Integrated PET/CT in the preoperative staging of lung cancer: A prospective comparison of CT, PET and integrated PET/CT

Mona A. El-Hariri a,*, Ghada K. Gouhar a, Ali M. Refat b

a Department of Radiodiagnosis, Faculty of Medicine, Zagazig University, Egypt
b Department of Cardio-Thoracic Surgery, Faculty of Medicine, Zagazig University, Egypt

Received 15 June 2012; accepted 19 September 2012
Available online 23 October 2012

KEYWORDS
Lung cancer; Integrated PET/CT; CT; PET

Abstract  Purpose: The purpose of this study was to evaluate the role of integrated PET/CT in the staging of lung cancer compared with CT alone or PET alone.
Materials and methods: Thirty-three patients underwent integrated PET/CT for the staging of lung cancer. The tumor, node and metastasis (TNM) stages were assessed with CT, PET and integrated PET–CT and compared with the surgical and pathological staging.
Results: CT correctly evaluated the (T) status in (64%) of the patients, PET in (59%) and PET/CT in (86%). CT correctly evaluated the (N) status in (73%) of the patients, PET in (76%), and PET/CT (88%) with accuracy, sensitivity, specificity, PPV and NPV were 73%, 78%, 71%, 50% and 94% for CT, 76%, 67%, 79%, 55% and 95% for PET and 88%, 89%, 88%, 73% and 100% for PET/CT respectively, and for (M) status were 91%, 86%, 92%, 75% and 96% for CT, 88%, 71%, 92%, 71% and 92% for PET and 97%, 100%, 96%, 88% and 100% for PET/CT respectively. Regarding the overall TNM staging CT correctly staged 24 patients. PET correctly staged 23 cases while PET/CT correctly staged 30 cases. A significant difference in the accuracy of overall tumor staging between PET/CT and CT (P = 0.0412) or PET (P = 0.0233).
Conclusion: The integrated PET/CT is superior to either CT or PET in the staging of lung cancer which has an important impact on selection of the appropriate treatment regimen.

1. Introduction
Lung cancer is the most common cancer in the world and is the leading cause of cancer related death in many countries (1,2). Accurate staging of lung cancer is mandatory to choose the optimal treatment and to select patients who are likely to benefit from surgery (3–5). Staging of lung cancer is based on accurate determination of the tumor size, infiltration of
the contiguous structures, the presence or absence of satellite nodules, the involvement of hilar and mediastinal lymph nodes and the presence of distant metastasis. Tumor, node, metastasis (TNM) staging, as defined by the American Joint Committee on Cancer (AJCC), is a very important tool not only to determine the prognosis but also to choose the most appropriate therapy for patients with lung cancer (6–9).

Conventional chest radiography, computed tomography (CT), magnetic resonance imaging, radionuclide scintigraphy, and positron emission tomography (PET) have all been used for the staging of lung cancer (10).

Computed tomography (CT) is most frequently used in the suspected lung tumors. It gives imaging information about the localization and the extent of the tumor, the presence of enlarged lymph nodes and the presence of metastatic disease but it is limited by the inability to distinguish between benign and malignant disease entities (11,12). Theoretically, one could perform CT of the head, neck, chest, abdomen, pelvis, and even the extremities, to stage lung cancer. However, this is not a reasonable approach because of excessive radiation exposure, expense, and the use of scanner time. Obviously, the chest must be scanned for complete evaluation of the primary lung tumor and for assessment of hilar and mediastinal lymph node involvement and thoracic metastases (13).

Positron emission tomography (PET) with the glucose analog 2-18F-fluoro-2-deoxy-D-glucose (FDG) is based on the enhanced glucose metabolism of lung cancer cells. FDG undergoes the same uptake as glucose but it is metabolically trapped and accumulated in the cancer cell after phosphorylation by hexokinase. Reading of the FDG distribution in the body by the PET camera allows differentiation between normal and malignant tissues and improves identification of nodal involvement, distant metastases, and early tumor recurrence (14–17). However, the relatively poor spatial resolution, the low contrast between different tissues and the blurring due to motion and partial volume effects in small foci can result in difficulties to localize lesions that show pathologic FDG uptake. Furthermore, false-positive FDG uptake is seen in inflammatory conditions such as bacterial pneumonia. On the other hand false-negative results can occur in lesions smaller than 1 cm because a critical mass of metabolically active malignant cells is required for PET diagnosis. Some tumor tissues also show no or little FDG uptake, like biologically weak tumors such as bronchoalveolar cell carcinoma (14,18–20).

