Limited value of ^{99m}Tc depreotide single photon emission CT compared with CT for the evaluation of pulmonary lesions

¹S W HARDERS, MD, ¹H H MADSEN, MD, ²K HJORTH AUG, MD, PhD, ²M REHLING, MD, ³T R RASMUSSEN, MD, PhD, ⁴U PEDERSEN, MD, DMSc, ⁵H K PILEGAARD, MD, ⁶P MELDGAARD, MD, PhD, ⁷U T BAANDRUP, MD, PhD and ¹F RASMUSSEN, MD, DMSc

¹Department of Radiology, Aarhus University Hospital, Aarhus, Denmark, ²Department of Nuclear Medicine, Aarhus University Hospital, Aarhus, Denmark, ³Department of Pulmonology, Aarhus University Hospital, Aarhus, Denmark, ⁴Department of Otorhinolaryngology, Aarhus University Hospital, Aarhus, Denmark, ⁵Department of Thoracic Surgery, Aarhus University Hospital, Aarhus, Denmark, ⁶Department of Oncology, Aarhus University Hospital, Aarhus, Denmark, and ⁷Center for Clinical Research, Vendsyssel Hospital, Hjoerring, Denmark

Objectives: A contrast-enhanced multidetector CT (MDCT) scan is the first choice examination when evaluating patients with suspected lung cancer. However, while the clinical focus is on CT, research focus is on molecular biological methods whereby radiolabelled pharmaceuticals are injected into participants and target malignant lung tumours. We examined whether a contrast-enhanced MDCT scan supplied with an additional non-contrast enhanced high-resolution CT scan, or a newer but more expensive ^{99m}Tc depreotide single photon emission CT (SPECT) scan, was the better first-choice examination for the work-up of pulmonary lesions. Furthermore, we examined whether a ^{99m}Tc depreotide SPECT scan was an appropriate second-choice examination for patients with indeterminate lesions.

Methods: 140 participants were included in the analysis. CT images were given a malignancy potential rating of 1, 2 or 3 with higher rating being indicative of disease. ^{99m}Tc depreotide SPECT images were graded either positive or negative. Histopathology and CT follow-up were used as reference standard. Sensitivity, specificity and diagnostic accuracy were calculated.

Results: Overall sensitivity, specificity and diagnostic accuracy of CT were 97%, 30% and 84%, respectively. Overall sensitivity, specificity and diagnostic accuracy of ^{99m}Tc depreotide SPECT were 94%, 58% and 76%, respectively. For indeterminate lesions sensitivity, specificity and diagnostic accuracy of ^{99m}Tc depreotide SPECT were 71%, 68% and 69%, respectively.

Conclusion: Both CT and ^{99m}Tc depreotide SPECT made valuable contributions to the evaluation of pulmonary lesions. ^{99m}Tc depreotide SPECT results were not superior to CT results and did not contribute further to the diagnostic work-up. Regarding indeterminate lesions, ^{99m}Tc depreotide SPECT sensitivity was too low.

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Lung cancer has a poor prognosis with an overall 5-year mortality rate of approximately 84%. However, with early detection and surgery the mortality rate can be as low as 47% [1]. Lung cancer is a major indication for chest imaging. Many years of CT imaging have seen a steady evolution of methods used to evaluate lung nodules and mass lesions. A contrast-enhanced multidetector CT (MDCT) scan is the first-choice examination when lung cancer is suspected.

While the clinical focus is on MDCT, the research focus is on molecular biological methods whereby radiolabelled pharmaceuticals are injected into participants to target malignant lung tumours. Examples of such functional modalities include ^{99m}Tc depreotide single photon emission CT (SPECT) and 18-fluoro-2-deoxyglucose positron emission tomography (18-FDG PET). However, while numerous studies have been published

regarding 18-FDG PET, only a limited number, including a preliminary report by our group [2], have focused on ^{99m}Tc depreotide SPECT [3].

In this study we examine whether a contrast-enhanced MDCT scan supplied with an additional non-contrast-enhanced high-resolution CT (HRCT) scan or a newer but more expensive ^{99m}Tc depreotide SPECT scan is the better first-choice examination when dealing with the work-up of pulmonary nodules and mass lesions. Furthermore, we examined whether a ^{99m}Tc depreotide SPECT scan is an appropriate second-choice examination for the subgroup of patients with indeterminate lesions.

