Journal of BUON **15:** 147-152, 2010

ORIGINAL ARTICLE

Contribution of ^{99m}Tc-depreotide (Neospect) scintigraphy in lung cancer staging

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Summary

Purpose: *The aim of this study was to evaluate the usefulness of scintigraphy with ^{99m}Tc-depreotide in the staging of lung cancer, especially in cases where CT findings are doubtful.*

Methods: *53 patients with suspected lung cancer were investigated with whole body planar acquisition and single photon emission computed tomography (SPECT) of the thorax after i.v. injection of 740 MBq ^{99m}Tc-depreotide (Neospect®). The results were compared with CT and correlated with histological findings.*

Results: *In 50 of 53 patients the biopsy was positive for bronchogenic carcinoma (31 patients with non small cell lung cancer [NSCLC], 18 with small cell lung cancer [SCLC], and 1 patient with neuroendocrine cancer). In the remaining 3, biopsy revealed no bronchogenic carcinoma (3 patients with inflammation). In 2/31 patients with NSCLC and doubtful CT findings, uptake of ^{99m}Tc-depreotide was the only non invasive reliable staging method.*

Conclusion: *It seems that scintigraphy with ^{99m}Tc-depreotide in patients with SCLC does not change the tumor stage, whereas in NSCLC the contribution of Neospect in lung cancer staging may be a helpful tool, especially in cases where CT alone is unable to distinguish between IIIA and IIIB stages (operable from non operable status).*

Key words: CT imaging, lung cancer staging, ^{99m}Tc-depreotide scintigraphy

Introduction

More than 99% of malignant lung tumors arise from the respiratory epithelium and are termed bronchogenic carcinoma which can be divided into 2 subgroups: SCLC and NSCLC.

SCLC accounts for 20-25% of all lung cancers and is primarily diagnosed in smokers or former smokers. NSCLC accounts for 75-80% of all lung cancers and is divided into 3 subtypes: squamous cell carcinoma (also called epidermoid carcinoma), large cell carcinoma and adenocarcinoma.

The diagnosis of lung cancer follows some algorithms based on several examinations which include invasive methods (i.e. mediastinoscopy, video assisted thoracoscopic surgery, bronchoscopy, transthoracic, transbronchial or transoesophageal needle biopsy) and non invasive imaging techniques (i.e. chest radiograph, computed tomography, MRI, nuclear medicine procedures), cytological and tumor markers, and is finally confirmed with biopsy.

The therapy is based on the type and stage of cancer. SCLC is divided into 2 stages referred to as limited and extensive disease. Limited disease is potentially curable only with chemotherapy or combined with radiation therapy [1]. Extensive disease has already spread to both lungs or is detectable beyond them. Treatment of choice is always aggressive chemotherapy. Although non surgical treatment is the method of choice for patients with SCLC, Lucchi et al. suggest the combination of surgical resection with adjuvant chemotherapy as a more effective treatment in cases of localized disease without lymph node involvement [2].

NSCLC is divided into 4 stages (I-IV) according to the TNM system (Tables 1 and 2) [3].

For stages I-IIIA, treatment of choice is surgical resection, whereas IIIB and IV stages are non operable.

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Received 01-02-2009; Accepted 17-03-2009

Table 1. TNM staging of non small cell lung cancer [3]

Stage	*TNM*
0	T_{is}, N_0, M_0
IA	T_1, N_0, M_0
IB	T_2, N_0, M_0
IIA	T_1, N_1, M_0
IIB	T_2, N_1, M_0 or T_3, N_0, M_0
IIIA	T_3, N_1, M_0 or $T_{(1-3)}$, N_2, M_0
IIIB	T_4, anyN, M_0 or anyT, N_3, M_0
IV	anyT, anyN, M_1

Methods

Patient population

Patients with suspected lung cancer (based on clinical and chest CT findings) were investigated at our department using ^{99m}Tc-depreotide (Neospect®-Amersham) between September 2003 and November 2007. Patients with diabetes, severe chronic renal failure (serum creatinine > 2 mg/dl), acute renal failure and liver failure were excluded. Finally, a total of 53 patients (42 men and 11 women, mean age 61.3 years, median age 3 years, range 48-70 years) were included in the study. All patients were examined with chest CT and the final diagnosis was made by biopsy (bronchoscopic or surgical resection of the lesion).