Combining detailed anatomical information obtained by CT with the metabolic information obtained by FDG-PET in PET/CT enables more accurate characterization of pulmonary lesions that are indeterminate on CT, more accurate staging of lung cancer and this in turn frequently alters the management strategy, reduces the number of futile thoracotomies and provides important prognostic information (21–26).

PET and CT can be combined using different techniques.
The integrated PET/CT study using a single machine provides the best co-registration of physiologic and anatomic details (6).

The purpose of this study is to evaluate the role of integrated PET/CT in the staging of lung cancer in comparison with CT alone or PET alone.

2. Patients and methods

2.1. Patients

Thirty-three patients (28 men and five women) having lung cancer with a median age of 64 years (range 34–76 years) were included in our study. They underwent whole body integrated PET/CT imaging for staging lung lesions in the period from September 2010 till December 2011. CT, PET, and combined PET/CT data were evaluated separately for staging of the primary tumor (T), regional lymph nodes (N) and distant metastasis (M). Imaging findings were compared with histopathological findings (Gold standard). Institutional review board approval and informed consent was taken from all patients.

2.2. PET/CT imaging

Combined PET/CT imaging was conducted by using the Siemens medical solution system (Siemens biograph 64 PET/CT scanner). The CT component of the biograph corresponds to a Somatom sensation 64 section (Siemens Medical Solutions). CT images were acquired with 130 mAs, 130 kV and slice thickness of 5 mm. The scanning area for CT and PET was defined on a CT topogram with a field of view from the head to the middle thigh. To ensure diagnostic CT image quality, 120 ml of iodinated contrast agent was administered intravenously using an automated injector. CT was performed during breath-hold at expiration tidal volume. This limited breath-hold technique was used to avoid respiration artifacts on the CT images and for a good matching between the CT and the PET images.

The PET component of the combined PET/CT tomography is based on an ECAT ACCEL Siemens Medical Solutions), a full-ring Lutetium ortho silicate (LSO)-based PET system with an in-plane spatial resolution of 4.6 mm and an axial field of view of 15.5 cm for each bed position. PET imaging was performed 60 min after the administration of 300 MBq (about 8 mci) of FDG by multiple overlapping bed positions (5 min per bed position). Patients rested in the supine position during the tracer uptake phase to avoid muscular tracer accumulation. Attenuation correction was based on the CT data. Patients had been instructed to fast for 6 h prior to starting the examination. Blood samples collected before the injection of the radioactive tracer ensured blood glucose levels in the normal range.

3. Imaging data analysis

3.1. CT images

CT staging was done using the CT images obtained from the integrated PET/CT scanner. The radiologist was asked to assign a T, N, and M status of the tumor using the 7th edition of the AJCC (The American Joint Committee on Cancer) TNM system for the classification of lung cancer. Tumor assessment was based on lesion size and localization, its relation to the surrounding structures and chest wall and the distance of the primary tumor from the carina. Lymph node assessment was based on its size. Lymph nodes with a short axis diameter greater than 10 mm were considered positive. Assessment of the M status for lung, liver, adrenal glands, brain, bone and other organs was performed using criteria such as size, localization and contrast enhancement.
3.2. PET images

PET images were assessed qualitatively for regions of focally increased FDG uptake, as well as quantitatively by determining standardized uptake values. An increase in FDG uptake to a level greater than that in the surrounding tissue at qualitative analysis and a standard uptake value of more than 2.5 were considered to characterize malignancy. T, N and M status of each patient was assessed using the AJCC TNM system.

3.3. Integrated PET/CT images

Fused PET/CT images were evaluated to assign the T, N and M status of each patient using the AJCC TNM system. Tumor staging was performed as in CT. A lesion suggestive of a primary tumor on CT but negative on PET was considered positive, and a lesion not suggestive on CT but positive on PET was considered positive for tumor on integrated PET/CT. Lymph nodes with increased FDG uptake were considered positive for metastatic spread even when they were smaller than 1 cm in short-axis diameter. PET negative lymph nodes were considered as benign, even when they were larger than 1 cm in short-axis diameter. Concerning distant metastasis (M) pulmonary nodules suggestive for lung metastases on CT but negative at PET were considered as lung metastases. Lesions in the liver, spleen and brain suspicious of metastases...
on PET or CT were considered as positive for metastases. An enlarged adrenal gland on CT but negative at PET was considered as negative. Mediastinal hotspots on PET but without a visible lesion on CT were considered as negative on integrated PET/CT.

