The Value of HRCT and Tc-Depreotide in the Evaluation of Pulmonary Lesions

Karin Rasmussen, MD, Hans H. Madsen, MD,† Finn Rasmussen, DMSc,† Torben R. Rasmussen, PhD,‡ Ulrik Baandrup, PhD,§ Hans K. Pilegaard, M.D.,‖ Ulrik Pedersen, DMSc,¶ Torben Palshof, DMSc,** and Michael Rehling, DMSc**

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Lung cancer is one of the most common cancers worldwide, and the overall incidence continues to increase. Despite advances in treatment, the overall 5-year survival is still approximately 10% to 15%. A better therapeutic impact depends on the ability to diagnose the cancer in an early stage.

When the suspicion of lung cancer is raised, a computed tomographic (CT) scan is necessary.

A number of screening studies of lung cancer have been published.[1–4] In these studies, the sub-centimeter, non-calcified lesions were identified in 30% to 60% of cases. However, only 1% to 3 % of these lesions turned out to be malignant. Thus, the final diagnosis can not rely on CT alone; invasive procedures are needed.

Imaging-guided fine-needle aspirations have an overall accuracy of 64% to 100% for detecting malignancy,[5,6] and bronchoscopy-guided biopsies of centrally located lesions have an accuracy of 70% to 90%.[7] Follow-up CT is therefore still needed in a number of patients.

Recently, new techniques for detecting lung cancer have become available. It seems that refinement of the CT technique with high-resolution CT (HRCT) in subgroups of lesions increases the specificity solely by morphological characterization, thereby reducing the need for invasive procedures.[8,9] Thus, Furuya et al.[8] found an accuracy for malignancy of more than 93% by using specific morphologic criteria on HRCT.

Nuclear medicine methods have also emerged. The high level of somatostatin receptor expression on various tumor cells has provided the molecular basis for the successful use of radiolabeled somatostatin analogs as tumor tracers. Somatostatin-receptor scintigraphy is a well documented method of diagnosing neuroendocrine tumors[10] and has been used since 1989. Furthermore, it has been shown to be able to detect both small cell lung cancer (SCLC), which possesses neuroendocrine characteristics, as well as non-small cell lung cancer (NSCLC).[11] Until recently, an ^{111}Indium-labeled somatostatin analogue, octreotide, was the only tracer used for imaging. However, in 2000, a ^{99m}Tc-labeled somatostatin analogue depreotide became commercially available for scintigraphic imaging of suspected malignant tumors in the lung.

So far, studies have found that ^{99m}Tc-depreotide has a high sensitivity for detecting lung cancer (89% to 100 %) but low specificity (43% to 73%).[12–19]

^{18}F-fluoro-2-deoxy-D-glukose (FDG) positron emission tomography (PET) has an integral role in the management of many oncological tumors, including lung tumors, in regard to characterization and staging.[20] However, compared with single emission computerized tomography (SPECT) scanners, PET scanners are still more costly, and availability is still rather limited, even in developed countries.

The aim of this study was to assess the diagnostic impact of HRCT and ^{99m}Tc-depreotide separately and in combination among patients with pulmonary lesions demonstrated by conventional CT.

PATIENTS AND METHODS

Patients

Fifty-seven consecutive patients (32 women, 25 men) with an average age of 63 years (range, 38 to 82 years) were included in the study. All patients were referred from the primary sector to the Department of Pulmonology because of suspicion of lung cancer. The inclusion criteria were based on the CT detection of one or more peripheral lung lesions that could not be reached by bronchoscopy. Supplementary HRCT of the lesions and a ^{99m}Tc-depreotide imaging was then performed. The final diagnosis was based on fine-needle aspiration, bronchoalveolar lavage (BAL) or brush biopsies, core biopsies, biopsies of the surgical removed tissue, chest radiograph, or CT follow-up as per normal protocols (Table 1).

Fluoroscopic-guided trans-thoracic fine-needle aspiration (TTFNA) was performed up to three times to increase the sensitivity for malignant lesions. In malignant lesions, the fluoroscopic- and ultrasonic- (US) guided TTFNA was suf-

Departments of *Clinical Physiology and Nuclear Medicine, †Radiology, ‡Pulmonology, §Pathology, ‖Cardiothoracic Surgery, ¶Otorhinolaryngology, **Oncology, Aarhus University Hospital, Aarhus, Denmark.

