-cell lung cancer.

METHODS

In a prospective study, integrated PET–CT was performed in 50 patients with proven or suspected non–small-cell lung cancer. CT and PET alone, visually correlated PET and CT, and integrated PET–CT were evaluated separately, and a tumor–node–metastasis (TNM) stage was assigned on the basis of image analysis. Nodal stations were identified according to the mapping system of the American Thoracic Society. The standard of reference was histopathological assessment of tumor stage and node stage. Extrathoracic metastases were confirmed histopathologically or by at least one other imaging method. A paired sign test was used to compare integrated PET–CT with the other imaging methods.

RESULTS

Integrated PET–CT provided additional information in 20 of 49 patients (41 percent), beyond that provided by conventional visual correlation of PET and CT. Integrated PET–CT had better diagnostic accuracy than the other imaging methods. Tumor staging was significantly more accurate with integrated PET–CT than with CT alone (P=0.001), PET alone (P<0.001), or visual correlation of PET and CT (P=0.013); node staging was also significantly more accurate with integrated PET–CT than with PET alone (P=0.013). In metastasis staging, integrated PET–CT increased the diagnostic certainty in two of eight patients.

CONCLUSIONS

Integrated PET–CT improves the diagnostic accuracy of the staging of non–small-cell lung cancer.

From the Divisions of Thoracic Surgery (D.L., W.W., S.K.) and Nuclear Medicine (T.F.H., E.M.K., G.K.S., H.C.S.), University Hospital of Zurich; and the Department of Biostatistics, University of Zurich (B.S.) — both in Zurich, Switzerland. Address reprint requests to Dr. Steinert at the Division of Nuclear Medicine, University Hospital of Zurich, Rämistrasse 100, 8091 Zurich, Switzerland, or at hans.steinert@dmr.usz.ch.

N Engl J Med 2003;348:2500-7.

Computed tomography (CT) has an important role in the initial determination of the stage of disease in lung cancer. CT provides excellent morphologic information on the extent of disease but has limited ability to differentiate between benign and malignant lesions in an organ or in lymph nodes. Whole-body positron-emission tomography (PET) with fludeoxyglucose F 18 ([18F]fluoro-2-deoxy-D-glucose) has a higher rate of detection of mediastinal lymph-node metastases as well as of extrathoracic metastases.[1-6] It has also proved effective in the management of non–small-cell lung cancer.[7-10] Since commercial PET scanners provide nominal spatial resolution of 4.5 to 6.0 mm in the center of the axial field of view, even lesions that are less than 1 cm in diameter can be detected on the basis of an increased uptake of fludeoxyglucose F 18.

However, fludeoxyglucose F 18 is also taken up by muscles and inflammatory processes.[11-13] Furthermore, PET provides imprecise information on the exact location of focal abnormalities. Thus, even if the results of PET and CT are visually correlated, the precise location of lesions is sometimes difficult to determine. Recently, integrated PET–CT scanners have been introduced.[14] Initial results in oncology have been encouraging.[15-17] Therefore, we prospectively compared the accuracy of integrated PET–CT with that of other imaging methods in staging non–small-cell lung cancer.

METHODS

PATIENTS

Fifty patients with proven or suspected non–small-cell lung cancer were enrolled in the study at the University Hospital of Zurich, Zurich, Switzerland. Our institution is a teaching and tertiary care hospital and a major referral site for patients with cancer. Thoracic surgeons at the facility have been using PET routinely for preoperative assessment of disease stage since 1994. All patients underwent conventional staging based on a review of the medical history, physical findings, and results of blood tests, bronchoscopy, and contrast-enhanced CT of the chest and upper abdomen, and all also underwent integrated whole-body PET–CT. All consecutive patients referred for surgery between July 2001 and February 2002 were included in the study after giving written informed consent in accordance with the regulations of the institutional review board. One patient was excluded from further study because histologic analysis revealed mucosa-associated lymphoma. Thus, 49 patients (28 men and 21 women) with a mean age of 62 years (range, 46 to 81) remained in the study. Histologic analysis revealed adenocarcinoma in 28 patients, squamous-cell carcinoma in 13, and large-cell carcinoma in 8.

