Does Whole-Body 2-[18F]-Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography Have an Advantage Over Thoracic Positron Emission Tomography for Staging Patients With Lung Cancer?

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Background: Whole-body (WB) positron emission tomography (PET) with 2-[18F]-fluoro-2-deoxy-D-glucose (FDG) is more accurate than other imaging studies for detecting lung cancer and extrathoracic metastatic disease. Thoracic PET (from the skull base through the kidneys) may be equally as useful as WB PET (skull base to mid-thigh). With the recent introduction of hybrid CT-PET systems, use of thoracic PET would minimize radiation dose.

Methods: A retrospective review of a series of WB PET scans performed in our department was performed to identify patients evaluated for a solitary pulmonary nodule or newly diagnosed lung cancer who had distant extracranial and extrathoracic metastases detected by PET. All patients with true extrathoracic metastases were documented by ancillary radiologic and clinical data. Patients were staged according to the American Joint Committee on Cancer TNM system based on findings within the confines of a thoracic PET and WB PET. Comparison was made between staging based on thoracic and WB PET to determine if there was a significant difference.

Results: Of 1,026 studies, distant extracranial metastases were described in 35 patients with lung cancer. Findings were determined to be false-positive in nine patients. Of the 26 patients with true metastases on WB PET, 25 patients had metastatic lesions within the confines of thoracic PET. Relative to WB PET, the sensitivity of thoracic PET is 96.2% (95% confidence interval, 1 to 99.3%) for detection of distant metastases. Only one patient had an isolated metastasis that was detected only by WB PET. This patient would have been staged IIIB by thoracic PET as opposed to stage IV by WB PET.

Conclusions: Thoracic PET, when compared to WB PET, is 96.2% sensitive for detecting extrathoracic metastases in patients with newly diagnosed non-small cell lung cancer.

(CHEST 2004; 126:755–760)

Key words: cancer staging; carcinoma, non-small cell lung; lung cancer; neoplasms; radiography, thoracic; tomography, emission-computed

Abbreviations: FDG = 2-[18F]-fluoro-2-deoxy-D-glucose; PET = positron emission tomography; WB = whole body

According to guidelines published by the American Thoracic Society and European Respiratory Society and Silvestri et al, evaluation for distant metastases in patients with lung cancer should be limited to those who have suspicious clinical exami-
PET have not assessed the outcome that detection of distant metastases has on overall staging when compared to thoracic PET alone. The purpose of the current study was to determine if the detection of metastatic disease (stage IV) is significantly better with WB PET compared with thoracic PET, and if this difference alters patient management.

Materials and Methods

Patients

This study was approved by the Human Research Committee of our institution. A retrospective review of serial WB PET scans performed in our department between from 1999 to 2001 was conducted to identify the number of patients evaluated for a pulmonary nodule or newly diagnosed lung cancer who had distant extracranial and extrathoracic metastases interpreted by PET. Examinations were excluded for the following reasons: previous history of a nonpulmonary malignancy, small cell lung cancer, previous surgery for lung cancer, imaging for posttherapy restaging, or evaluation for recurrent lung cancer. Studies were also excluded if outside radiologic or ancillary clinical studies were not available to verify findings on PET.

All patients underwent WB PET that was performed from the angle of the mandible to the mid-thigh level. For definition of thoracic PET, we used the inferior margin of the kidneys as the lower cut-off. Although this would include the majority of the spleen and liver, not all of these organs were completely imaged by our definition of thoracic PET. In our review, each study was grouped into one of the following categories based on the detection of metastases in the following locations: group 1: skeleton metastases that were found within the confines of a standard thoracic PET scan (lower cervical, thoracic, and upper lumbar spine, ribs, clavicles); group 2: skeleton metastases outside the confines of a thoracic PET but within those of a WB PET (mid and lower lumbar spine, sacrum, pelvis, upper femurs); group 3: skeleton metastases present in both thoracic and WB PET; group 4: metastases within the liver included on thoracic PET vs only seen in the lower liver included on the WB PET; group 5: metastases within the spleen included on thoracic PET vs WB PET; group 6: metastases in the adrenals; group 7: metastases within the intra-abdominal and/or pelvic lymph nodes included on thoracic vs WB PET; group 8: metastases within the supraclavicular lymph nodes; and group 9: metastases within the chest wall soft tissue other than the supraclavicular lymph nodes. Pulmonary nodules and pleural disease were not categorized as distant metastases, and therefore were not included in this analysis.