^{99m}Tc-depreotide imaging

Scanning was performed some days after the CT imaging. ^{99m}Tc-depreotide (740 MBq, 20 mCi) was administered in an antecubital vein. All patients were placed in a supine position with arms extended over the head and the following scans were carried out: a) 1 and 3 hours after injection: a whole body scanning and static scanning of the thorax; and b) 3-4 hours after injection: a single photon emission tomography (SPECT) of the thorax and the abdomen.

A double headed camera (Sopha) with low energy, high resolution parallel hole collimators was used and static and whole body images were acquired in a 256×256 matrix (1×10^6 counts), whereas tomographic images were acquired in a 64×64 matrix through 360° rotation with 64 projections (30 sec acquisition frame time). Tomographic images were post-filtered with a

Table 2. TNM descriptors for NSCLC staging [3]

Site	Descriptor	Comment
Primary tumor (T)	T_X	Primary tumor cannot be assessed or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
	T_0	No evidence of primary tumour
	T_{is}	Tumor < 3 cm in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie, not in the main bronchus)
	T_1	Tumor with any of the following features of size or extent: > 3 cm in greatest dimension; involves main bronchus; > 2 cm distal to the carina; invades the visceral pleura; associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
	T_2	Tumor with any of the following features of size or extent: > 3 cm in greatest dimension; involves main bronchus; > 2 cm distal to the carina; invades the visceral pleura; associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
	T_3	Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium, or tumor in the main bronchus < 2 cm distal to the carina but without involvement of the carina or associated atelectasis or obstructive pneumonitis of the entire lung
	T_4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina, or tumor with a malignant pleural or pericardial effusion or with satellite tumor nodules within the primary-tumor lobe of the lung
Regional lymph nodes (N)	N_X	Regional lymph nodes cannot be assessed
	N_0	No regional lymph node metastasis
	N_1	Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes involved by direct extension of the primary tumour
	N_2	Metastasis to ipsilateral mediastinal and/or subcarinal lymph nodes
	N_3	Metastasis to contralateral mediastinal, contralateral, hilar ipsilateral, or contralateral scalene or supraclavicular lymph nodes
Distant metastasis (M)	M_X	Presence of distant metastasis cannot be assessed
	M_0	No distant metastasis
	M_1	Distant metastasis present (Even nodal involvement on the controlateral lung)

3D Fourier filter (Butterworth filter with a cut-off frequency of 0.5 cycles/cm, order 5). Coronal, sagittal and transverse slides were displayed on 18.0 mm thickness. The scintigraphic findings were compared and correlated with CT and biopsy results.

Results

Of the 53 patients included, 50 were diagnosed with cancer and 3 with benign lesions (inflammation) of the lungs. Thirty-one (58.5%) of them had NSCLC and 18 (33.97%) SCLC. The histological types for the aforementioned patients with malignant disease are presented on Table 3.

Of the 31 patients with NSCLC 13 (41.94%) were operated (stages I-IIIA) and 18 (58.06%) were given chemotherapy (stages IIIB and V). Skeletal metastasis in stage IV patients was confirmed with ^{99m}Tc-MDP bone scanning. All 18 patients with SCLC were found to have extensive-stage disease and treated with chemotherapy. CT and Neospect findings, as well as staging, are presented on Table 4.

From the above Table it is shown that in 31 patients with NSCLC, uptake of Neospect detected the lesion in all cases (31 true positive results) and additionally, in 2 cases where CT findings were doubtful, Neospect was the only non invasive reliable staging method confirmed by thoracotomy and biopsy (Figures 1,2).

In 18 patients with SCLC, Neospect study revealed 17 true positive and 1 false negative results. In the false negative case Neospect study, CT imaging was doubtful.

In one neuroendocrine tumor Neospect showed positive uptake (1 true positive result) and finally in 3 patients with inflammatory disease, Neospect revealed 2 false positive and 1 true negative results.

The accumulated results concerning accuracy, sensitivity, specificity, positive and negative predictive value of Neospect are shown on Table 5.

Discussion

Accurate staging of lung cancer is very important to define the best therapeutic approach for the patient. In the case of SCLC, operation is almost always excluded and staging is easy to make. NSCLC staging seems to be more complicated and is carried out through invasive and non invasive means. The most important step in NSCLC staging is the presence or not of distant metastasis and nodal involvement, because these factors change the treatment modality to be used. Thus, presence of distant metastasis and/ or lymph node involvement even in the controlateral lung denotes IV stage and excludes resection of the primary lesion. It is also crucial to distinguish between IIIA and IIIB stages as patients with IIIA stage are operable whereas those with IIIB stage are not.

