CLINICAL SCIENCE

Preoperative nodal staging of non-small cell lung cancer using ^{99m}Tc-sestamibi spect/ct imaging

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OBJECTIVES: The proper nodal staging of non-small cell lung cancer is important for choosing the best treatment modality. Although computed tomography remains the first-line imaging test for the primary staging of lung cancer, its limitations for mediastinum nodal staging are well known. The aim of this study is to evaluate the accuracy of hybrid single-photon emission computed tomography and computed tomography using ^{99m}Tc-sestamibi in the nodal staging of patients with non-small cell lung cancer and to identify potential candidates for surgical treatment.

METHODS: Prospective data were collected for 41 patients from December 2006 to February 2009. The patients underwent chest computed tomography and single-photon emission computed tomography/computed tomography examinations with ^{99m}Tc-sestamibi within a 30-day time period before surgery. Single-photon emission computed tomography/computed tomography was considered positive when there was focal uptake of sestamibi in the mediastinum, and computed tomography scan when there was lymph nodes larger than 10 mm in short axis. The results of single-photon emission computed tomography and computed tomography were correlated with pathology findings after surgery.

RESULTS: Single-photon emission computed tomography/computed tomography correctly identified six out of 19 cases involving hilar lymph nodes and one out of seven cases involving nodal metastases in the mediastinum. The sensitivity, specificity, positive predictive value, and negative predictive value for ^{99m}Tc-sestamibi single-photon emission computed tomography/computed tomography in the hilum assessment were 31.6%, 95.5%, 85.7%, and 61.8%, respectively. The same values for the mediastinum were 14.3%, 97.1%, 50%, and 84.6%, respectively. For the hilar and mediastinal lymph nodes, chest tomography showed sensitivity values of 47.4% and 57.1%, specificity values of 95.5% and 91.2%, positive predictive values of 90% and 57.1% and negative predictive values of 67.7% and 91.2%, respectively.

CONCLUSION: Single-photon emission computed tomography/computed tomography with ^{99m}Tc-sestamibi showed very low sensitivity and accuracy for the nodal staging of patients with non-small cell lung cancer, despite its high level of specificity. In addition, the performance of single-photon emission computed tomography/computed tomography added no relevant information compared to computed tomography that would justify its use in the routine preoperative staging of non-small cell lung carcinoma.

KEYWORDS: Lung cancer; Lymph nodes; MIBI; Single-photon emission computed tomography; Functional imaging.

INTRODUCTION

The survival of lung cancer patients is related to the extent of their disease at the time of diagnosis. In the absence of distant metastases, the spread of tumors to the mediastinal lymph nodes is a major determinant of both the prognosis and the therapeutic approach. Proper staging is important for selecting patients who may benefit from surgical resection and for defining the treatment modalities of patients who will undergo radiotherapy.

The histopathologic evaluation of lymph nodes is considered the gold standard in assessing the presence or absence of metastases in the mediastinum. There are several invasive methods that can be used for this purpose: mediastinoscopy, anterior mediastinotomy, transthoracic needle aspiration, endobronchial or esophageal ultrasound with needle aspiration, and thoracoscopy.[1,2] Mediastinoscopy is the most

common invasive test. It has a mean sensitivity of up to 80%, with a range of 44% to 97%. With this method, only high and low paratracheal, pre-tracheal, and subcarinal lymph nodes are accessible; there is also a low but real risk of morbidity and mortality.[1]

In an attempt to reduce the frequency of invasive methods or to guide the most appropriate procedures for lymph node biopsies, noninvasive imaging tests are used when applicable. Computed tomography (CT) is the imaging method of choice in the evaluation and staging of primary cancers. The diagnostic CT criteria for the involvement of lymph nodes are based on their sizes, especially when their minor axes are longer than ten millimeters. However, small lymph nodes that are considered normal according to such criteria may contain tumor cells, while inflammatory and infectious diseases may be responsible for enlarged lymph nodes, limiting the overall effectiveness of this diagnostic test. In a meta-analysis by Toloza that evaluated 20 studies, chest CT examinations showed a sensitivity of 57%, specificity of 82%, and positive and negative predictive values of 56% and 83%, respectively.[3]

Tomographic imaging in nuclear medicine is based on the metabolic activity of tissues and may be useful for identifying pathological changes before they are detected by radiological examinations such as CTs. PET (positron emission tomography) scans with ^{18}F-FDG (^{18}F-fluorodeoxyglucose) have superior sensitivity and specificity compared to chest CTs and are considered the most accurate imaging method for staging patients with lung cancers.[3-5] However, there are limitations related to positive predictive value of this method because there may be FDG uptake in inflammatory cells.[6] The sensitivity can also be decreased when lymph node metastasis is microscopic or below the spatial resolution threshold of current, state-of-the-art scanners.[7] In Brazil, the availability of PET is restricted to a few institutions because of equipment costs and availability of comercial doses of FDG regarding the number of cyclotrons installed in Brazil.