Address for correspondence: Karin Rasmussen, Department of Clinical Physiology and Nuclear Medicine, Noerrebrogade 44, 8000 Aarhus C, Denmark. E-mail: karinr@dadlnet.dk

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TABLE 1. Frequency of methods used for final diagnosis

30 malignant lesions in 29 patients	Bi-planar fluoroscopic-guided TTFNA	24
	US-guided TTFNA	1
	Bi-planar fluoroscopic-guided TTCB	1
	US-guided TTCB	1
	Thoracoscopic-guided core biopsy	1
	Brush biopsy	1
	Brocheoalveolar lavage	1
29 benign lesions in 28 patients	Bi-planar fluoroscopic-guided TTFNA	13
	Bi-planar fluoroscopic-guided TTCB	2
	US-guided TTCB	1
	Thoracoscopic-guided core biopsy	1
	Follow-up	1
		2

TTFNA, trans-thoracic fine-needle-aspiration; US, ultrasonic; TTCB, Trans-thoracic core biopsy.

ficient for the final diagnosis for 25 patients; the procedure was performed once for 20 patients, twice for three patients, and three times for two patients. The final malignant diagnosis was the result of histological examination of the surgically removed tissue for 21 patients.

For benign lesions, TTFNA was performed once for eight patients, two times for three patients, and three times for two patients. For 12 patients, a benign diagnosis was obtained by chest radiography or CT follow-up. In all 12 patients the lesions decreased in size or disappeared. One patient underwent surgery despite the fact that a TTFNA showed inflammatory disease because of an extreme malignant presentation at CT. The final diagnosis was inflammatory disease.

The results of the ^{99m}Tc-depreotide scintigraphy were not included in the definitive diagnostic decision-making process.

CT/HRCT Scan

CT examinations were performed by using a Philips MX8000IDT 16-row CT scanner (Best, Netherlands). The usual protocol in the management of patients with suspected lung cancer was used (collimation 16 ×1.5 mm, RI = 1 mm, RW = 2 mm, 120 kV, 150 mAs, rotation time 0.75 seconds, pitch 1.5). Iodixanol (Visipaque 270 mg/ml; GE Healthcare, Oslo, Norway) 2 ml/kg body weight was injected at 4 ml/sec. A soft reconstruction algorithm was used. The lungs were scanned after a 35-second delay after contrast medium was injected. The upper abdomen was scanned after a 65-second delay during the portal venous phase. If an infiltrate in the lung was detected, additional HRCT slices through the infiltrate were performed: collimation 0.75 mm, RI = 0.5 mm, RW = 1 mm, rotation time 0.75 seconds, 120 kV, 150 mAs.

^{99m}Tc-depreotide Imaging

Vials of 47-μg depreotide (NeoSpect) were provided by GE Healthcare. ^{99m}Tc-depreotide was prepared, and quality control was performed according to the manufacturing manual. ^{99m}Tc-depreotide was injected within 5 hours after preparation.

No special preparations for the patients were required. SPECT of the chest was performed 2 to 4 hours after injection with a dual-headed gamma camera. SPECT was performed at 120 angles using a 128 × 128 matrix with 30 seconds per angle. Image reconstruction was performed using an iterative algorithm without attenuation correction. Images were post-filtered with a low-pass filter (cut-off 0.30, order number 5.0).

Tumor to non-tumor activity ratios were calculated. Regions of interest were drawn around the tumor on the transaxial tomograms that showed the highest tumor uptake. A region of the same pixel size was drawn in the same area in the contralateral normal lung, and the total counts obtained in the two areas were divided.

Image Interpretation

The CT/HRCT was evaluated by two radiologists in collaboration, and lesions were classified into one of three categories: high, intermediate, or low probability of malignancy.[8,9] High probability of malignancy included HRCT findings as spiculation, ragged configuration and a halo around the lesion combined with other signs, including feeding vessels and pleural retraction. Low probability of malignancy included HRCT morphologic findings as benign calcifications, fat content, well defined margins, or obvious signs of infection on CT. All other lesions were defined as having an intermediate probability of malignancy.

Two nuclear medicine physicians in collaboration evaluated the ^{99m}Tc-depreotide scan visually. The images were graded positive if there was an increase in uptake activity in the area of the CT-detected lesions. Only a written description of the location of the lesions was known before these assessments.

After grading, the ^{99m}Tc-depreotide images and the CT/HRCT scan were compared directly by the two radiologists and the two nuclear medicine physicians to confirm that the lesions on both scans were indeed located in the same area. Software for image fusion was not available.

Statistical Analysis

Sensitivity, specificity, positive and negative predictive values, and mean values (± standard deviation) were computed in the standard manner.

Ethics

Before the study, ethical approval was obtained from the Regional Ethics Committee, and written consent was obtained from all patients included in the study.