Positive findings on PET were compared with the results of standard cross-sectional imaging (CT and MRI), WB radionuclide bone imaging with $^{99m}$Tc methylene diphosphonate, and follow-up studies for verification of the presence of metastases. All studies with verified evidence of extrathoracic metastases were staged according to the American Joint Committee on Cancer TNM system based on results found within the confines of a thoracic PET (from skull base through the bottom of kidneys) and a WB PET (shoul base to mid-thigh). A comparison was made between staging based on thoracic and WB PET to determine if there was a significant difference between these studies.

WB PET

WB 2-$[^{18}F]$-fluoro-2-deoxy-D-glucose (FDG)-PET studies were acquired with an ECAT-HR+ (Siemens/CTI; Knoxville, TN) or a PC 4096 camera (General Electric; Milwaukee, WI) PET camera. Image spatial resolution was 5.0 mm (full width, half maximum) with slice thickness 2.4 mm for the ECAT-HR+ and 6.0 mm (full width, half maximum) with slice thickness 6.0 mm for the PC 4096. Patients fasted for at least 6 h before scanning. Approximately 15 to 20 mCi (555 to 740 MBq) of FDG was injected IV as a bolus. Emission images, each of 10 min in duration, were obtained beginning 60 min after injection of FDG. Patients were imaged in 6 to 10 contiguous bed positions (6 to 7 positions on ECAT-HR+; 9 to 10 positions on PC 4096) for WB studies. Transmission scans, measured with rotating rod sources containing $^{68}$Ge were obtained for each patient and used for attenuation correction. PET image reconstruction was performed by filter back projection (PC 4096) or an iterative algorithm: ordered subset expectation maximization (ECAT-HR+).

All PET studies were interpreted by nuclear medicine physicians experienced in PET interpretation. Image interpretation sessions were held in the presence of a thoracic radiologist who consulted on the CT study. PET images were reviewed on dedicated clinical workstations. The images were displayed in multiplanar axial, coronal, and sagittal projections and rotating maximum intensity projection displays. Focal areas of FDG uptake were classified as abnormal if the intensity of uptake was greater than overall mediastinal background.

Results

Between 1999 and 2001, our department performed 1,511 WB FDG-PET scans for the evaluation of a pulmonary nodule or primary lung cancer staging in adult patients. 485 of these studies were excluded from analysis based on the criteria described above. Thus, the study population consisted of 1,026 adult patients who underwent FDG-PET studies. This included 434 studies performed for the evaluation of a pulmonary nodule and 592 studies for the primary lung cancer staging.

Of the 1,026 studies, findings interpreted as suspicious for distant metastases were described in 35 patients. Nineteen patients were men, and 16 were women (mean age, 58.8 ± 16 years) [± SD]. On review of ancillary radiologic and clinical studies, these findings were determined to be false-positive in nine patients. Areas of false-positive interpretation were found in the skeleton (n = 5) [verified by subsequent negative bone scan and or follow-up imaging] and liver (n = 4) [verified by negative MRI findings and or follow-up imaging], or both. Twenty-six patients had true distal metastases beyond the lymph nodes of the mediastinum, lung, and supraclavicular region (14 men and 12 women; mean age, 65 ± 10 years) [Table 1]. Areas of soft-tissue metastases were confirmed by MRI, CT, or biopsy, and included the liver (n = 10), adrenal glands (n = 5),
spleen (n = 2), and abdominal lymph nodes (n = 3). Skeleton metastases were confirmed by bone scan and/or CT. They included metastases within confines of thoracic PET (n = 12) and distal skeletal metastasis only seen on WB PET (n = 1, in L5 lumbar spine). Eleven patients who had skeletal metastases (n = 8) or abdominal metastases (n = 3) within the confines of thoracic PET had additional skeletal metastases that were detectable by WB PET (Fig 1).

Staging by the American Joint Committee on Cancer TNM classification was performed for each patient based on information derived from PET and CT scans that were available at the time of PET interpretation (Table 2). Three patients had T1, 4 patients had T2, 9 patients had T3 tumor, and 10 patients had T4 tumors. Seventeen patients had N3 disease—8 patients with N2 (of which 4 patients had T4 disease) and 1 patient had N0/N1 (with pleural metastases). When M or metastatic staging was based on information from thoracic PET alone, 25 of 26 patients had stage IV disease and one patient had stage IIIB disease. With WB PET, all of these patients had stage IV disease. The patient with IIIB disease based on thoracic PET (T2N3) had a single metastasis in the L5 lumbar spine (Fig 2). If we assume WB PET as the reference standard for detection of metastases and comprehensive staging, and thoracic PET as the index test, we calculate a sensitivity of 96.2% (95% confidence interval, 81.1 to 99.3%).