Alternatively, single-photon emission computed tomography (SPECT) is widely available, has lower costs than PET, and does not require the presence of a cyclotron adjacent to the hospital. Sestamibi (hexakis-2-methoxyisobutyl-isonitrile) labeled with technetium (^{99m}Tc-sestamibi) is a lipophilic cation that is routinely used in myocardial perfusion imaging and has been used as a tumor-seeking agent.[8]

Encouraging results have been obtained with SPECT scanning using sestamibi to detect primary lung malignancies[9-11] and to perform mediastinal staging with a higher diagnostic accuracy higher than chest CTs.[12,13]

Despite the positive results obtained with sestamibi, particularly regarding its specificity, there are difficulties in the analysis of mediastinal images. The main difficulty is related to the limited spatial resolution of SPECT. Furthermore, the vascular structures in the mediastinum and heart, where sestamibi is taken up, interfere with the correct interpretation of the images and could cause false positive results and decrease the diagnostic capability of the method.

The association of functional images and anatomical information from CTs may be useful in interpreting SPECT by providing more accurate data regarding the location and extent of tumor lesions. Hybrid devices usually have dual detectors, with scintillation cameras and low-dose CT scanners. Sequentially, data from both CT and SPECT are acquired. The two images are merged, creating SPECT images that are superimposed on corresponding anatomical planes. This image fusion may help to differentiate between tumors and other areas of physiological activity.[14,15]

The aim of this study is to evaluate the accuracy of SPECT/CT using the radiotracer ^{99m}Tc-sestamibi in the mediastinal lymph node staging of patients with non-small cell lung cancer and candidates to surgical treatment.

MATERIALS AND METHODS

Patients

A cross-sectional study with prospective data collection was conducted from December 2006 to February 2009 at the Hospital de Câncer de Barretos-SP. The study was approved by the Institutional Ethics Committee. The inclusion criteria were as follows: 1) patients of either sex, 2) patients who were at least 18 years old, 3) patients with histological diagnoses of non-small cell lung cancer (e.g., squamous cell carcinoma, adenocarcinoma or large cell carcinoma) or pulmonary lesions that were strongly suspicious for neoplasia, 4) patients with clinical stages I, II, or III, as classified by the sixth edition of TNM[16] with performance status that allowed surgery enrollment (ECOG PS zero or 1), and 5) patients who agreed to participate in the study and signed the informed consent form. Patients were excluded if their diagnosis of non-small cell lung cancer was not confirmed after surgical resection. Patients with bulky lymph node metastases that were considered unresectable and pregnant patients were also excluded.

The clinical evaluation included: physical examination, hematologic and biochemic screening, cardiologic evaluation, bronchoscopy when the pulmonary lesions were considered accessible for this method, bone scan, chest and upper abdomen CT, brain MRI or CT. Forty one patients were enrolled in the study. All of the patients were submitted to surgical procedures for diagnosis and treatment which were performed within 30 days after chest CT and SPECT/CT. The type of resection performed on each patient was defined by the thoracic surgery team in accordance with the extent of the primary tumor. Mediastinal systematic lymph node dissection was performed for adequate pathological staging according to the tumor location. For tumors of the right lung, a mediastinal dissection included the ipsilateral hilar region as well as the upper and lower paratracheal, subcarinal and paraesophageal lymph nodes. For left lung tumors, the left hilar region, lower paratracheal area, aortopulmonary window, and para-aortic, subcarinal, and paraesophageal lymph nodes were sampled. Lymph nodes were identified according to the Mountain nodal station classification system[16] and were sent for histopathological analysis, which was performed by an experienced pathologist with expertise in lung cancer. The largest diameter of the metastatic foci in the lymph nodes was divided into two groups: those <10 mm and those ≥10 mm.

^{99m}Tc-sestamibi SPECT/CT

The GE Medical Systems, Millennium VG, Hawkeye hybrid equipment was used. Every patient received an injection of 1,110 MBq (30 mCi) of ^{99m}Tc-sestamibi, which was prepared following the manufacturer's instructions (Bristol-Myers Squibb Medical Imaging, Massachusetts,

USA). Images were acquired 10 minutes after the administration of sestamibi with patients placed in supine positions with their arms elevated.

SPECT: Emission images were acquired using a dual-head, large field-of-view scintillation camera equipped with a low-energy, high-resolution collimator (VPC-45). The images were acquired every 20 seconds, at a 3° angle, in a circular orbit of 180° per detector array, and using a 128×128 matrix. The equipment was calibrated for a photopeak of 140 keV with a symmetric 20% window.

CT images were acquired sequentially in a non-dedicated 3rd-generation scanner installed in the SPECT camera gantry, with a 10 mm slice thickness (maximum of 40 slices), a maximum current of 2.5 mA and a 140 kV potential.