3.4. Surgical and histopathological analysis

Tumor resection and mediastinal lymph node dissection were performed in 22 patients. Surgery was performed within a maximum of 10 days after imaging. The surgeon sampled all visible and palpable lymph nodes that were accessible in the hilum and mediastinum. A pathologist assessed the primary tumor regarding the histopathological type, size, invasion of the surrounding structures and the distance from the resection margin and the location of the involved lymph nodes. Specimens were stained with hematoxylin and eosin and examined with light microscopy. Surgical and pathological staging for the tumor (T) and the lymph node (N) was done for these 22 patients. The remaining 11 patients underwent mediastinoscopy for lymph node staging. Verification of distant metastasis stage (M stage) was done by biopsy or radiological follow up (for 5–7 months).

3.5. Statistical analysis

Statistical analysis was performed using specialized software (SPSS for Windows v10). Analysis for the tumor (T stage), lymph nodes (N stage), and metastases (M stage) with CT
alone, PET alone and integrated PET/CT was performed and compared with the pathological staging which was used as the standard of reference. The sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV) and accuracies of the three different imaging techniques in the assessment of the T, N, and M stages and of the TNM system stage were calculated. The accuracies of the three different imaging techniques were compared by McNemar’s test.

4. Results

Thirty-three patients (28 men and five women) having lung cancer with a median age of 64 years were included in our study. Twenty-two patients underwent surgical resection and staging. The remaining 11 patients underwent mediastinoscopy and lymph node biopsy. Representative cases are seen in (Figs. 1–7). CT correctly evaluated the primary tumor (T) status in 14 of 22 patients (64%), under staged 5 patients and over staged three patients. PET correctly staged 13 patients (59%), under staged 3 patients and over staged six patients while PET/CT correctly staged 19 patients (86%) and under staged three patients (Tables 1 and 2).

CT correctly evaluated the lymph node involvement in 24 of 33 patients (73%), under staged 2 patients and over staged 7 patients. PET correctly staged 25 patients (76%), under staged two patients and over staged six patients while PET/CT correctly staged 29 patients (88%), under staged one patient and over staged three patients (Tables 3 and 4).

The accuracy, sensitivity, specificity, PPV and NPV for the detection of malignant lymph nodes were 73%, 78%, 71%, 50% and 94% for CT, 76%, 67%, 79%, 55% and 95% for PET and 88%, 89%, 88%, 73% and 100% for PET/CT respectively.

Distant metastases were detected in seven cases; one to the brain, four to bone, one to the spleen and one to the lung (Table 5). CT correctly detected six cases (true positive) but could not detect one case to the bones (false negative). On the other hand it had two false positive cases (one to the lung and one to the adrenal). PET correctly detected five cases (true positive) but could not detect two cases (false negative); one to the brain and the other to the spleen, while it had two false positive cases (one to the lung and one to the colon). PET/CT correctly detected the seven cases (true positive) and had one false positive case to the lung.

The accuracy, sensitivity, specificity, PPV and NPV for the detection of distant metastases were 91%, 86%, 92%, 75% and 96% for CT, 88%, 71%, 92%, 71% and 92% for PET and 97%, 100%, 96%, 88% and 100% for PET/CT respectively.

Overall TNM staging was done for all cases. Twenty-two cases underwent surgical staging for the primary tumor, two cases were histopathologically proven N2 without distant metastasis (stage IIIa), two cases were N3 without distant metastasis (stage IIIb) and seven cases with distant metastasis (stage IV). CT alone correctly staged 24 patients (73%), over staged five cases and under staged four cases. PET alone

---

### Table 1 Primary tumor (T) staging in CT, PET and PET/CT in comparison with pathological staging.

<table>
<thead>
<tr>
<th>Pathological stage</th>
<th>Number</th>
<th>CT</th>
<th>PET</th>
<th>PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>T0</td>
<td>T1</td>
<td>T2</td>
</tr>
<tr>
<td>T1</td>
<td>6</td>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>T2</td>
<td>12</td>
<td>0</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>T3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>T4</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
correctly staged 23 cases (70%), over staged seven cases and under staged three cases. PET/CT correctly staged 30 cases (91%), over staged one case and under staged two cases. Differences in the accuracy of overall tumor staging between PET/CT and CT \((P = 0.0412)\) and between PET/CT and PET \((P = 0.0233)\) were significant.

