Role of $^{99m}$Tc-Hexakis-2-Methoxy-Isobutylisonitrile in the Diagnosis and Staging of Lung Cancer*

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Background: Preliminary studies have shown that $^{99m}$Tc-hexakis-2-methoxyisobutylisonitrile (MIBI) is an interesting tracer for various tumors. The aim of this study was to determine the feasibility of using $^{99m}$Tc-MIBI as a diagnostic and staging procedure for lung cancer.

Methods: We prospectively compared the results of biopsy with $^{99m}$Tc-MIBI imaging in patients with potentially resectable lung lesions (stages IIIA or lower). In the patients with radiopharmaceutical uptake, the staging provided by CT was compared with that obtained with $^{99m}$Tc-MIBI.

Results: Ninety-nine of the 116 patients examined had lung cancer. For the diagnosis of malignancy, the specificity of $^{99m}$Tc-MIBI was 100%, sensitivity was 89.8%, positive predictive value was 100%, negative predictive value was 62.9%, and accuracy was 91.4%. In the 87 patients with radiopharmaceutical uptake in their lung cancer, the values for the specificity and sensitivity of $^{99m}$Tc-MIBI in the detection of mediastinal lymph node metastases were 100% and 54.5%, respectively. The corresponding values for CT in the same patients were 87.6% and 63.3%, respectively. The difference in specificity is statistically significant ($p = 0.011$).

Conclusions: This study demonstrates that $^{99m}$Tc-MIBI provides significant diagnostic and staging information in patients with lung lesions. The high specificity and positive predictive value of $^{99m}$Tc-MIBI suggest that this radiopharmaceutical could be a very useful tool for the diagnosis of lung cancer, especially in consideration of its low costs and wide availability.

Key words: lung cancer; staging; $^{99m}$Tc-hexakis-2-methoxyisobutylisonitrile

Abbreviations: FDG-PET = 18-fluorodeoxyglucose positron emission tomography; MIBI = hexakis-2-methoxy-isobutylisonitrile; SPET = single-photon emission tomography

Lung cancer is the leading cause of death from cancer in Western countries. Although screening is a controversial problem, early diagnosis is closely related to survival. Surgical resection remains the preferred treatment for stage I or stage II non-small cell lung cancer. Because the involvement of the mediastinal lymph nodes limits survival after surgical resection, accurate preoperative staging is important to avoid inappropriate surgery in patients with advanced N2–3 disease.

CT of the chest is the standard procedure for the diagnosis and staging of lung cancer. CT provides very good anatomic imaging but has limitations in the detection of nodal metastases (sensitivity, 61 to 73%; specificity, 62 to 86%).1–3 The relatively poor performance of CT in the identification of nodal metastases has led to a search for new approaches. Several studies4–6 have reported the superior accuracy of 18-fluorodeoxyglucose positron emission tomography (FDG-PET) over CT in the mediastinal staging of lung cancer (sensitivity, 62 to 97%; specificity, 79 to 99%). Unfortunately FDG-PET has some limitations: the increase in glucose metabolism is not specific to neoplastic diseases, the anatomic resolution of the images is limited, the availability of positron emission tomography scanners is still limited, and their costs are high.

Various radionuclides, such as $^{67}$Ga and $^{201}$Tl, have been utilized in lung cancer for staging, follow-up, and monitoring the response to therapy. $^{99m}$Tc depreotide has also proven itself to be a highly sensitive method of evaluation of lung lesions. Encouraging results have also been obtained with single photon emission tomography (SPET) scanning using...
Materials and Methods

Patients with potentially resectable lung lesions (TNM stages IIA or lower) considered indeterminate or suspect of malignancy by clinical-radiographic criteria were eligible. Their data were prospectively gathered. Patients with previous malignancies or those who had already undergone neoadjuvant therapy were excluded. All of the patients gave their informed written consent for participation in the study. The clinical assessment included a physical examination, hematologic and biochemical screening, bronchoscopy, bone scan, CT of the chest and upper abdomen, and 99mTc-MIBI SPET. The pathologic diagnosis of lung lesions was achieved by fine-needle aspiration cytology or thoracoscopy as previously reported. Confirmation of the presence or absence of mediastinal lymph node metastases in the patients with lung cancer was achieved by mediastinoscopy, thoracoscopy, or thoracotomy. Patients with stage I or II non-small cell lung cancer underwent lung resection and mediastinal lymph node dissection.

All of the CT scans were performed in our institution with a Hispeed CT/i (General Electric; Milwaukee, MI) using a contrast medium (120 mL of iopentolol at a rate of 2 mL/s). The spiral CT scans were acquired from the apex of the lung to the suprarenal glands, including the liver. Mediastinal lymph nodes >1 cm in diameter were classified as metastatic. The staging was carried out according to the TNM criteria.