The raw data from SPECT and CT were transferred from the acquisition equipment to an Entegra workstation (General Electric Healthcare), and the tools provided by the manufacturer were used to process the data. The following iterative processing protocol in standard 2-D was used. The image reconstruction was made after automatic pre-processing, which included the reconstruction of the SPECT plane imaging, the reformatting of the anatomical and functional sections according to the type of organ and the creation of maximum-intensity projection imaging. The Butterworth filter was used with a cutoff frequency of 0.28 Nyquist and an order of 10. After this initial step, the images were reoriented to obtain transaxial, coronal, and sagittal views.

All images were independently interpreted by two nuclear physicians who were blinded to the chest CT and pathology findings. Disagreements in the analysis were resolved by consensus.

The following aspects were analyzed regarding the primary pulmonary lesion: 1) presence or absence of sestamibi uptake; 2) qualitative visual assessment of sestamibi uptake, which was classified as mild, moderate or intense. As a parameter, the uptake in primary tumor was compared with uptake in physiological thoracic structures as follows: more than soft tissues (mild) and less than hepatic uptake; similar to hepatic uptake (moderate); similar to cardiac uptake (intense). The intensity of uptake was correlated with histology and tumor size. 3) a semi-quantitative analysis obtained by outlining the regions of interest (ROI) over the tumor (T) and in the contralateral normal lung (L). ROI was defined manually on coronal images that showed the tumors' highest degree of uptake. The maximum ROI values were measured, and the TL/T index was calculated. This analysis was correlated with the histology, tumor size and tumor size was analyzed as a continuous variable and also divided into three categories: 1) less than or equal to 3.0 cm, 2) greater than 3.0 cm and less than or equal to 7.0 cm and 3) greater than 7.0 cm.

With regard to the lymph nodes, the following aspects were analyzed: 1) the presence or absence of focal uptake in the mediastinum or hilum; 2) a qualitative visual assessment of the sestamibi uptake, which was classified as mild, moderate or intense; 3) a semi-quantitative analysis that was performed in the same manner as the analysis conducted for the primary lesion, comparing radiotracer uptake in the lymph nodes and the lung; and 4) the identification of uptake lymph node chains in accordance with the international system adopted by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer

(UICC), which is the classification proposed by the American Thoracic Society and modified by Mountain-Dresler (MD-ATS).[17]

Chest CT

All CT scans were performed on a Hispeed CT (GE, Milwaukee) after intravenous administration of an iodinated contrast agent at a dose of 1.0 ml/kg. Helical CT scans were performed with a slice thickness of 7 mm, pitch of 1.5 and reconstruction thickness of 5 mm. The scans had a window for the lung parenchyma and a window for the mediastinum and were acquired from the lower cervical region to the upper lumbar region, including the adrenal glands.

The images were read independently by two radiologists who were blinded to the SPECT and pathological findings. Disagreements in the assessments were resolved by consensus. In the axial plane, those lymph nodes larger than 10 mm on their smallest axis were considered suspicious for metastasis. The lymph node stations were identified according to the international system adopted by the AJCC and the UICC.[17]

Statistical analysis

To calculate the diagnostic efficacy as determined by the sensitivity, specificity, positive predictive value and negative predictive value, the SPECT/CT results were compared to pathology analyses, which were defined as the reference test. The same assessment was conducted to evaluate the accuracy of chest CTs. A descriptive analysis was performed by measuring the central tendency, dispersion, and relative frequencies of patient and tumor characteristics.

The inter-observer agreement was calculated by the Kappa index. In the analysis of the correlation between numerical variables, a Spearman's correlation coefficient test was used. The chi-square test was used to assess the relationships between categorical variables. Kruskal-Wallis and Mann-Whitney nonparametric tests were used to evaluate the relationships between continuous and categorical variables. The level of significance was set at 0.05.

All statistical analyses were performed with the SPSS (version 18.0) software package.

RESULTS

From December 2006 to February 2009, 46 patients with potentially resectable lung lesions were included in our study. Among these patients, five were excluded for the following reasons. In one patient, the pathological results revealed a carcinoid tumor. For another patient, a chest CT was not performed at our institution. In three other cases, SPECT evaluations were not performed.

The characteristics of the 41 patients that were included in this study are summarized in Table 1. Two lesions, a squamous cell carcinoma, and an adenocarcinoma, were diagnosed in one patient. Therefore, we analyzed a total of 42 primary lung lesions in 41 patients.

Primary tumor

Primary tumor: SPECT/CT. We found evidence of radiotracer uptake in 39 out of 42 pulmonary lesions (92.8%). Thirty-one lesions were classified as mild in intensity, and eight lesions were classified as moderate in intensity. In three patients (7.2%), the primary tumor did not

Table 1 - Patient characteristics (n = 41).