5. Discussion

The rationale of accurate preoperative staging of lung cancer is to choose the optimal treatment. CT is the standard modality used to assess the intra-thoracic spread but false negative CT scans have been reported and were related to the presence of metastasis in normal sized lymph nodes and false positive findings have been related to lymph node enlargement due to benign process. PET is most widely used in thoracic oncology because of its superiority over other imaging techniques in staging nodal and metastatic disease, however, the poor anatomic details of PET can lead to errors in diagnosis and staging. To circumvent this problem, CT is combined with PET to provide spatially matched morphological and functional data. The diagnostic capability of PET/CT in the preoperative staging of lung cancer is superior to that of CT alone and PET alone as it has the advantage of a more accurate assignment of tumor stage (T stage) and defining the lymph node stage (N stage) as well as reduction of the number of futile thoracotomies \((3,6,26,27)\).

In our study integrated PET/CT was better than PET alone and CT alone in the assessment of the primary tumor stage (T stage). CT correctly evaluated the tumor (T) stage in 14 of 22 patients (64%), PET correctly staged 13 patients (59%), while PET–CT correctly staged 19 patients (86%). This is in agree-

### Table 2
Agreement of CT, PET and PET/CT with pathological staging in primary tumor (T) staging.

<table>
<thead>
<tr>
<th>Pathological stage</th>
<th>Number</th>
<th>CT</th>
<th>PET</th>
<th>PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Agreement</td>
<td>Under staging</td>
<td>Over staging</td>
</tr>
<tr>
<td>T1</td>
<td>6</td>
<td>4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>T2</td>
<td>12</td>
<td>8</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>T3</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>T4</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>14</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

### Table 3
Lymph node (N) staging in CT, PET and PET/CT in comparison with pathological staging.

<table>
<thead>
<tr>
<th>Pathological stage</th>
<th>Number</th>
<th>CT</th>
<th>PET</th>
<th>PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Agreement</td>
<td>Under staging</td>
<td>Over staging</td>
</tr>
<tr>
<td>N0</td>
<td>24</td>
<td>17</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>N1</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>N2</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>N3</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td>24</td>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>

### Table 4
Agreement of CT, PET and PET/CT with pathological staging in lymph node (N) staging.

<table>
<thead>
<tr>
<th>Pathological stage</th>
<th>Number</th>
<th>CT</th>
<th>PET</th>
<th>PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Agreement</td>
<td>Under staging</td>
<td>Over staging</td>
</tr>
<tr>
<td>N0</td>
<td>24</td>
<td>17</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>N1</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N2</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>N3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td>24</td>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>

### Table 5
Distant metastasis (M) staging in CT, PET and PET/CT in comparison with pathological staging.

<table>
<thead>
<tr>
<th>Pathological stage</th>
<th>Number</th>
<th>CT</th>
<th>PET</th>
<th>PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Agreement</td>
<td>Disagreement</td>
<td>Agreement</td>
</tr>
<tr>
<td>M0</td>
<td>26</td>
<td>24(true negative)</td>
<td>2(false positive)</td>
<td>24(true negative)</td>
</tr>
<tr>
<td>M1</td>
<td>7</td>
<td>6(true positive)</td>
<td>1(false negative)</td>
<td>5(true positive)</td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td>30</td>
<td>3</td>
<td>31</td>
</tr>
</tbody>
</table>
ment with an earlier study (28) in which the T stage was accurately determined with PET/CT in 15 of 16 patients while PET and CT enabled accurate staging in 12 patients. Also this coincides with the study carried out by Wever et al. (29) who reported that in 43 (86%) patients, integrated PET/CT could correctly evaluate the T status, while CT was correct in 34 (68%) and PET in 23 (46%). In the study performed by Subedi et al. (30) T staging at CT was only concordant with the final histology in 42 (58%) patients while PET/CT was concordant with final pathological T stage in 47 patients (64%). In another study (27) the primary tumor was correctly staged in 84 patients (79%) at CT and in 91 patients (86%) at PET/CT.

This limited ability of PET alone and CT alone in T staging can be explained as follows, limited spatial resolution and the lack of depicted anatomic landmarks limit the ability of PET to enable the assessment of either tumor size or potential infiltration of the thoracic wall, mediastinum, or other adjacent structures. On the other hand, CT frequently does not enable differentiation of tumor tissue from adjacent structures.