**Table 1—Sites of Extrathoracic Metastases**

<table>
<thead>
<tr>
<th>Sites of Metastases</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver, all detectable on thoracic PET</td>
<td>10</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>5</td>
</tr>
<tr>
<td>Spleen, all detectable on thoracic PET</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal lymph nodes</td>
<td>3</td>
</tr>
<tr>
<td>Skeletal on thoracic PET</td>
<td>12</td>
</tr>
<tr>
<td>Skeletal only on WB PET</td>
<td>1</td>
</tr>
<tr>
<td>Skeletal in both thoracic and WB PET</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal metastases on thoracic PET with skeletal metastases only on WB PET</td>
<td>8</td>
</tr>
</tbody>
</table>

**Table 2—Tumor and Node Status of Patients With Extrathoracic Metastases**

<table>
<thead>
<tr>
<th>Nodal Stage</th>
<th>T1 (n = 3)</th>
<th>T2 (n = 4)</th>
<th>T3 (n = 9)</th>
<th>T4 (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0/N1 (n = 1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>N2 (n = 8)</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>N3 (n = 17)</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

**Discussion**

According to reports by the American Lung Association, the vast majority of patients with lung cancer (85%) have metastatic disease at the time of presentation. Patients with metastatic lung cancer have a 5-year survival rate of 2.1%, compared to those who have disease limited to the lungs at 48.5%. The correct staging of patients is essential for appropriate care and cost containment. Patients, who are suitably staged with local cancer limited to the lung and hilar lymph nodes, receive more aggressive therapy (surgery) with a higher likelihood for cure. In contrast, patients with nonresectable metastatic disease receive palliative therapy. The detection of metastatic disease is therefore important in order to avoid costly...
surgery in patients who will not benefit but may in fact have complications from surgery and anesthesia. Numerous studies have reported on the usefulness of PET for improved staging of lung cancer. Although image resolution is less optimal, PET is far more sensitive and specific than CT scan for detecting metastatic nodal disease. Additionally, studies have shown that PET can detect distant metastases that are frequently missed by conventional diagnostic procedures. The reported incidence of occult distant metastases detected by PET ranges from 9 to 11%.

The likelihood of having distant metastases increases with more advanced nodal disease. MacManus et al found a greater percentage of patients who had more advanced disease had distant metastases on thoracic PET. The most common sites for metastases were the upper abdomen followed by lung and pleura and lastly bone. Pieterman et al reported a 11% incidence of distant metastases detected only by WB PET. In this study, 9 of 29 hot spots that were considered to be suspicious for metastases were false-positive, and were located in colon, lung, liver, adrenal glands, and rib. However, the authors did not specify the exact location of the remaining true metastases that were identified. In addition, correlation between nodal staging and the presence of extrathoracic metastases was not reported.

Other studies included the location of extrathoracic metastases that were identified on PET. Valk et al also reported finding distant metastases in 11% of their study patients. Although the locations of most bone and soft-tissue metastases were not specified in five patients, the remaining patients had metastases in the liver (n = 3), perip儒al region (n = 1), adrenal gland (n = 1), and thoracic spine (n = 1), all of which would be within the confines of a thoracic PET. They confirmed metastases detected in the liver and adrenal glands by CT in 7% of their patients.

Weder et al were more specific in reporting the locations of extrathoracic metastases on PET. Of 94 patients with lung cancer who underwent WB PET, the incidence of metastases was greater in patients with more advanced nodal disease. They found metastatic lesions in 9% of patients with N0/N1 disease and 28% of patients with N2 disease. Twelve of 13 distant metastases were found between the neck and upper abdomen: liver (n = 3), adrenal gland (n = 2), cervical lymph nodes (n = 2), ribs (n = 4), and L1 vertebral body (n = 1). One had metastases in the CNS and unspecified skeleton.

In previous report of a different series of 313 patients imaged by WB FDG-PET for lung cancer staging or pulmonary nodule evaluation, we demon-
strated similar results to the findings of the current study. Our results clearly indicate that the overwhelming majority of metastatic lesions in patients evaluated for a solitary pulmonary nodule or for lung cancer staging are detectable by thoracic PET. However, because our study is retrospective, the outcome of all our patients including those with true negative PET scans (ie, with benign nodules) is unknown. Therefore, we are not able to calculate the true prevalence of extrathoracic metastases among those with lung cancer.

The single case that had a distant metastasis outside the confines of thoracic PET had N3 nodal disease (stage IIIb) by PET. Thus, the findings of our study establish that the chances of detecting isolated distant metastases in a patient with lung cancer who has no evidence of coexisting thoracic nodal metastases is small. All other patients who had distant metastases in our study group had evidence of nodal disease. Therefore, we suggest that any radiologic evidence of nodal disease should raise suspicion for potential distant metastases.