Age (years), range (mean)	45-78 (62.6)
Gender (male/female)	28 (68.3%)/13 (31.7%)
Histopathology diagnosis	
Thoracotomy	24 (58.5%)
Fine-needle aspiration	11 (26.8%)
Bronchoscopy	6 (14.6%)
Histology	
Adenocarcinoma	22 (52.2%)
Squamous cell carcinoma	13 (31%)
Broncholoalveolar	5 (12%)
Adenosquamous	1 (2.4%)
Non-small cell carcinoma	1 (2.4%)
Primary tumor size (cm), range (mean)	1.5-11.5 (4.7)
Tumor classification (TNM)	
T1	9 (21.4%)
T2	23 (54.8%)
T3	9 (21.4%)
T4	1 (2.4%)
Lesion size	
Range (mean) without sestamibi uptake (cm)	1.5-2.5 (1.9)
Range (mean) with sestamibi uptake (cm)	2.0-11.5 (5.0)
Number of resected hilar lymph nodes	2-28 (10.3)
Number of resected mediastinal lymph	4-44 (22.3)
Hilar metastasis	19 (46.3%)
Mediastinal metastasis	7 (17.7%)
Size of metastatic foci	
Hilar lymph nodes	
<10 mm	12 (63.1%)
≥10 mm	7 (36.9%)
Mediastinal lymph nodes	
<10 mm	3 (42.9%)
≥10 mm	4 (57.1%)

concentrate sestamibi. The mean size of these lesions was 1.9 cm. For those tumors that concentrated sestamibi, the mean size was 5.0 cm. Although the mean size of those lesions that showed sestamibi uptake was significantly higher than the mean size of those lesions that did not ($p = 0.009$), no statistically significant differences between the intensity of uptake (mild or moderate) and the tumor size ($p = 0.8$) or between the degree of uptake and the tumor histological type ($p = 0.2$) were found.

Regarding the quantitative analysis, the rate of uptake in primary tumors ranged from 0.17 to 0.76 (average of 0.50). There was no correlation between the rate of uptake and the tumor size (correlation coefficient = 0.081, $p = 0.6$). Furthermore, there was no statistically significant difference between the rate of uptake and primary tumor lesions that were smaller than or equal to 3.0 cm, greater than 3.0 cm and less than or equal to 7.0 cm or greater than 7.0 cm ($p = 0.8$). The histological type did not influence the rate of uptake ($p = 0.55$).

Lymph Nodes

The mean number of resected hilar and mediastinal lymph nodes and the number of patients with hilar and mediastinal metastases by pathology examination, which was considered to be the reference method, are described in Table 1. Of the seven patients with metastases in the mediastinal lymph nodes, six also had metastases in the hilum. There was only one case of metastasis in the mediastinum with no involvement of the hilar lymph nodes (skip metastasis). The metastatic foci were smaller than 10 mm in 12 out of 19 patients (63.1%) with metastases of the hilar lymph nodes and in three out of the seven patients (42.9%) with mediastinal lymph node metastases.

With regard to the pathological staging of the lymph nodes, 21 patients (51.3%) had no regional metastases and were therefore classified by the TNM system as pN0. Thirteen (31.7%) had metastases only in the hilar lymph nodes and were staged as pN1, and seven patients (17%) were classified as pN2 because they had metastases in the mediastinal lymph nodes.

Lymph nodes: SPECT/CT and CT

SPECT/CT with sestamibi correctly identified six out of 19 cases with involvement of the hilar lymph nodes (Figure 1). In four of these cases, the metastatic foci were larger than or equal to 10 mm. In two cases, the foci were smaller than 10 mm. In ten out of 13 cases in which SPECT was falsely negative, the metastases were smaller than 10 mm (i.e., below the spatial resolution threshold of SPECT).

In 22 cases, there was no involvement of the hilar lymph nodes by pathology examination, and sestamibi correctly staged 21 of these cases. Therefore, there was one false positive result where the analysis of this lymph node showed a reactive process, with the presence of sinus histiocytosis and follicular hyperplasia.

Regarding mediastinum staging by SPECT/CT, the method correctly evaluated only one out of seven patients with nodal metastases, as confirmed by pathology examinations. The positive node in this case was located on the aorto-pulmonary window, and the metastasis was larger than 10 mm (Figure 2). In the six false negative cases, the sizes of the lymph node metastases were smaller than 10 mm in three cases and larger than 10 mm in three other cases. SPECT/CT made a correct diagnosis in 33 out of 34 patients without lymph node involvement, as confirmed by pathology examinations. Therefore, there was one false positive result, which occurred in the same patient in which there was a false positive finding in the hilum.

The degree of uptake was considered to be mild in all cases. The mediastinal lymph node uptake index was 0.14 and ranged from 0.2 to 0.47 for the hilar lymph nodes.

CT provided the correct diagnosis in nine out of 19 cases with metastasis of the hilum. Of the 22 patients without lymph node involvement, CT was negative in 21 patients. Regarding the mediastinum, CT correctly assessed four out of seven cases with nodal metastases and 31 out of 34 patients without lymph node involvement.

The sensitivity, specificity, positive predictive value, and negative predictive value of SPECT/CT and CT in the analyses of the hilar and mediastinal lymph nodes are described in Table 2.