INTEGRATED PET AND CT

Patients received an intravenous injection of 350 to 400 MBq of fludeoxyglucose F 18 and then rested for approximately 50 minutes before undergoing imaging. Image acquisition was performed with use of an integrated PET–CT device (Discovery LS, GE Medical Systems) consisting of an Advance NXi PET scanner and a four-slice Light Speed Plus CT scanner. The axes of both systems were mechanically aligned so that shifting the examination table by 60 cm moved the patient from the CT into the PET gantry. The resulting PET and CT images were coregistered on hardware.

An unenhanced CT image was obtained from the patient's head to the pelvic floor with use of a standardized protocol involving 140 kV, 80 mA, a tube-rotation time of 0.5 second per rotation, a pitch of 6, and a section thickness of 5 mm, which was matched to the section thickness of the PET images.[17] Immediately after CT, PET was performed that covered the identical axial field of view. The acquisition time for PET was 4 minutes per table position and 24 minutes in all. Patients were instructed to hold their breath in normal expiration for 22 seconds during the acquisition of the CT images and to breathe shallowly during the acquisition of the PET images.[18] PET-image data sets were reconstructed iteratively with segmented correction for attenuation with use of the CT data.[19,20] Coregistered images were displayed by means of eNTEGRA software (GE Medical Systems).

SURGERY

Lung resections were performed with mediastinal lymph-node dissection, which consisted of en-bloc dissection of all nodes at stations 2 through 4 and 7 through 9 on the right side and of stations 4 through 9 on the left side, according to the mapping system of the American Thoracic Society.[21-23] Surgery was performed in 40 patients and consisted of lung resection and mediastinal lymphadenectomy in 35 patients, exploratory thoracotomy in 3, and wedge resection in 2. Eight patients who presented with occult extrathoracic metastases and one patient who had malignant cells in pleural flu-

id were excluded from surgery. In the two patients who underwent wedge resection, lung function was too limited for a lobectomy. Lymphadenectomy was not performed in these patients, since mediastinal lymph nodes were less than 5 mm on CT and PET was negative for lymph-node involvement. Of the three patients who underwent only exploratory thoracotomy, one had pleural dissemination and two had infiltration of the aorta.

Four patients received adjuvant chemotherapy because stage IIIA disease was found after mediastinoscopy. Three with N2 disease on tumor–node–metastasis (TNM) staging had unquestionable stage T1 or T2 disease without any evidence of chest-wall or mediastinal invasion. One patient had a superior sulcus tumor with Pancoast's syndrome. Complete pathological TNM staging was performed in 35 patients and disease was classified as stage IA in 10 patients, stage IB in 5, stage IIB in 6, stage IIIA in 9, and stage IIIB in 5.

ASSESSMENT OF EXTRATHORACIC METASTASES

After PET, extrathoracic focal abnormalities were described according to their locations with the use of integrated PET–CT. Further evaluation of suspected metastases included biopsies or the use of other imaging methods if biopsy was not ethically justified.

STATISTICAL ANALYSIS

The images were prospectively analyzed by two independent review boards whose members had no knowledge of the patients' clinical data or the results of other imaging studies. Review Board A, consisting of a nuclear-radiology physician and a thoracic surgeon, first analyzed all CT images and assigned a TNM stage. After reviewing the CT images for each patient, the reviewers assessed attenuation-corrected PET images. Thus, the reviewers interpreted the PET images with the knowledge of the CT findings and visually correlated the PET and CT images. This approach was chosen because it represents the standard practice of combined reading of PET and CT images. On the basis of their visual correlation, the reviewers again assigned a TNM stage. When a clear differentiation between different tumor stages was not possible, both stages were noted and the findings were deemed equivocal.

Review Board B, consisting of a different nuclear physician and a different thoracic surgeon, analyzed the attenuation-corrected PET images first and assigned a TNM stage. Then, the CT images, attenuation-corrected PET images, and coregistered PET–CT images were displayed together on the monitor, and the reviewers again assigned a TNM stage. When a clear differentiation between stages was not possible, both stages were noted. After completion of the image analysis, the two review boards showed the complete set of images to surgeons so that surgery could be planned. Finally, TNM stages based on the various imaging procedures were correlated with pathological stages.