RESULTS

A total of 59 lesions were detected by CT. The average size of the lesions was 31 mm (range, 5 to 74 mm), and the median size was 25 mm. Thirteen lesions were ≤15 mm, and 46 were >15 mm. Thirty lesions were malignant and 29 were benign. The overall prevalence of a malignant lesion was 0.51. In the two groups of lesions (≤15 mm and >15 mm), the prevalence was 23% and 59%, respectively (Table 2).

HRCT

The findings of HRCT compared with the final diagnosis are presented in Table 3. HRCT classified 26 lesions (44%) as having a high probability of malignancy and 13 (22%) as having low probability, of which one was false-negative. Twenty (34%) were classified as having an intermediate probability of malignancy. If the lesions in this latter group are considered to be malignant, as would be the case in a clinical setting, the sensitivity of HRCT is 97%, the specificity is 41%, the negative and positive predictive values are 92% and 63%, respectively. The four HRCT false-positive cases represented one atelectasis, supported by the TTFNA. The lesion disappeared on follow-up CT 2 months later, after treatment with antibiotics and physiotherapy. The three other cases represented inflammation/abscess that disappeared on follow-up CT 2, 2, and 3 months later, respectively, after treatment with antibiotics.

^{99m}Tc-Depreotide

The results for ^{99m}Tc-depreotide compared with the final diagnosis are presented in Table 4.

^{99m}Tc-depreotide did not result in any false negatives, but 14 false-positive lesions were seen (sensitivity 100%, specificity 52%). The positive and negative predictive value of ^{99m}Tc-depreotide was 68% and 100%, respectively. The false-positive results were the result of infection/inflammation in four cases; fibrosis in four cases; atelectasis, tuberculosis, and a hamartoma in one case each; and three had changes that resolved over time.

Table 5 summarizes the definitive diagnosis for the true-positive, false-positive, and true-negative lesions.

A detailed description of the two size groups of lesions (>15 mm or <15 mm) is presented in Table 2 and is related to SPECT sensitivity, specificity, accuracy, and prevalence of malignancy. The smallest lesion detected by ^{99m}Tc-depreotide was 10 mm.

The mean tumor-to-non-tumor ratio was 2.1 ± 0.8 (1.2; 4.2). The mean ratio in the true-positive group was 2.2 ± 0.7 (1.3; 4.2), which is very similar to the mean ratio in the false-positive group of 2.0 ± 0.8 (1.3; 3.6).

TABLE 2. Prevalence of malignancy, sensitivity, specificity, and accuracy of ^{99m}Tc-depreotide

Size	Prevalence	Sensitivity	Specificity	Accuracy
≤15 mm	3/13 (23%)	3/3 (100%)	7/10 (70%)	10/13 (77%)
>15 mm	27/46 (59%)	27/27 (100%)	8/19 (42%)	35/46 (76%)

TABLE 3. Findings of HRCT compared with the final diagnosis

HRCT	Malign	Benign	
High	22	4	26
Intermediate	7	13	20
Low	1	12	13
	30	29	59

TABLE 4. Findings of ^{99m}Tc-depreotide compared with the final diagnosis

^{99m}Tc-depreotide	Malign	Benign	
Positive	30	14	44
Negative	0	15	15
	30	29	59

TABLE 5. Final diagnosis for the true-positive, false-positive, and true-negative lesions at ^{99m}Tc-depreotide scan

Final diagnosis	Lesions
True-positive	
NSCLC	3
Adenocarcinoma	18
Squamous cell carcinoma	7
SCLC	2
Total	30
False-positive	
Non-malignant	3
Fibrosis	4
Inflammation	2
Infection	2
Atelectasis	1
Tuberculosis	1
Hamartoma	1
Total	14
True-negative	
Non-malignant	11
Hamartoma	2
Fibrosis	1
Inflammation	1
Total	15

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

HRCT and ^{99m}Tc-Depreotide

The findings of ^{99m}Tc-depreotide compared with the final diagnosis in each of the three groups: high, intermediate, and low probability of malignancy classified by HRCT are presented in Table 6.

HRCT showed a high probability of lung cancer in 26 lesions, 22 of which were malignant (positive predictive value of 84%). Of the four benign cases, only one was ^{99m}Tc-depreotide–negative.

HRCT showed a low probability of lung cancer in 13 lesions. One was erroneously classified as benign (negative

TABLE 6. The ^{99m}Tc-depreotide results compared with the final diagnosis in *A* the 26 lesions with high probability of malignancy, *B* the 20 lesions with intermediate probability, and *C* the 13 lesions with low probability of malignancy classified by HRCT

A. ^{99m}Tc-depreotide	Malign	Benign	
Positive	22	3	25
Negative	0	1	1
	22	4	26
B. ^{99m}Tc-depreotide	Malign	Benign	
Positive	7	6	13
Negative	0	7	7
	7	13	20
C. ^{99m}Tc-depreotide	Malign	Benign	
Positive	1	5	6
Negative	0	7	7
	1	12	13

predictive value of 92%). ^{99m}Tc-depreotide correctly detected this lesion but also had five false-positive results.