Table 3 describes the locations and sizes of the primary tumors, histology, chains with positive nodes, sizes of lymph node metastases, and diagnoses of the two imaging methods (SPECT/CT and CT) for the seven patients with positive lymph nodes in the mediastinum.

The reproducibility analysis of the imaging method in relation to the pathology results revealed regular kappa values for CT in the analysis of the mediastinum (0.5) and the hilum (0.4) and a weak agreement for SPECT/CT for the mediastinum (Kappa 0.1) and the hilum (Kappa 0.3).

Between the two observers who evaluated the SPECT/CT results, there was complete diagnostic agreement in all 41 cases for the evaluation of the mediastinum (Kappa 1) and disagreement in two cases for the hilum analysis (kappa 0.8). For the CT images, the diagnosis differed in only one
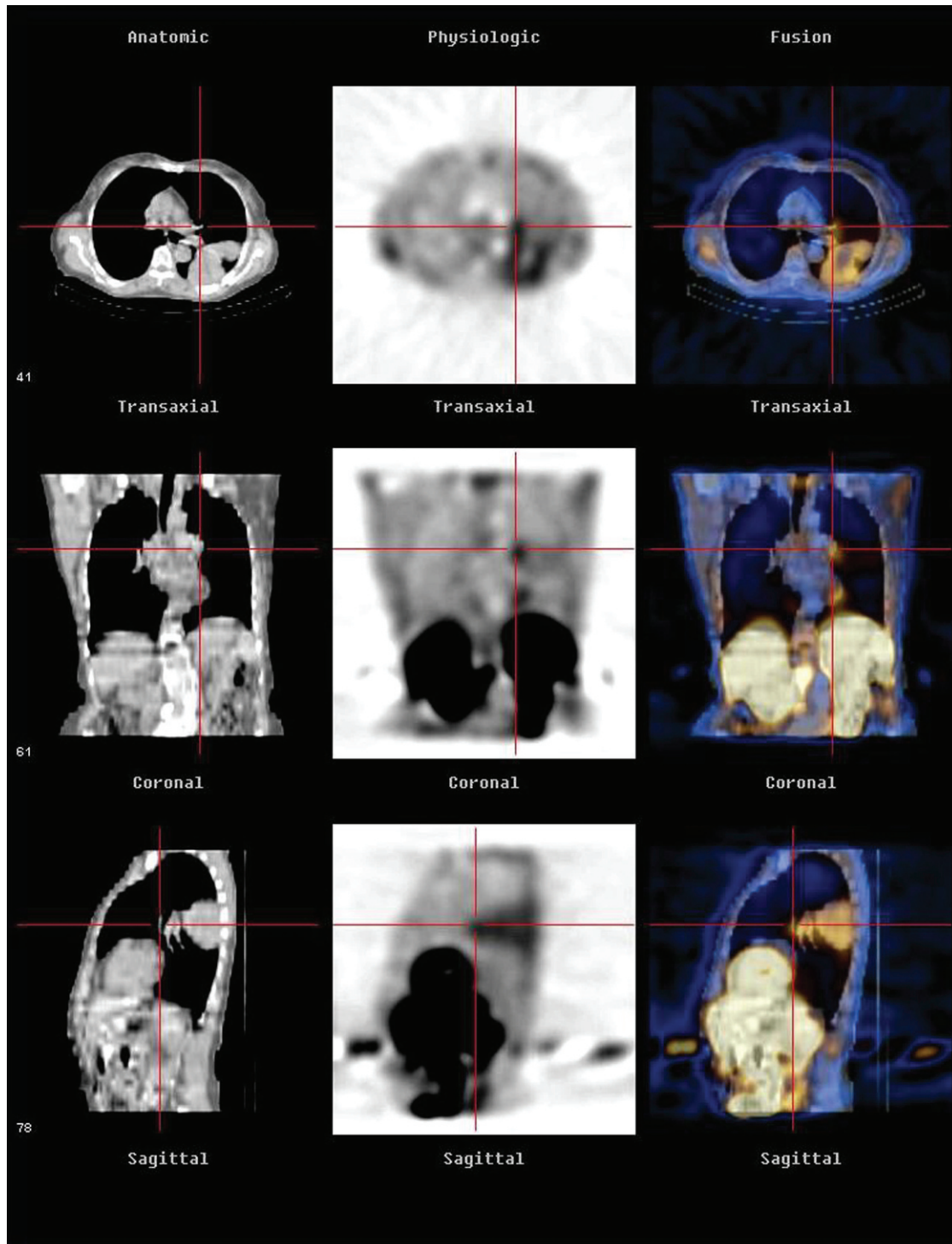
Figure 1 - SPECT/CT showing left hilar sestamibi uptake in a patient with an adenocarcinoma of the left lung.

case in the assessment of the hilum (Kappa 0.9) and in two cases in the assessment of the mediastinum (Kappa 0.8).