Statistical analysis was carried out with SPSS software. To identify any improvements in the accuracy of staging associated with the use of coregistered PET–CT, the tumor and node stage of each imaging method was assessed by means of a score ranging from 0 to 3, in which a score of 0 indicated incorrect findings, a score of 1 equivocal but incorrect findings, a score of 2 correct but equivocal findings, and a score of 3 correct findings. If the stage was correctly determined (that is, it matched the stage determined by conventional means), but owing to equivocal findings, more than one stage was noted by the review board, the result was classified as correct but equivocal. A paired sign test was used to compare coregistered PET–CT with the other imaging methods. Because both a score of 0 and a score of 1 were incorrect, we combined them in the analysis and assigned them a score of 0. To address the problem of multiple comparisons, Bonferroni's correction was applied. Thus, P values less than 0.017 were considered to indicate statistical significance. All P values are two-sided.

RESULTS

DIAGNOSTIC ACCURACY

As compared with visual correlation, integrated PET–CT provided 24 items of additional information in 20 of 49 patients (41 percent). The additional information consisted of the exact location of lymph nodes in nine patients, precise evaluation of chest-wall infiltration in three patients and of mediastinal invasion in three patients, correct differentiation between tumor and peritumoral inflammation or atelectasis in seven patients, and the exact location of distant metastases in two patients. Overall, integrated PET–CT provided more accurate information on the stage of disease than did the other two imaging methods, including visual correlation of PET and CT. Statistically significant improvements were found particularly in terms of the tumor stage (Table 1).

TUMOR STAGING

In 40 patients the tumor stage was confirmed histologically. Table 2 shows the diagnostic accuracy of the various imaging methods. Of 26 patients whose tumor stage was classified correctly by means of visual correlation of PET and CT, 24 patients were also classified correctly by means of integrated PET–CT, and in 2 the results were classified as correct but equivocal. Of the five patients in whom the results of visual correlation of PET and CT were classified as correct but equivocal, four were classified correctly on the basis of integrated PET–CT, and in one the results remained correct but equivocal. Of the nine patients classified incorrectly by visual correlation of PET and CT, seven were classified correctly by integrated PET–CT, in one the results were classified as correct but equivocal, and in one the results remained incorrect. In the evaluation of chest-wall infiltration (Fig. 1) and mediastinal invasion in 19 patients, PET–CT staging was correct in 16 patients (84 percent), correct but equivocal in 3 (16 percent), and incorrect in none and visual correlation was correct in 10 (53 percent), correct but equivocal in 5 (26 percent), and incorrect in 4 (21 percent).

NODE STAGING

In 37 patients, the node stage was confirmed histologically. Table 3 shows the diagnostic accuracy of the various imaging methods. Of 22 patients classified correctly by visual correlation of PET and CT, 21 patients were also classified correctly by integrated PET–CT and in 1 the results were classified as correct but equivocal. Of the four patients whose results were classified as correct but equivocal on the basis of visual correlation of PET and CT, all were classified correctly by integrated PET–CT. Of the 11 patients whose results were classified as incorrect on the basis of visual correlation of PET and CT, 5 were classified correctly by integrated PET–CT, and 6 remained incorrect. In one patient, PET–CT diagnosed contralateral mediastinal nodal metastases, but histologic analysis revealed inflammatory changes. In two patients classified as having N1 disease on PET–CT, hilar extension of the tumor was falsely interpreted as nodal metastases. In three patients, no increase in nodal radionuclide uptake in the mediastinum could be detected by PET–CT, but micrometastases were found on histologic analysis in two. In one patient, no increased uptake was found in a 5-mm lymph node. In one other patient, a small focal abnormality was identified at the apex of the thorax (Fig. 2). However, the precise location of the abnormality could not be identified with PET, CT, or visual correlation of PET and CT. Integrated PET–CT showed that the focal abnormality was in a normal-sized supraclavicular lymph node. This information enabled the surgeons to perform a straightforward resection of this lesion, and a 5-mm metastatic lymph node was confirmed histologically.