Non invasive methods lack complications but are not always reliable. For example chest radiograph is used as a screening test but is not sufficient to detect spread of the disease to the mediastinum and has very low sensitivity in the detection of the primary lung tumor [1]. To improve its diagnostic accuracy, some special procedures have been used, including computer-aided diagnosis (CAD) and fractal text analysis (FTA) [2].

CT is a widely used imaging modality for evaluation of the primary tumor and its metastases, and is the non invasive method of choice for the staging and evaluation of lung cancer. The most common used CT criterion to define malignant involvement is a short axis lymph node diameter of ≥1 cm on a transverse CT scan [1]. The use of i.v. contrast medium enhances the ability of CT to distinguish vascular structures from lymph nodes as well as in delineating mediastinal invasion by centrally located tumors [1]. Despite its wide application, CT has certain disadvantages: it is of limited predicted value in diagnosing pleural/chest wall invasion with the sensitivity ranging from 38 to 87% and specificity between 40 and 89%. The only reliably CT criterion of chest wall invasion is definitive bone destruction in case of tumor mass extending into the chest wall [4]. CT has great difficulty in differentiating between visceral and parietal pleura invasion, because peritumoral inflammatory adhesions often simulate true invasion [5]. It has also a meaningful number of false positive results [2]. The limitation of CT in detecting mediastinal lymph node enlargement is evident considering that up to 15% of patients with clinical stage T1N0 lesions will be found to have positive lymph node involvement by surgical node sampling [6]. In general, CT is applied in the preoperative staging of NSCLC but with limitations in differentiating IIIA from IIIB stages for evaluation of tumor resectability [4].

MRI is more accurate than CT to evaluate local invasion of superior sulcus tumors, particularly their extension to vertebral bodies, spinal canal, branchial plexus and subclavian artery [7]. It seems also superior to CT to demonstrate heart and vessel invasion, while

Table 3. Histological cancer types of the studied cases

Histology	*n*	*%*
Adenocarcinoma	18	36
Squamous cell carcinoma	10	20
Large cell carcinoma	3	6
Small cell lung carcinoma	18	36
Neuroendocrine tumor	1	2
Total	50	100

Table 4. Staging and imaging findings in 53 patients

Histological type	*Staging (according to CT and/or bronchoscopic findings)*	*Comments*
18 NSCLC	I-IIIA (operable cases)	• In 16/18 cases CT and Neospect findings were positive (Coincidence between the two methods-Both of them revealed the lesion; 16 true positive findings for Neospect).
Adenocarcinoma: 10	• IB stage: 3 cases (3 adenocarcinoma)	
	• IIA stage: 2 cases (2 adenocarcinoma)	
Squamous cell carcinoma: 6	• IIB stage: 6 cases (2 adenocarcinoma, 4 squamous cell carcinoma)	• In 2/18 cases, positive nodal uptake of Neospect (confirmed on thoracotomy) did not agree with CT (which was doubtful-could not distinguish between tumor and inflammation). Biopsy revealed 2 IB stage adenocarcinoma; 2 true positive findings for Neospect.
Large cell carcinoma: 2	• IIIA stage: 7 cases (3 adenocarcinoma, 2 squamous cell carcinoma, 2 large cell carcinoma)	
13 NSCLC	IIIB-IV (non operable cases)	• In all cases CT and Neospect findings were positive (Coincidence between the two methods-Both of them revealed the lesion; 13 true positive findings for Neospect).
Adenocarcinoma: 8	• IIIB stage: 4 cases (2 adenocarcinoma, 1 squamous cell carcinoma, 1 large cell carcinoma)	
Squamous cell carcinoma: 4		
Large cell carcinoma: 1	• IV stage: 9 cases (6 adenocarcinoma, 3 squamous cell carcinoma)	
18 SCLC	18 cases with extensive disease	• In 16/18 cases CT and Neospect findings were positive (Coincidence between the two methods; 16 true positive findings for Neospect).
		• In 1/18 cases: mismatch between positive Neospect and doubtful CT (Biopsy revealed malignancy; 1 true positive case for Neospect).
		• In 1/18 cases: mismatch between negative Neospect (no uptake) and positive CT (Biopsy revealed malignancy; 1 false negative case for Neospect).
1 Neuroendocrine tumor		• Coincidence between the two methods-Both of them revealed the lesion (1 true positive finding for Neospect).
3 inflammations		• In 2/3 cases: Uptake of Neospect, but CT and biopsy revealed no malignancy (2 false positive cases for Neospect).
		• In 1/3 cases: mismatch between negative Neospect (no uptake) and positive CT (biopsy revealed no malignancy; 1 true negative case for Neospect).