All of the patients received an IV injection of 740 megabecquerels of 99mTc-MIBI that was prepared according to the instructions of the manufacturer. SPET acquisition commenced approximately 20 to 40 min after administration. The data were acquired using a triple-head gamma camera (Prism 3000xp; Picker International; Bedford Heights, OH) equipped with a low-energy, high-resolution collimator. The images were visually examined for evidence of focal uptake in the lung and mediastinum. The SPET reader (M.G.) was unaware of the CT and pathologic results. An illustrative image of 99mTc-MIBI SPET in a patient with true-positive results is shown in Figure 1.

The 99mTc-MIBI SPET results were compared with the pathologic diagnoses to assess the sensitivity, specificity, positive and negative predictive values, and accuracy in differentiating benign from malignant pulmonary lesions. In patients with lung lesions positive to 99mTc-MIBI SPET, we determined the sensitivity, specificity, positive and negative predictive values, and accuracy of CT and SPET in detecting mediastinal metastases. Because surgical treatment was not planned in patients with small cell lung cancer, they were excluded from this second part of the study.

A χ² test was performed to determine the statistical differences. The degree of agreement between CT, SPET, and pathologic test was quantified using the κ statistic test.

Results

Between March 1998 and March 2000, 116 patients with a potentially resectable pulmonary lesion (TNM stages IIA or lower) were enrolled in the study. Their mean age was 64.7 years. Table 1 presents the characteristics and pathologic diagnoses of the patients. Non-small cell lung cancer was diagnosed in 97 patients, small cell lung cancer was diagnosed in 2 patients, and benign lesions were diagnosed in 17 patients. Of the 99 patients with malignant tumors, 88 patients (88.8%) had a positive 99mTc-MIBI SPET result. None of the patients with a benign lesion had a positive SPET result. The characteristics of the 97 patients with proven non-small cell lung cancer are listed in Table 2. 99mTc-MIBI SPET demonstrated a 100% specificity and positive predictive value for the diagnosis of malignancy. The sensitivity, accuracy, and nega-

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\text{Table 1—Characteristic of 116 Patients With Potentially Resectable Lung Lesions*}
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<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total Value</th>
<th>Positive SPET Result</th>
<th>Negative SPET Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>116</td>
<td>89</td>
<td>27</td>
</tr>
<tr>
<td>Male/female gender</td>
<td>87/29</td>
<td>68/21</td>
<td>19/8</td>
</tr>
<tr>
<td>Average age (SD), yr</td>
<td>64.7 (8)</td>
<td>64.8 (8.2)</td>
<td>64 (9.2)</td>
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<tr>
<td>Non-small cell lung cancer</td>
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<td>87</td>
<td>10</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
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<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Granuloma</td>
<td>7</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Hamartoma</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Tuberculoma</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Aspergillum</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Inflammatory pseudotumor</td>
<td>1</td>
<td>0</td>
<td>1</td>
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</tbody>
</table>

*Data are presented as No. unless otherwise indicated.
The statistic measure of agreement was 0.64. Age, sex, histologic type, grading, and location of the lung
value were 54.5%, 88.5%, and 86.6%, respectively. The sensitivity, accuracy, and negative predictive
detection of metastatic mediastinal lymph nodes. 100% specificity and positive predictive value in the
differences between CT and 99mTc-MIBI SPET in
substitution99mTc-MIBI results. None of the patients
logic investigation, 12 patients had positive medias-
tinal lymph nodes positive to patho-
Grade 3 51 45 6

Table 2—Characteristic of 97 Patients With Proved Non-Small Cell Lung Cancer*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total Value</th>
<th>Positive SPET Result</th>
<th>Negative SPET Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>97</td>
<td>87</td>
<td>10</td>
</tr>
<tr>
<td>Male/female gender</td>
<td>75/22</td>
<td>67/20</td>
<td>8/2</td>
</tr>
<tr>
<td>Average age (SD), yr</td>
<td>64.7 (8)</td>
<td>64.8 (8.2)</td>
<td>63.6 (6.3)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>69</td>
<td>62</td>
<td>7</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>27</td>
<td>24</td>
<td>3</td>
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<tr>
<td>Undifferentiated</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Grade 1</td>
<td>13</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Grade 2</td>
<td>33</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>Grade 3</td>
<td>51</td>
<td>45</td>
<td>6</td>
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</table>

*Data are presented as No. unless otherwise indicated.

tive predictive value were 89.8%, 91.4%, and 62.9%, respectively. The agreement between the pathologic and 99mTc-MIBI SPET results was good (κ = 0.72). Age, sex, histologic type and grade of lung cancer, or type of benign lesion did not appear to affect the agreement between the pathologic results and 99mTc-MIBI SPET results. The mean size of the lung lesions was 2.52 cm (from 1 to 5.5 cm); no relation was found between the size and the 99mTc-MIBI SPET result.