HRCT showed an intermediate probability of lung cancer in 20 lesions, seven of which were malignant and 13 of which were benign. Seven of the 13 benign lesions were ^{99m}Tc-depreotide–negative.

Figure 1 shows an example of ^{99m}Tc-depreotide in a patient with an adenocarcinoma.

DISCUSSION

The main findings of the present study demonstrate that ^{99m}Tc-depreotide after HRCT has considerable diagnostic value in the group of patients with lung lesions classified as having an intermediate probability of malignancy.

HRCT alone seems to be relatively accurate in the group of lesions that could be classified as either high or low probability of malignancy with a positive predictive value of 84% in the first group and a negative predictive value of 92% in the second group. However, as many as one third of the lesions could not be classified in one of these groups by HRCT; they were classified as indeterminate lesions, which is the group that constitute the major clinical challenge.

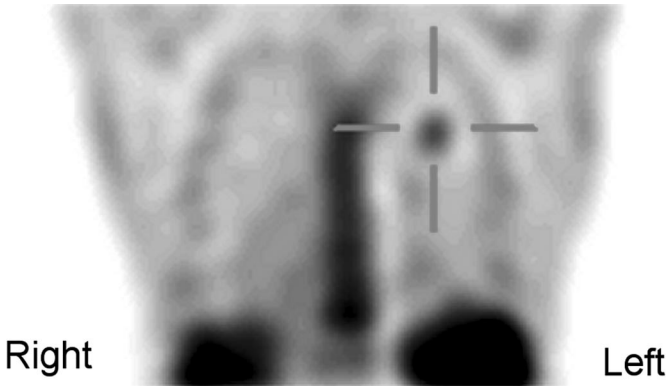

FIGURE 1. A 64-year-old woman with increased uptake in the left upper lobe on the ^{99m}Tc-depreotide scan. Histology showed an adenocarcinoma.

The sensitivity of ^{99m}Tc-depreotide for detecting lung cancer was high because all malignant tumors in the study showed an increased uptake of ^{99m}Tc-depreotide. There were no false-negative results. A negative ^{99m}Tc-depreotide therefore indicates that further investigations, such as invasive procedures or control CT scans, are unnecessary. However, in other studies, false-negative findings were reported,[12,14,15,17,18] and a large-scale study is necessary before a final recommendation can be made. The number of false-positive results was high. These overall results are confirmed by other investigators [12–15,17].

Despite its low specificity, ^{99m}Tc-depreotide can probably reduce the need for further diagnostic procedures by 35% in the group of indeterminate lesions classified by HRCT.

The 14 false-positive ^{99m}Tc-depreotide scans represented inflammatory or infectious diseases, fibrosis, one granuloma, atelectasis, and one hamartoma (see Table 5). Two hamartomas were ^{99m}Tc-depreotide–negative. The positive findings in granulomas and in inflammatory and infectious diseases are probably caused by an increased expression of somatostatin receptors on the surface of activated lymphocytes.[21] High uptake in fibrosis, atelectasis, and hamartomas has previously been reported,[12,17,18,22] but the reason is still unclear, unless it can be explained by some infiltration of activated lymphocytes in the area surrounding these lesions. To our knowledge, no one has investigated the presence of somatostatin receptors in hamartomas and fibrotic tissue.

Like Baath et al.[13] and Grewal et al.,[17] we found no relationship between histology and tumor-to-non-tumor ratio, which means that a high intensity in uptake is no indication of malignancy in our study. However, we did not correct for a partial volume effect, which might cause distortion of the scintigraphic findings depending on the size of the lesions. Such correction was made by Plaschcinska et al.,[23] who did find a significant difference between the semi-quantitative uptake in malignant and benign pulmonary nodules.

The mean size of lesions was 31 mm, and the median size was 25 mm. It is a well known phenomenon that the risk of malignancy increases in correlation with the size of the lesion.[24] Accordingly, we found a higher prevalence of cancer when the size of the lesions was >15 mm, whereas the specificity was higher in the group of lesions of ≤ 15 mm (see Table 2).

Because it has not yet been proven that ^{99m}Tc-depreotide is able to detect lesions <10 mm, such lesions should be followed using CT.