Table 1. Comparison of the Diagnostic Accuracy of Integrated PET–CT with CT Alone, PET Alone, and Visual Correlation of PET and CT Images.*

Variable	P Value
Tumor stage (n=40)	
PET–CT vs. CT alone	0.001†
PET–CT vs. PET alone	<0.001†
PET–CT vs. visual correlation of PET and CT	0.013†
Node stage (n=37)	
PET–CT vs. CT alone	0.12
PET–CT vs. PET alone	0.013†
PET–CT vs. visual correlation of PET and CT	0.021

* The paired sign test was used to calculate P values. Stages assigned on the basis of CT alone, PET alone, and PET and CT were assessed by Review Board A, and stages assigned on the basis of integrated PET–CT were assessed by Review Board B.
† The P value was significant after Bonferroni's correction.

Table 2. Diagnostic Accuracy of the Imaging Methods with Respect to Tumor Stage in 40 Patients.

Imaging Method	Classification Correct (Score of 3)	Classification Correct but Equivocal (Score of 2)	Classification Incorrect (Score of 0 or 1)
	no. of patients (%)		
CT alone	23 (58)	8 (20)	9 (22)
PET alone	16 (40)	16 (40)	8 (20)
Visual correlation of PET and CT	26 (65)	5 (12)	9 (22)
Integrated PET–CT	35 (88)	4 (10)	1 (2)

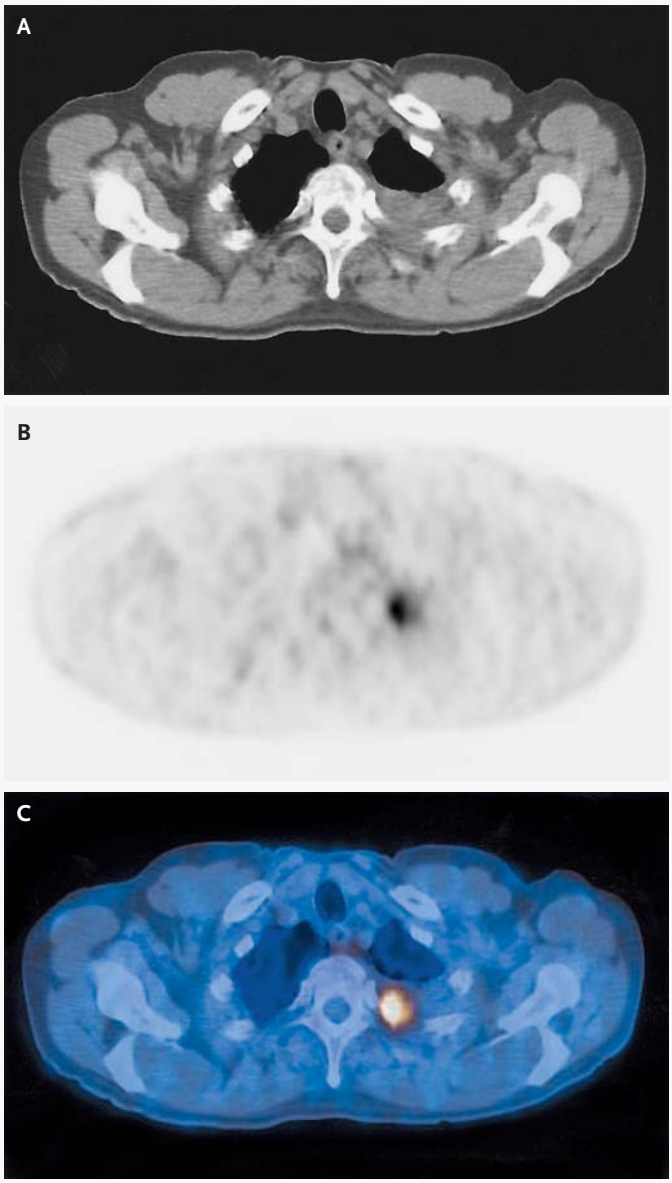

Figure 1. CT Scan, Attenuation-Corrected PET Scan, and Coregistered PET–CT Scan of a Patient with Non–Small-Cell Lung Cancer.