In our study Integrated PET/CT was better than PET alone and CT alone in the assessment of the lymph node stage (N). The accuracy, sensitivity, specificity, PPV and NPV for the detection of malignant lymph nodes were 88%, 89%, 88%, 73% and 100% for PET/CT versus 73%, 78%, 71%, 50% and 94% for CT and 76%, 67%, 79%, 55% and 95% for PET respectively. Our results coincide with several earlier reports (27–30). In one of these studies, (29) the sensitivity, specificity, PPV, NPV and accuracy were respectively 83%, 84%, 75%, 90% and 84% for integrated PET/CT versus 83%, 68%, 60%, 88% and 74% for CT and 83%, 81%, 71%, 89% and 82% for PET. Another study (28) reported that the sensitivity, specificity, PPV, NPV and accuracy were respectively 89%, 94%, 89%, 94% and 93% for integrated PET/CT versus 70%, 59%, 50%, 77% and 63% for CT and 89%, 89%, 80%, 94% and 89% for PET. Fischer et al. (26) showed that the accuracy of PET/CT in detection of malignant lymph nodes was superior to CT alone (85% versus 70%). Also Subedi et al. (30) reported that nodal staging at PET/CT had a higher sensitivity (74% vs. 53%), specificity (87% vs. 84%), positive predictive value (67% vs. 53%), negative predictive value (90% vs. 84%) and accuracy (84% vs. 76.6%) than CT.

This can be attributed to the fact that the characterization of N stage on CT images is based on lymph node size. Nodes greater than 10 mm are considered malignant however some literatures (31,32) reported that up to 21% of nodes smaller than 10 mm are malignant, whereas 40% of nodes larger than 10 mm are benign. On the other hand PET can detect malignant nodes but its poor spatial resolution makes it difficult to reveal the exact location of the metastatic lymph nodes.

In the current study CT was superior to PET and PET/CT was superior to each of the CT and PET separately in the detection of distant metastases. The accuracy, sensitivity, specificity, PPV and NPV were 91%, 86%, 92%, 75% and 96% for CT versus 88%, 71%, 92%, 71% and 92% for PET and 97%, 100%, 96%, 88% and 100% for PET/CT respectively.

These findings support the previous study (28) which reported also that CT is superior to PET and PET/CT is superior to each of the CT and PET separately in the detection of distant metastases. De Wever et al. (29) reported that integrated PET/CT evaluated the M status correctly in 98% of patients, while CT alone was correct in 88% and PET in 96% of patients. Subedi et al. (30) found that PET/CT revealed metastasis in 25 (16%) patients in whom CT failed to detect them. On the other hand another study (33) showed that integrated PET/CT was only a little better to assess metastatic disease compared with PET alone (92% versus 87%).

In the current study, integrated PET/CT evaluated the overall TNM stage correctly in 91% of the patients, while CT and PET were correct in respectively 73% and 70% of the patients. The difference between integrated PET/CT and CT (P = 0.0412) and PET (P = 0.0233) was significant. This coincides with the previous study (28) which showed that of 27 patients, the overall tumor stage was correctly determined by CT, PET and PET/CT in 19, 20 and 26 patients respectively. The differences in the accuracy of overall tumor staging between PET/CT and CT (P = 0.008) and between PET/CT and PET (P = 0.031) were statistically significant. This is in agreement with a previous study (29) which reported also that integrated PET/CT was correct in 70% of the patients, while CT and PET were correct in 46% and 30% of the patients respectively and the difference between integrated PET/CT and CT (P = 0.0153) and PET (P < 0.0001) was significant also. Shim et al. (27) showed that the correct overall staging (tumor and nodes only) for 106 patients was statistically higher by integrated PET/CT (n = 92: 87%) than CT alone (n = 70: 66%).

The rationale for accurate preoperative staging of lung cancer is to choose the optimal treatment, select patients suitable for surgery and reduce the number of futile thoracotomies (3). In our study PET/CT over staged only one case and under staged two cases, CT alone over staged five cases and under staged four cases while PET alone over staged 7 cases and under staged three cases. The impact of PET/CT on the treatment strategy was shown by Subedi et al. (30) who found that 66 (41%) patients had a change in management as a direct result of PET/CT. The most important change was regarding if to proceed to surgery or not. As of 102 patients who were initially planned to undergo surgery, only 64 had the same plan after PET/CT evaluation.

6. Conclusion

The integrated PET/CT linking the anatomic and functional information is superior to CT alone or PET alone in the staging of lung cancer which has an important impact on the selection of the appropriate treatment regime.

References