All 87 patients with a positive 99mTc-MIBI SPET result for non-small cell lung cancer underwent cervical mediastinoscopy and/or mediastinal lymph node dissection during lung resection. Of the 22 patients with N2–3 lymph nodes positive to pathologic investigation, 12 patients had positive mediastinal 99mTc-MIBI SPET results. None of the patients with negative mediastinal lymph nodes had a positive SPET result. 99mTc-MIBI SPET demonstrated a 100% specificity and positive predictive value in the detection of metastatic mediastinal lymph nodes. The sensitivity, accuracy, and negative predictive value were 54.5%, 88.5%, and 86.6%, respectively. The statistic measure of agreement was 0.64. Age, sex, histologic type, grading, and location of the lung cancer did not affect the SPET results.

The values of sensitivity and specificity of CT for detecting mediastinal nodal metastases in these 87 patients were 63.3% and 87.6%, respectively; the positive and negative predictive values were 63.6% and 87.6%, respectively; accuracy was 81.6%; and the κ measure of agreement was 0.51. No statistical differences between CT and 99mTc-MIBI SPET in terms of sensitivity and accuracy were demonstrated, but SPET was more specific (p = 0.011).

**Discussion**

99mTc-MIBI is a radiopharmaceutical used for myocardial perfusion imaging. The exact mechanism of increased uptake of this lipophilic cation in neoplastic cells is still not completely understood. Some studies13,14 have indicated that the uptake of 99mTc-MIBI is dependent on the negative potential of the cytoplasmatic and mitochondrial membrane; this uptake occurs passively.

Active transposition of 99mTc-MIBI out of cancer cells, against the potential gradient, has also been demonstrated.15 The same mechanism is responsible for the multidrug resistance of some tumor cells to cytotoxic agents. For this reason, some authors16 are evaluating the usefulness of 99mTc-MIBI for the determination of the chemosensitivity of some lung cancers.

Numerous studies have used 99mTc-MIBI as an oncologic marker for a variety of tumors, including lung cancer.17 Because the evaluation of such lung lesions represents a daily dilemma for surgeons, a noninvasive diagnostic method for the identification of malignancies is desirable. This study demonstrates that 99mTc-MIBI SPET has a high specificity for malignancy, as is also suggested by a similar study by the Cleveland Clinic Foundation.18 It is interesting to note that the specificity and positive predictive value were 100% in both studies. This result may depend on the selection of the patients, namely, on the high prevalence of malignant lesions. Nevertheless, this is true of any patient population selected for the resection of indeterminate or possibly malignant lung lesions.

The clinical implication of the lack of false-positive results in our study is that a positive 99mTc-MIBI SPET result may help to avoid invasive diagnostic procedures in high-risk patients. In addition, a positive 99mTc-MIBI SPET result may be helpful in the decision for surgical intervention when noninvasive diagnostic procedures performed on a patient are inconclusive. Published reports demonstrate that FDG-PET has a specificity of 81% for distinguishing malignant lung tumors,19 but the major concern remains the cost. In our institute, the cost of whole-body FDG-PET is $1,000, whereas a 99mTc-MIBI SPET costs $290.

Depending on the dimensional criteria for the acceptance of a lymph node as malignant, the sensitivity and specificity of CT range from 60 to 86%. Thus, mediastinoscopy is the accepted standard for the mediastinal staging of lung cancer. Mediastinoscopy has a sensitivity of 72% and a specificity of 100%.20 but it nonetheless remains an invasive method with acknowledged risk of morbidity. If lung cancer has a 99mTc-MIBI uptake, our study demonstrates that SPET is statistically more specific than CT in detecting N2–3 metastases. Furthermore, SPET has the same specificity as mediastinoscopy but no risk of morbidity and lower costs. Although

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**Table 2—Characteristic of 97 Patients With Proved Non-Small Cell Lung Cancer**
FDG-PET mediastinal staging has been proven to be statistically superior to CT staging in numerous studies, the false-positive results of positron emission tomography nonetheless require histologic confirmation of the mediastinal lesions detected. The same problem affects the good results obtained by 99mTc depreotide in the evaluation of pulmonary nodules. On the contrary, histologic confirmation may not be necessary for lymph nodes positive to 99mTc-MIBI SPET if the specificity and positive predictive value of 100% are confirmed by other wide clinical trials. Therefore, a possible algorithm of the staging of lung cancer using 99mTc-MIBI SPET is shown in Figure 2.

In conclusion, 99mTc-MIBI SPET is an inexpensive diagnostic imaging procedure that may be useful in the evaluation of lung lesions, especially for its high specificity and positive predictive value. Because FDG-PET does not provide sufficient information to avoid surgical confirmation of the mediastinal staging in potentially operable lung cancers, 99mTc-MIBI SPET mediastinal staging may provide an interesting, inexpensive, and widely available alternative.

REFERENCES