The CT scan (Panel A) and the PET scan (Panel B) showed the primary tumor in the left upper lobe, indicating that tumor invasion was probable. Tumor invasion was evident on the coregistered PET–CT scan (Panel C). This finding was confirmed intraoperatively, resulting in an en-bloc resection of the tumor with part of the chest wall.

METASTASIS STAGING

In 8 of 49 patients (16 percent), PET detected unsuspected extrathoracic focal abnormalities suggestive of metastases. PET precisely determined the location of these lesions in six: three patients with bone metastases, one patient with adrenal metastasis, and two patients with cerebral dissemination of the disease. In two other patients, PET detected focal abnormalities in the pelvic region but could not pinpoint their location. Visual correlation of the CT images with the PET images did not reveal any abnormality in this region. Integrated PET–CT showed that the focal abnormalities were in the pelvic bone in both patients.

INTEROBSERVER VARIABILITY

To assess the variability of staging between the two teams of reviewers, we compared the kappa values of the PET ratings of both review boards. The kappa value was 0.56 for the tumor stage and 0.55 for the node stage. No significant difference in the diagnostic accuracy of PET findings was found between the two review boards ($P=0.06$ for tumor stage and $P=1.0$ for node stage).

DISCUSSION

Our results suggest that integrated PET–CT is superior to PET alone, CT alone, or visual correlation of PET with CT in determining the stage of disease in non–small-cell lung cancer. Significant improvements in tumor staging were found with integrated PET–CT. The anatomical correlation of the radionuclide uptake made possible a more precise delineation of the location of the primary tumor. Integrated PET–CT improved the diagnosis of chest-wall infiltration and mediastinal invasion by the tumor.

PET has proved to be very effective for the staging of mediastinal nodes.[24] Since PET images have a fairly high resolution, lesions that are less than 1 cm can be detected. This is a critical advantage over conventional CT and magnetic resonance imaging. However, tracing focal abnormalities to specific lymph nodes is difficult or even impossible with the use of PET alone.[25] To pinpoint mediastinal lesions, PET images must be correlated with CT images. Several studies have demonstrated that fusion of images of the trunk obtained by CT and PET from different scanners is technically possible.[26-28] However, this approach did not increase the accuracy of mediastinal staging over that obtained by PET alone. In all these studies, the images from separate scanners were coregistered. Use of the same positions during PET and CT is important for proper coregistration of the images obtained with separate scanners during whole-body examinations.

To overcome the problems related to the fusion

Table 3. Diagnostic Accuracy of the Imaging Methods with Respect to Node Stage in 37 Patients.

Imaging Method	Classification Correct (Score of 3)	Classification Correct but Equivocal (Score of 2)	Classification Incorrect (Score of 0 or 1)
	no. of patients (%)		
CT alone	22 (59)	2 (5)	13 (35)
PET alone	18 (49)	14 (38)	5 (14)
Visual correlation of PET and CT	22 (59)	4 (11)	11 (30)
Integrated PET–CT	30 (81)	1 (3)	6 (16)

of images with the use of software, various prototypical systems have been developed that combine PET and CT. Townsend and his colleagues combined a CT scanner and a partial-ring, rotating PET scanner in a single gantry.[14] Such systems are attractive not only because of their capacity to coregister images with use of hardware, but also because the CT data can be used to correct PET scans for absorption of the emission rays by the patient's tissues. This approach obviates the need for the time-consuming attenuation correction based on germanium-68 transmission sources and decreases the acquisition time by up to 30 percent, depending on the CT system used.

In our study, integrated PET–CT was clearly superior to the other imaging methods, especially with regard to tumor stages. The high level of reliability of integrated PET–CT with respect to identifying hilar lymph nodes, mediastinal lymph nodes, and supraclavicular lymph nodes, and providing precise information on chest-wall or mediastinal invasion may have therapeutic implications.

Despite the fact that integrated PET–CT improved the accuracy of mediastinal staging, the resolution of PET is not sufficient to detect microscopic lymph-node metastases. If the radionuclide uptake is not increased on PET, integrated PET–CT will certainly not provide further information. In our study, two micrometastases and one lymph-node metastasis of 5 mm were missed in three patients. These results demonstrate that integrated PET–CT does not necessarily obviate the need for mediastinoscopy for mediastinal staging.