Findings reported by Tanaka et al\textsuperscript{13} support our recommendations. In their study of 755 patients with clinical T1–2N0 disease, occult metastases were detected by radiologic studies in 0.5% of patients with T1N0 disease and 0.9% of patients with T2N0 disease. Metastases were in the brain, liver, or both, in four of five patients with occult metastases. Only one patient had an occult bone metastasis, the anatomic site of which was not described. A WB FDG-PET would not have routinely surveyed for brain metastases, and therefore these metastases would have been occult regardless if a conventional WB or thoracic PET was performed. Although the exact location of the liver metastases were not mentioned, a thoracic PET would have potentially identified these lesions since a large proportion of the liver is included in a thoracic PET scan.

According to the recently published guidelines of the American Thoracic Society and European Respiratory Society\textsuperscript{1} and those by Silvestri et al\textsuperscript{2} for pretreatment evaluation of patients with lung cancer, the workup for extrathoracic metastases should not be undertaken unless clinical findings are suspicious. With the recent introduction of hybrid PET-CT imaging devices into clinical practice and the use of CT for PET transmission attenuation correction, the issue of radiation dose needs to be addressed. WB PET with these new imaging systems will lead to additional radiation exposure to patients who may not require such extensive imaging through the lower abdomen and pelvis. Patients receiving a PET study for evaluation of a nodule or lung cancer will have received a thoracic CT with imaging through the adrenals and upper abdomen as part of an initial workup. Patients who have no evidence of advanced nodal disease or clinical findings to indicate extrathoracic metastases or who are receiving a PET scan for single pulmonary nodule evaluation (and no previous history of malignancy) may only need a thoracic PET and not the additional imaging of a WB PET. The estimated dose a patient would receive for a CT transmission scan (of a dual CT-PET unit) using a low-dose multidetector CT scan at 120 kV, 40 mA would be approximately 150 millirem.\textsuperscript{14} The addition of the remaining abdomen, pelvis, and part of the upper thighs of a WB CT at 120 kV, 50 mA would approximately double the dose at twice the length. In this patient group, who either may not have a malignancy (ie, if PET scan finding is negative) or have potentially curable disease, the need to minimize radiation dose is important since their life expectancy should be greater.

There are some limitations to our study. There is an intrinsic selection bias when using a retrospectively collected group of patients. Additionally, we were not able to accurately track how many of those patients with single pulmonary nodules and negative uptake on PET were truly benign. Studies have shown that some neoplasms such as carcinoid tumor\textsuperscript{15,16} or bronchoalveolar cell carcinoma\textsuperscript{17,18} have low metabolic activity and may not be detectable by FDG-PET. In addition, data were not available to comprehensively confirm that all PET scan findings that were interpreted as negative for metastases and therefore excluded from our study group were truly free of metastatic disease.

In busy PET centers such as ours, scheduling delays for a patient to undergo PET scanning can be >2 weeks. This delay can have a substantial impact on patient management in terms of timely staging and therapy. By appropriately scheduling patients with no clinical evidence of nodal disease or distant metastases for a thoracic PET rather than WB PET, more patients can be imaged in a more timely fashion. A standard PET camera with 15-cm axial field of view requires approximately 12 min for each bed position. A thoracic PET requires approximately five bed positions, compared to a WB PET, which takes approximately eight bed positions, depending on patient size. This would save up to 35 min of scan time. Due to the reduction in imaging time required for a thoracic PET study, the possibility of image degradation due to patient motion would be reduced and the procedure better tolerated by fragile patients. Alternatively, with quicker scan times, additional special imaging techniques may be incorporated during the scheduled study such as high image count density with respiratory gating for better lesion definition or delayed or dual-point imaging for differentiating tumor from inflammatory processes.\textsuperscript{19,20}
In less busy PET facilities, the dose of radiopharmaceutical used for a thoracic PET study could be reduced by increasing the time per bed position. This would result in reduced cost for FDG and as well as less radiation exposure to technologists.

In summary, our results suggest that thoracic PET is adequate in the evaluation of patients receiving a scan for a single pulmonary nodule or who have no clinical or thoracic CT findings suspicious for nodal disease, or intrathoracic or extrathoracic metastases. Although thoracic PET was nearly as accurate in staging patients as WB PET, we recommend WB PET for any patient with newly diagnosed lung cancer in which there is significant clinical or radiologic concern for distant metastases.

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