In vitro studies have shown somatostatin receptor expression on the surface of SCLC,[25] but the reason for the accumulation of somatostatin analogues in NSCLC is not yet fully understood. Several studies have endeavored to establish the presence of somatostatin receptors in NSCLC in vitro, but the results have so far been inconsistent. Thus, some studies have failed to demonstrate the presence of somatostatin receptors in NSCLC in vitro,[10,11,25] whereas others have succeeded in demonstrating the presence of

somatostatin receptors. O'Byrne et al. [26] found specific binding sites for an octapeptide analogue of somatostatin, RC-160, in cells of three squamous cell carcinomas but given the mixed histology of the tumors, the binding may be to tissue other than the tumor cells (i.e., lymphocytes). The results from other studies have shown that different tumor cells express a high degree of heterogeneity including somatostatin receptor subtypes.[27–29] In conclusion, the reason for the accumulation of somatostatin analogues in NSCLC in vivo seems to be the presence of somatostatin receptors in tumor cells, although the studies vary considerably in both design and outcome. The subtype most consistently reported is subtype 2. It is likely that expression of receptors in peritumoral vessels and activated lymphocytes affects the results in the study containing resected tumors masses.[21,30] The subject is reviewed by Plachcinska et al.,[31] who reached almost the same conclusion.

Blum et al.[12] had three false-negative results that represented adenocarcinomas, all ≤20 mm in size. High background activity adjacent to the tumors was mentioned as a probable explanation for not detecting these tumors. The same explanation was given for the only false-negative adenocarcinoma in the study by Baath et al.[17] Kahn et al.[14] had seven false-negative results, two of which were bronchoalveolar carcinomas; the remaining five were of unknown histological origin. The size of the false negatives, except one, was ≤20 mm. The size of the two bronchoalveolar carcinomas was not specified. Martins et al.[15] reported on one false negative and a bronchoalveolar carcinoma, 10 mm in size. One other bronchoalveolar carcinoma, 30 mm in size, in the same patient was correctly identified, as were all bronchoalveolar carcinomas in two other patients as well. In general, there seem to be three reasons for false-negative results: small tumors, tumors adjacent to areas with high activity uptake, and bronchoalveolar carcinomas. The first two were to be expected, whereas the results in bronchoalveolar carcinomas are more confusing because well differentiated tumors are known to express an increased number of somatostatin receptors.[32] Perhaps the number of false-negative bronchoalveolar carcinomas can be explained by their small size rather than the histology.

Two studies have compared ^{99m}Tc-depreotide with ^{18}F-FDG PET in evaluating pulmonary nodules.[14,18] Kahn et al. found similar sensitivity but a higher specificity with ^{18}F-FDG PET. Sensitivity and specificity with ^{18}F-FDG PET were 96 % and 71%, respectively, which is in compliance with the results of other studies.[33–35] Halley et al. found ^{18}F-FDG PET to be more sensitive but not more specific than ^{99m}Tc-depreotide in the diagnosis of lung cancer of any size. The false-negative results of ^{18}F-FDG PET were found in patients with small foci (≤10 mm) or highly differentiated tumors such as bronchoalveolar carcinomas.[33–35] The false-positive results were mainly the result of uptake in granulomas and processes with inflammation or infection.

Several studies have claimed the superiority of ^{18}F-FDG PET compared with CT in the staging of patients with lung cancer.[33–35] However, ^{18}F-FDG PET, as well as ^{99m}Tc-depreotide, is to some extent incorrect regarding T-staging and the determination of the exact anatomic localization. In this regard, image fusion using combined scanners (SPECT/CT or PET/CT) seem promising.[36] Only one study[14] has compared ^{99m}Tc-depreotide and ^{18}F-FDG PET with regard to staging. No significant difference between the two modalities was found, and the study also concluded that none of these investigations can be used for staging. In this study, we did not evaluate the uptake in the mediastinal lymph nodes.

CONCLUSION

The sensitivity and negative predictive value of ^{99m}Tc-depreotide was 100% in patients with CT-verified pulmonary lesions. HRCT alone was reliable in the group of patients classified as having high or low probability of malignancy. However, HRCT classified one third of the patients as having an intermediate probability of malignancy. In this group, the diagnostic value of ^{99m}Tc-depreotide after HRCT seem to contribute to a clinical algorithm in which patients with lesions indeterminate on HRCT but negative on ^{99m}Tc-depreotide do not need further invasive investigations or follow-up examinations. However, further studies are needed before a change in clinical strategy can be recommended, especially among patients with small lesions. As the availability of PET increases, comparative studies between ^{99m}Tc-depreotide and ^{18}F-FDG PET are needed as well.

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