Previous studies demonstrated the high accuracy of whole-body PET in the detection of unsus-

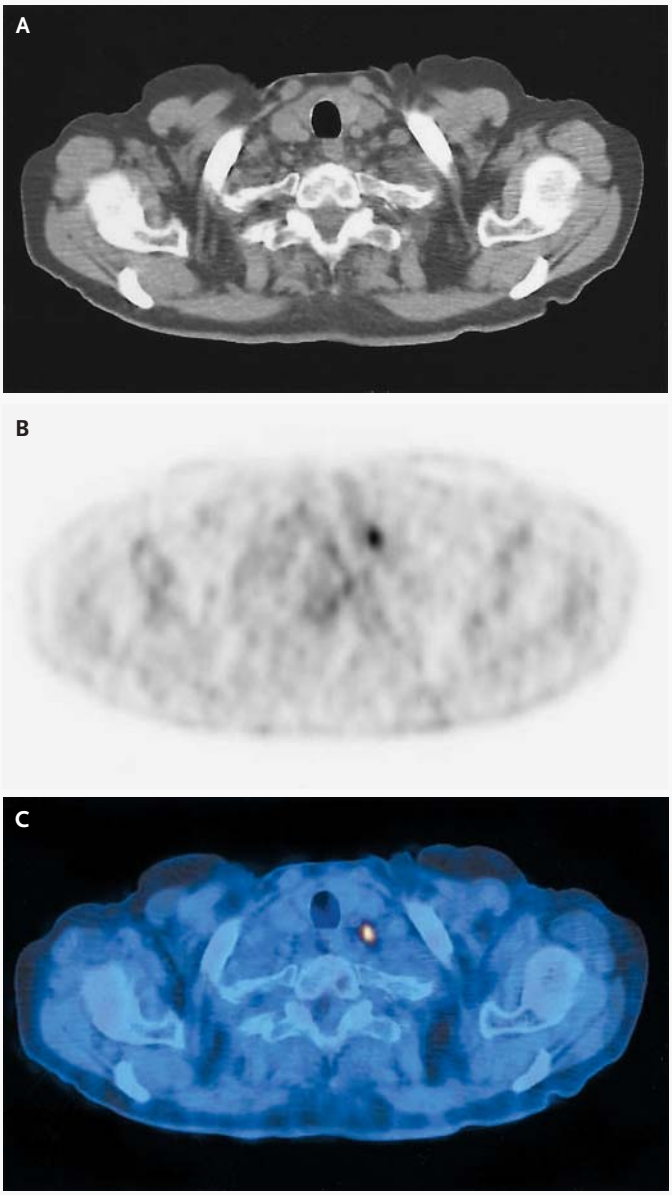

Figure 2. CT Scan, Attenuation-Corrected PET Scan, and Coregistered PET–CT Scan in a Patient with Non–Small-Cell Lung Cancer.

No enlarged lymph nodes were seen in the apex of the thorax on CT (Panel A), but a focal area of increased radionuclide uptake was found on PET (Panel B). The exact location of the lesion remained unclear. Coregistered PET–CT revealed that the area of increased radionuclide uptake matched a normal-sized lymph node. Owing to the accumulation of fludeoxyglucose F 18, this lymph node was interpreted as a potential site of metastasis. The capacity of PET–CT to pinpoint the location of this focal abnormality made possible the precise excision of the node. Histologic analysis revealed a 5-mm lymph-node metastasis, and induction chemotherapy was initiated.

pected extrathoracic metastases.[3-6] In various studies, whole-body PET detected unsuspected M1 disease in 6 to 17 percent of patients (mean, 12 percent)[29]; in the present study, such metastases were found in 8 of 49 patients (16 percent). However, the clinical significance of the finding of a single focal abnormality on PET remains unclear, especially when no morphologic alterations are identified on CT. Integrated PET–CT permits the focal abnormality to be traced to a specific location, as exemplified in two of our patients in whom integrated PET–CT identified single-bone metastases.