tumors invading the aorta may be best shown by cine CT [8,9]. MRI is a good alternative for patients who cannot tolerate i.v. contrast agent but is inferior to CT to detect calcification (therefore an enlarged node with calcification might be considered to be malignant on MRI but benign on CT) and is less practical than CT for clinical use due to the relatively poor spatial resolution in the lung, the cost and time consuming [3,10].

Nuclear medicine methods seem to be reliable in detecting the primary lung cancer. ^{99m}Tc-depreotide has been used successfully in the evaluation of solitary pulmonary nodes. Depreotide, a 5 amino acid peptide, (MW-1358Da) is a somatostatin analog which seems to have high binding capacity with somatostatin receptors, especially with 2, 3 and 5 subtypes. There are 5 somatostatin receptors ($SSTR_{1-5}$) with the subtype $SSTR_2$ mostly expressed on tumor cells (tumors of APUD cell system-accounting for 25% of all lung cancers, endocrine pancreatic tumors, metastatic carcinoids, GH-producing pituary adenomas, paragangliomas, breast tumors, lymphomas, astrocytomas, and some colorectal cancers) [11,12]. Normal depreotide uptake is observed in the spine, sternum and rib ends and low level increased uptake in the hilar and mediastinal regions [13]. Abnormal uptake is observed in many cancers, especially of neuroendocrine origin, as well as in sites of inflammation and round atelectasis [14]. In our study, in 2 cases with proven inflammation, Neospect showed positive uptake.

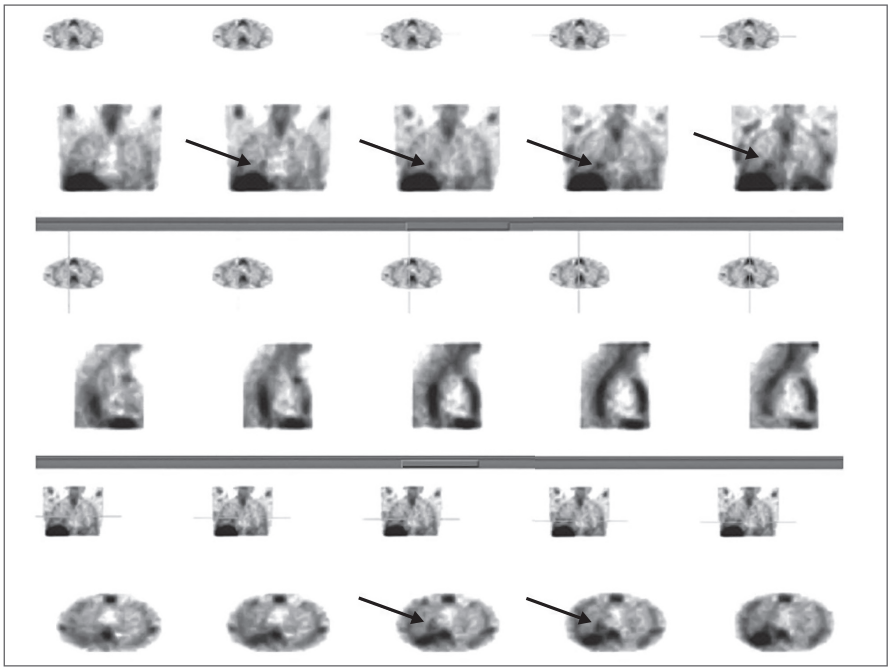

Figure 1. SPECT imaging of a patient with NSCLC (coronal, sagittal and transverse slides). Accumulation of the radiopharmaceutical in the area of the right lower mediastinum (arrows). Thoracotomy confirmed the nodal involvement and biopsy revealed squamous cell carcinoma.