DISCUSSION

Chest CT is the most commonly performed imaging test for the primary staging of lung cancers. However, it has low sensitivity and may compromise the selection of treatment options for patients. Currently, the sizes of the lymph nodes are the main radiological criteria used to classify lymph nodes as suspicious for metastatic disease; they are usually considered positive when the short axis diameter is larger than 10 mm. However, lymph nodes of a normal size may contain tumor cells and thus lead to false negative results and low sensitivity. With chest CTs, our study found a sensitivity of 57% in the evaluation of the mediastinum, which was similar to the sensitivity described in other studies.[3,18] For the hilar lymph nodes, the sensitivity of CT
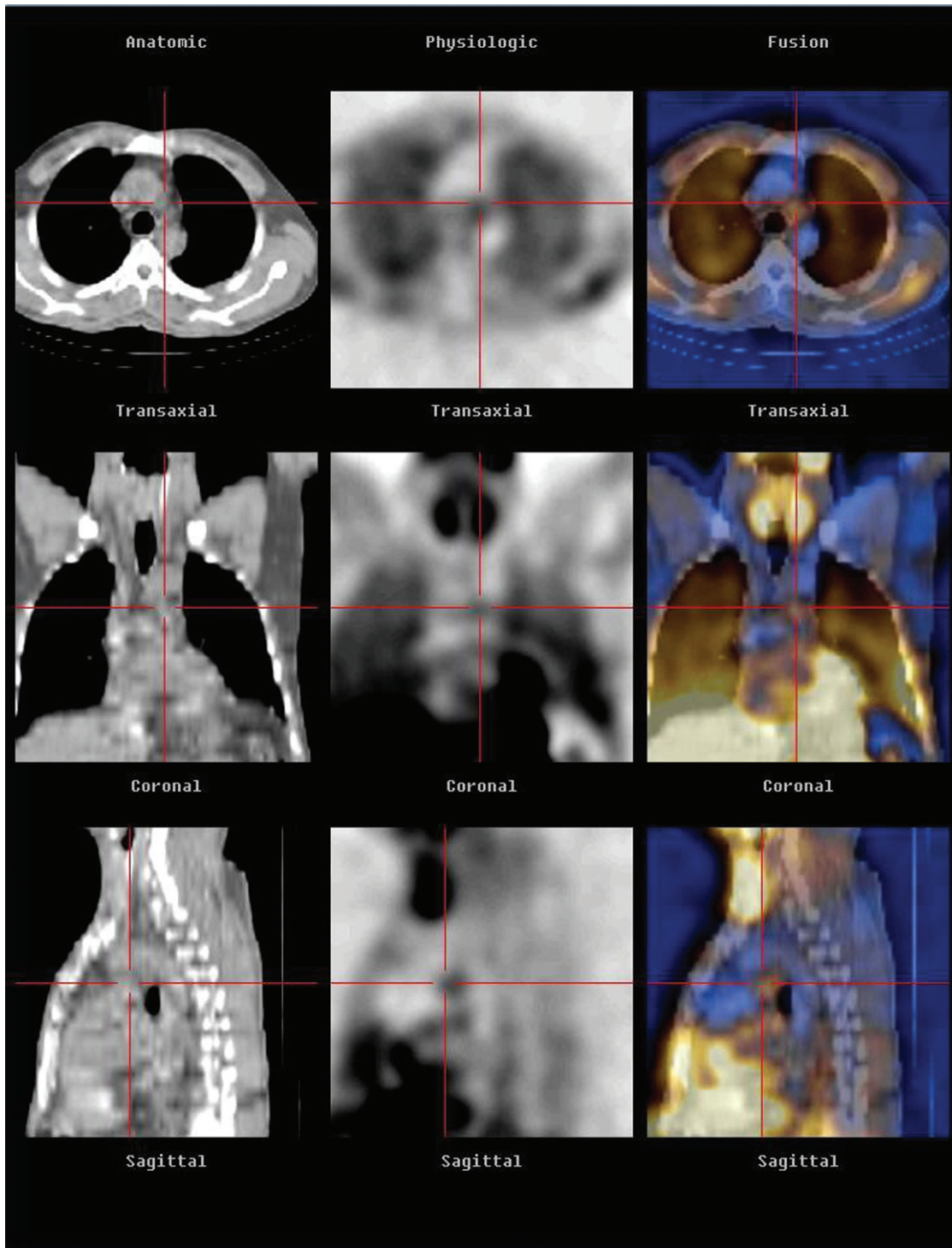
Figure 2 - SPECT/CT showing aorto-pulmonary window (station five) uptake in a patient with an adenocarcinoma of the left lung.

was 47.4%, which was lower than the mediastinal CT sensitivity.