We used unenhanced CT scans for integrated PET–CT imaging. We could not ethically justify the use of vascular contrast material, because all patients were referred after having undergone conventional contrast-enhanced CT for staging. Further evaluation is necessary to determine the conditions in which the use of intravascular contrast material might have an additional diagnostic impact in integrated PET–CT. However, in the case of infiltration of hilar and mediastinal vessels, conventional CT with contrast enhancement has a relatively low sensitivity, specificity, and accuracy (68 percent, 72 percent, and 70 percent, respectively).[30]

The main drawback of PET is the poor quality of the anatomical information, which often precludes a precise assessment of the tumor and node stage. In our study, equivocal findings were most common with PET. The low kappa values for both review boards in assigning stages on the basis of PET underline the difficulties inherent in the use of this approach for the determination of tumor and node stages, particularly with respect to tumor infiltration of surrounding structures and the exact location of single nodes.

Because integrated PET–CT has a faster acquisition time than does a conventional dedicated PET scanner, the duration of the examination — and thus of the patient's discomfort — is decreased. We used low-dose CT scans that were coregistered with PET scans. It was recently demonstrated that coregistration can pinpoint focal abnormalities with the use of an 80-mA CT scanner, an approach that keeps the level of exposure to radiation low.[17]

Our data suggest that once integrated PET–CT becomes more widely available, it will be the preferred approach for determining the stage of disease in non–small-cell lung cancer. If the results of forthcoming studies of larger numbers of patients confirm our results, integrated PET–CT may become the new standard approach to imaging in patients with lung cancer.

Supported in part by the Swiss Federal Commission for Scholarships for Foreign Students (to Dr. Kamel).

Presented in part at the 49th Annual Meeting of the Society of Nuclear Medicine, Los Angeles, June 15–19, 2002; the Annual Meeting of the Swiss Society of Surgery in Lausanne, June 19–22, 2002; and the 88th Scientific Assembly and Annual Meeting of the Radiological Society of North America, Chicago, December 1–6, 2002.

Dr. von Schulthess reports having received consulting fees from Amersham, owning equity in Mobile PET systems (San Diego, Calif.), and having received grant support from GE Medical Systems.

We are indebted to our colleagues S. Bodis, M.D., E. Russi, M.D., and R. Stahel, M.D., and others from the Interdisciplinary Tumor Board of the Thorax at the University Hospital of Zurich, Zurich, Switzerland, for critical discussions and support; to T. Berthold, C. Britt, M. Farrell, M. Griff, K. Zander, and C. Jenny for technical support; and to the PET radiopharmaceutical group for support.

REFERENCES

1. 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;202:441-6.
2. Dwamena BA, Sonnad SS, Angobaldo JO, Wahl RL. Metastases from non-small cell lung cancer: mediastinal staging in the 1990s — meta-analytic comparison of PET and CT. Radiology 1999;213:530-6.
3. Weder W, Schmid RA, Bruchhaus H, Hillinger S, von Schulthess GK, Steinert HC. Detection of extrathoracic metastases by positron emission tomography in lung cancer. Ann Thorac Surg 1998;66:886-92.
4. Pieterman RM, van Putten JWG, Meuzelaar JJ, et al. Preoperative staging of non–small-cell lung cancer with positron-emission tomography. N Engl J Med 2000;343:254-61.
5. Marom EM, McAdams HP, Erasmus JJ, et al. Staging non-small cell lung cancer with whole-body PET. Radiology 1999;212:803-9.
6. Kalff V, Hicks RJ, MacManus MP, et al. Clinical impact of (18)F fluorodeoxyglucose positron emission tomography in patients with non-small-cell lung cancer: a prospective study. J Clin Oncol 2001;19:111-8.
7. Gupta NC, Graeber GM, Rogers JS II, Bishop HA. Comparative efficacy of positron emission tomography with FDG computed tomographic scanning in preoperative staging of non-small cell lung cancer. Ann Surg 1999;229:286-91.
8. Dietlein M, Weber K, Gandjour A, et al. Cost-effectiveness of FDG-PET for the management of potentially operable non-small cell lung cancer: priority for a PET-based strategy after nodal-negative CT results. Eur J Nucl Med 2000;27:1598-609.
9. van Tinteren H, Hoekstra OS, Smit EF, et al. Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial. Lancet 2002;359:1388-93.
10. Seltzer MA, Yap CS, Silverman DH, et al. The impact of PET on the management of lung cancer: the referring physician's perspective. J Nucl Med 2002;43:752-6.
11. Engel H, Steinert H, Buck A, Berthold T, Huch Boni RA, von Schulthess GK. Whole-body PET: physiological and artifactual fluorodeoxyglucose accumulations. J Nucl Med 1996;37:441-6.
12. Strauss LG. Fluorine-18 deoxyglucose and false-positive results: a major problem in the diagnostics of oncological patients. Eur J Nucl Med 1996;23:1409-15.
13. Cook GJR, Maisey MN, Fogelman I. Normal variants, artefacts and interpretative pitfalls in PET imaging with 18-fluoro-2-deoxyglucose and carbon-11 methionine. Eur J Nucl Med 1999;26:1363-78.
14. Beyer T, Townsend DW, Brun T, et al.