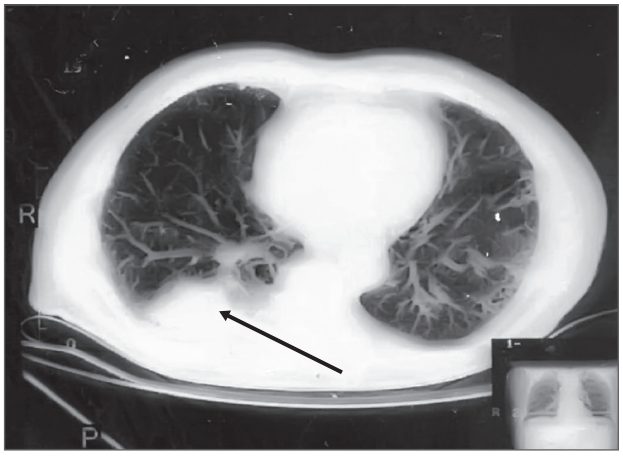

Figure 2. CT of the same patient where in the area of the right lower mediastinum a lesion with abnormal margins and little presence of pleural fluid is detected, probably due to inflammatory process (arrow).

Table 5. Parameters of Neospect in detecting tumor lesions of lungs

Parameter	*%*
Accuracy	94.34
Sensitivity	98.00
Specificity	33.33
Positive predictive value	96.08
Negative predictive value	50.00

In the evaluation of solitary pulmonary nodes, ^{99m}Tc-depreotide has shown specificity of 73.1% and sensitivity of 93-95.6% in the detection of malignant solitary pulmonary nodules and has excellent sensitivity (98%) and satisfactory specificity (80%) in differentiating malignant from benign solitary pulmonary lymph nodes [15,16]. Various studies show better specificity and negative predictive value than CT. Grewal-Ravinder et al. recommend ^{99m}Tc-depreotide scintigraphic evaluation of solitary pulmonary nodules, especially when positron emission tomography (PET) scanning is not available before biopsy [17]. The main cause of false negative results is the activation of lymphocytes in infectious granulomas, such as coccidiomycosis and tuberculosis, while false positive results have been associated with hamartomas and round atelectases [18-21].

PET scanning with ^{18}F-fluorodeoxyglucose appears more accurate than CT for the diagnosis of mediastinal node metastasis. In one study with 76 patients, mediastinal PET and CT findings were compared with the results of surgical staging. Sensitivity and specificity for the diagnosis of N2 disease were 83% and 94% for PET, and 63% and 73% for CT, respectively. PET is also capable to detect occult adrenal or liver metastasis not documented by other means of non surgical staging [5, 22]. Kahn et al. showed that the sensitivity for the detection of primary lung cancer was equally high for FDG PET and ^{99m}Tc-depreotide, the specificity was superior for FDG PET and the staging accuracy was similar with both methods; yet, compared to chest CT, neither scintigraphic examination was sufficiently accurate to stage NSCLC patients, because they were less accurate in evaluating metastatic disease spread. For this reason they recom-

mended using nuclear medicine techniques with caution to this purpose [23]. PET is superior to CT for mediastinal staging of NSCLC independent of performance index or clinical context of PET imaging [24]. Use of dual-modality PET/CT significantly increases the number of patients with correctly staged NSCLC, helping thus to select the most appropriate therapeutic approach [25].

Because PET/CT fusion image is of great cost and not all the nuclear medicine departments own a PET/CT camera, in our study we tried to check out the contribution of ^{99m}Tc-depreotide scanning in staging lung cancer, especially in cases where CT imaging was doubtful.

Conclusions

In this study, in all the operable cases, especially in those with NSCLC ≤IIIA, the combination of CT and Neospect imaging increased the correctly staged cases, helping thus not to proceed to mediastinoscopy. In the non operable cases (SCLC and NSLC ≥ IIIB stage) the combination of these two methods did not change essentially the stage.

The fact that only in 2/31 NSCLC cases with doubtful CT findings Neospect showed uptake in lymph nodes (as confirmed by thoracotomy) is a good but not a sufficient evidence for its wide use in lung cancer staging. Also, CT imaging is an operator-dependent technique. So, according to our study we can conclude that:

1. CT still remains the gold standard method for non invasive staging in patients with lung cancer, unless a PET/CT examination can be done.

2. Scintigraphy with Neospect does not change the stage in patients with SCLC.

3. Scintigraphy with Neospect has high sensitivity but poor specificity (in our study 98% and 33.33%, respectively) in detecting tumor lesions of lungs, but little evidence justifies its use in the non invasive staging of lung cancer. In case of doubtful CT findings, an invasive staging method seems to be the next step.

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