In a prospective study that assessed the role of chest CT in the preoperative staging of 49 patients with non-small cell lung cancer, the hilar CT sensitivity was only 11%, which was lower than the sensitivity of 67% found for mediastinal lymph nodes.[19] Perhaps this difference is due to the greater difficulty in evaluating the hilar region using this method

than in evaluating other regions. In our study, CT specificity was higher than 90% for both the pulmonary hilum and the mediastinum. Such a high specificity might be related to the study population, which included only patients who were being considered for surgical treatment and who therefore had no bulky adenopathies. Toloza et al. found a mean specificity of 82% (ranging from 57% to 93%) in their meta-analysis. Moreover, the accuracy of chest CTs in the staging

Table 2 - SPECT/CT and CT results for the analyses of the hilar and mediastinal lymph nodes.

Test	Sensitivity	Specificity	PPV	NPV
SPECT/CT (hilum)	31.6%	95.5%	85.7%	61.8%
CT (hilum)	47.4%	95.5%	90%	67.7%
SPECT/CT (mediastinum)	14.3%	97.1%	50%	84.6%
CT (mediastinum)	57.1%	91.2%	57.1%	91.2%

Note: PPV: positive predictive value; NPV: negative predictive value.

of the mediastinum was not superior to that found in earlier meta-analyses, suggesting that despite the superior resolution of most modern scanners, CTs did not lead to better accuracy for nodal staging.[3]

However, in a recent retrospective study that evaluated the accuracy of multi-slice chest CTs in mediastinum nodal staging in 86 patients with non-small cell lung cancer, the sensitivity, specificity, positive and negative predictive values, and accuracy were 100%, 98.5%, 94.4%, 100%, and 98.8%, respectively. For its diagnostic criteria, this study used not only lymph node size but also the locations of the lymph nodes in relation to the position of the primary tumor and the lymph node structure. For example, the presence of central calcification and fat density were used as common signs of negative or normal nodes. Peripheral calcifications and necrosis were also considered as positive findings. When only the sizes of the lymph nodes (short axis larger than 10 mm) were considered, the effectiveness of the test was decreased, with sensitivity, specificity, positive and negative predictive values and accuracy values of 64%, 61%, 87%, 40%, and 62%, respectively. These findings suggest that when factors other than size are also considered, the diagnostic efficacy of multi-slice CTs can be enhanced.[20]

Although PET results have been shown to be superior to chest CTs in the evaluation of regional lymph nodes, and although the association between PET and CT (PET/CT) seems to be more effective in staging the mediastinum than simply relying on PET imaging,[4-6] PET/CT was not available in our institution. The rationale for performing this study was based on the scarce and controversial evidence regarding the value of SPECT/CT with sestamibi

in staging lung cancers, especially considering its higher availability and lower costs compared to PET.[9-13]

SPECT/CT showed mild or moderate sestamibi uptake in 39 out of 42 pulmonary lesions (92.85%). Only three lesions did not concentrate sestamibi, and these lesions were the smallest tumors in the sample. However, the mean size of the lesions that showed no uptake was 1.9 cm, which is considered to be within the diagnostic power of modern SPECT scanners.

In 31 cases, the degree of uptake was mild according to the criteria adopted in the study (i.e., lower than the degree of uptake in the liver and higher than the degree of uptake in soft tissues). In eight cases, the degree of uptake was similar to the degree of liver uptake and was therefore considered moderate. Although the degree of uptake was considered mild for most lesions, it was much higher than the degree of uptake seen in soft tissues. It is possible that the comparison criteria that were selected in an attempt to make the interpretation more objective were not adequate because we observed that the degree of liver uptake was very similar to the degree of heart uptake, which can be considered intense in these two organs. In contrast to the findings reported with FDG-PET in lung cancer, our study did not show any direct correlation between the degree of sestamibi uptake in primary lesions and lymph nodes and the size and histology classification of tumors. That means, larger lesions or more agressive histology types of tumors were not associated with higher sestamibi uptake. One potential explanation is a difference in the transmembrane electrical potential, while another is the degree of neovascularity. Although aggressive histologies should show higher levels of sestamibi uptake, this phenomenon was not observed in our study sample. The size of the tumor is important because larger tumors are more easily detected by SPECT imaging. However, larger tumors have larger necrotic areas. In addition, necrotic, fibrotic and/or inflammatory tissues were not quantified by the pathology examinations in our study, and no corrective measurements were taken according to the histology findings.

In a study evaluating 25 patients with indeterminate pulmonary nodules, Minai et al. found a sensitivity of 85.7% and a specificity of 100% for sestamibi SPECT. Two of the three false negative cases occurred with the smallest nodules in the study, which had sizes ranging from 1.2 to

Table 3 - Patients with mediastinal lymph node metastasis (n = 7).