A combined PET/CT scanner for clinical oncology. J Nucl Med 2000;41:1369-79.
15. Kluetz PG, Meltzer CC, Villemagne VL, et al. Combined PET/CT imaging in oncology: impact on patient management. Clin Positron Imaging 2000;3:223-30.
16. Kamel EM, Goerres GW, Burger C, von Schulthess GK, Steinert HC. Detection of recurrent laryngeal nerve palsy in patients with lung cancer: detection with PET-CT image fusion — report of six cases. Radiology 2002;224:153-6.
17. Hany TF, Steinert HC, Goerres GW, Buck A, von Schulthess GK. PET diagnostic accuracy: improvement with in-line PET-CT system: initial results. Radiology 2002;225:575-81.
18. Goerres GW, Kamel E, Heidelberg TN, Schwitter MR, Burger C, von Schulthess GK. PET-CT image co-registration in the thorax: influence of respiration. Eur J Nucl Med Mol Imaging 2002;29:351-60.
19. Kamel E, Hany TF, Burger C, et al. CT vs 68Ge attenuation correction in a combined PET/CT system: evaluation of the effect of lowering the CT tube current. Eur J Nucl Med Mol Imaging 2002;29:346-50.
20. Burger C, Goerres G, Schoenes S, Buck A, Lonn AHR, Von Schulthess GK. PET attenuation coefficients from CT images: experimental evaluation of the transformation of CT into PET 511-keV attenuation coefficients. Eur J Nucl Med Mol Imaging 2002;29:922-7.
21. Clinical staging of primary lung cancer. Am Rev Respir Dis 1983;127:659-64.
22. Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. Chest 1997;111:1718-23.
23. Martini N. Mediastinal lymph node dissection for lung cancer: the Memorial experience. Chest Surg Clin N Am 1995;5:189-203.
24. Kernstine KH, McLaughlin KA, Menda Y, et al. Can FDG-PET reduce the need for mediastinoscopy in potentially resectable nonsmall cell lung cancer? Ann Thorac Surg 2002;73:394-402.
25. Belley G, Aquino SL, McLoud TC, Shepard JO, Halpern EF, Fischman AJ. Anatomic accuracy of FDG PET in nodal staging of bronchogenic carcinoma. Radiology 2000; 217:Suppl:361. abstract.
26. 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;191:371-7.
27. Vansteenkiste JF, Stroobants SG, Dupont PJ, et al. FDG-PET scan in potentially operable non-small cell lung cancer: do anatometabolic PET-CT fusion images improve the localisation of regional lymph node metastases? Eur J Nucl Med 1998;25: 1495-501.
28. Magnani P, Carretta A, Rizzo G, et al. FDG/PET and spiral CD image fusion for mediastinal lymph node assessment of non-small cell lung cancer patients. J Cardiovasc Surg (Torino) 1999;40:741-8.
29. Hellwig D, Ukena D, Paulsen F, Bamberg M, Kirsch CM. Metaaanalyse zum Stellenwert der Positronen-Emissions-Tomographie mit F-18-Fluorodesoxyglukose (FDG-PET) bei Lungentumoren. Pneumologie 2001;55:367-77.
30. Rendina EA, Bognolo DA, Mineo TC, et al. Computed tomography for the evaluation of intrathoracic invasion by lung cancer. J Thorac Cardiovasc Surg 1987;94:57-63.