Patient	Primary tumor localization	Size of primary tumor (cm)	Histology	Positive lymph node stations	Metastasis size	SPECT	TC
2	SRL	2.7	Adenocarcinoma	2	<10 mm	-	-
				3	<10 mm	-	-
				4R	≥10 mm	-	-
3	ILL	4.5	Adenocarcinoma	7	<10 mm	-	+1.7 cm
8	ILL	11.5	Adenocarcinoma	5	≥10 mm	+	+1.2 cm
				8	<10 mm	-	-
11	ILL	7.0	Adenocarcinoma	7	≥10 mm	-	-
				8	≥10 mm	-	-
13	IRL	2.4	Adenocarcinoma	4R	<10 mm	-	-
				7	<10 mm	-	-
				8	≥10 mm	-	-
22	SLL	11.0	Adenocarcinoma	4L	<10 mm	-	-
				5	<10 mm	-	+ 1.1 cm
				6	<10 mm	-	-
31	SLL	7.5	SCC	5	<10 mm	-	+1.2 cm

Note: SRL superior right lobe; ILL inferior left lobe; IRL inferior right lobe; SLL superior left lobe.

1.3 cm.[9] Santini et al. also studied the role of sestamibi in the diagnosis of pulmonary lesions. There was sestamibi uptake in 91.6% of the malignant lesions, while only 8.3% of the identified tumors showed no sestamibi uptake.[11] These results are consistent with the results of our study.

SPECT/CT with sestamibi correctly identified six of 19 cases with involvement of the hilar lymph nodes, with a sensitivity of 31.6%. Only one out of seven patients with mediastinal nodal metastases, identified by pathology examinations, were correctly identified, leading to a sensitivity of only 14.3%. SPECT/CT sensitivity values for both the hilum and the mediastinum were inferior to the sensitivity of chest CT; these values were also lower than the sensitivity values described in previous studies. One hypothesis is that the sizes of the metastases in the lymph nodes were smaller than the sizes reported in previous studies. In the 13 cases in which SPECT have a false negative result for the hilum, the majority of metastases were smaller than 10 mm (n = 10; 76.9%). In the mediastinum, 50% of the lymph nodes were smaller than 10 mm.

Regarding mediastinal nodal staging by sestamibi SPECT, Chiti et al. evaluated 36 patients with pulmonary lesions and showed a higher accuracy for SPECT than for chest CT. SPECT correctly staged 10 out of 11 patients with mediastinal metastases and 21 out of 25 without mediastinal metastases, with sensitivity and specificity values of 91% and 84%, respectively. However, node enlargement was seen by CT in the majority of the patients with confirmed nodal involvement (80%), in contrast to our findings.[12]

Nosotti et al. studied 87 patients with non-small cell lung cancer and found a sensitivity of 54.5% and a specificity of 100% for sestamibi SPECT in the analysis of nodal staging. The lymph nodes were evaluated by mediastinoscopy or thoracotomy; however, the numbers and sizes of the lymph nodes that were resected were not described in detail.[13]

In a prospective study evaluating the value of PET/CT in the nodal staging of 51 patients with lung cancers who were scheduled for surgery, the sensitivity was as low as 40%, mainly because of the small sizes of the lymph nodes (<10 mm).[7]

The sensitivity of PET/CT in the preoperative staging of regional thoracic lymph nodes was 54.2% in a study involving 159 patients with resectable lung cancers. The specificity was 91.9%. The mean size of the lymph nodes that were falsely negative on PET/CT was 7.8 mm, with a minimum size of 3 mm and a maximum size of 15 mm. The method correctly identified 85.3% of the lymph nodes that were larger than 10 mm and 32.4% of the patients with lymph node metastases that were smaller than 10 mm. The authors concluded that the spatial resolution of PET/CT appears to be inadequate to detect lymph node metastases that are smaller than 10 mm.[21] This finding is also more relevant for SPECT that has lower spatial resolution than PET.

Although the hybrid system used in the present study had an attached CT with a much lower resolution than a multidetector CT, the method was effective in excluding the areas of physiological uptake and possibly decreasing the rate of false positive results. There was only one false positive result, which was represented by an inflammatory reaction in the affected lymph node and found through a pathology examination.

Previous studies have shown that the fusion of SPECT and CT can help to differentiate tumor activity and physiological activity.[15] The main advantage of SPECT/CT in our study was the ability to distinguish areas of tumor uptake from those of cardiac and/or vascular uptake, helping to reduce the frequency of false positive results while simultaneously providing higher specificity (>95%).

Despite the limited resolution of SPECT, which made it difficult to interpret the results due to low sensitivity and many false negative results, the strong agreement between observers in the analysis of the mediastinum and the hilum should be noted. This agreement suggests that image interpretation was consistent between experts and that the poor results were likely due to the limitations of the method.

In conclusion, SPECT/CT using ^{99m}Tc-sestamibi seems to play no role in the nodal staging of patients with non-small cell lung carcinoma because the technique is associated with a much lower sensitivity than CT or pathology analyses. Moreover, no incremental diagnostic value of SPECT could be observed in the present study, especially when compared to the staging information provided by chest CT. However, more studies are needed that use devices equipped with multidetector CT scanners, which could provide more accurate registration and simultaneously offer more adequate attenuation corrections for emission scans.

AUTHOR CONTRIBUTIONS

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