Methods and materials

Participants

The study conformed to the Danish legal requirements. Institutional review board approval was obtained from

Address correspondence to: Dr Stefan Harders, Department of Radiology, Aarhus University Hospital, Noerrebrogade 44, bld. 6, Aarhus DK-8000, Denmark. E-mail: stefhard@rm.dk

Figure 1. CT and ^{99m}Tc depreotide single photon emission CT (SPECT) study flow diagram and overall results (modified from www.stard-statement.org). Excl, excluded; indt, indeterminate; Ref, refused.

the Aarhus County Committee on Biomedical Research Ethics (M-AAA-20010301) and written informed consent was collected from all participants. Good clinical practice (GCP) guidelines were followed and monitored.

We designed a prospective follow-up study. In a 48-month study period all adult patients, with no previous malignancies referred to the Department of Pulmonology at Aarhus University Hospital for the evaluation of suspected lung cancer, were clinically evaluated. Based on individual signs and symptoms they were referred for an MDCT scan of the thorax and upper abdomen. If a pulmonary lesion was found on MDCT, an additional non-contrast-enhanced spiral HRCT scan of the thorax including the lesion was performed immediately after to study the lesion in greater detail. The patients were offered a ^{99m}Tc depreotide SPECT examination within a few days. Consecutive patients with pulmonary lesions ≥ 5 mm who fulfilled the general criteria were eligible for inclusion; however, only nodules >10 mm were suitable for biopsy. 176 patients were eligible for inclusion and were asked to sign an informed consent form. 25 refused to participate, 2 did not have additional HRCT scans, 3 were excluded by the investigators owing to waiting time for ^{99m}Tc depreotide SPECT, 3 did not obtain useful ^{99m}Tc depreotide SPECT scans and 3 were excluded because of missing follow-up data. This left 140 participants for final analysis (Figure 1). Participants were only included once.

Procedures

Before standard MDCT scans, iodinated contrast material (Iodixanole, Visipaque[®] 270 or Iohexole, Omnipaque[®] 300; GE Healthcare, Oslo, Norway) was administered intravenously to all patients in weight-adjusted doses. MDCT scans were performed on a MDCT spiral scanner (Philips MX 16-channel CT scanner; Philips Healthcare, Best, the Netherlands). Acquisition parameters were

section thickness, 1.25 mm; scan mode helical; tube voltage, 120 kV; and filter B. Patients were scanned from the root of the neck to the upper abdomen including the liver and adrenals with a delay of 65 s to acquire proper portal filling. After standard MDCT scans, additional non-contrast-enhanced HRCT scans were performed. HRCT acquisition parameters were section thickness, 1.00 mm; scan mode, helical; tube voltage, 120 kV; and filter L. HRCT scans were planned to include lesions only.

Vials of 47 μg ^{99m}Tc depreotide (NeoSpect; GE Healthcare, Buckinghamshire, UK) were prepared, and quality control performed, accordingly to the instruction manual. 555–740 MBq ^{99m}Tc depreotide was injected within 5 h of preparation. No special preparations for the patients were required. SPECT was performed 2–4 h after injection with a dual-headed gamma camera at 120 positions using a 128×128 matrix with 30 s per position. 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).

Table 1. Lesion size and proportions of correctly identified lesions by CT and ^{99m}Tc depreotide single photon emission CT (SPECT)

Lesion size	n	CT	SPECT
Malignant lesions	69	67/69	65/69
0–10 mm	3	3/3	0/3
11–20 mm	14	13/14	13/14
21–30 mm	19	19/19	19/19
31–40 mm	18	17/18	18/18
41–50 mm	6	6/6	6/6
>51 mm	9	9/9	9/9
Benign lesions	71	21/71	41/71
0–10 mm	16	6/16	15/16
11–20 mm	17	5/17	12/17
21–30 mm	14	5/14	7/14
31–40 mm	11	1/11	5/11
41–50 mm	9	4/9	4/9
>51 mm	4	0/4	0/4

Figure 2. Non-parametric receiver operating characteristic (ROC) curves of overall sensitivity and 1-specificity of CT and ^{99m}Tc depreotide single photon emission CT (SPECT). When applicable, the area under the parametric ROC curve represents a measure of the unbiased overall diagnostic accuracy of a test. Non-parametric estimates of the area under the ROC curve tend to underestimate the "smooth curve" area (*i.e.* parametric estimates).

Collection and validation of the data

Two senior consultant radiologists (FR and HHM), who have clinical and research experience with lung cancer imaging, reviewed the CT scans. All reviews were by agreement and no participant data (name, patient ID and clinical data) were visible to the readers. Multiplanar images were reviewed.

Based on size [4], shape [5], attenuation [6], calcification patterns [4, 7, 8] and other signs associated with the presence of lung cancer [9–11], the readers gave an integrative malignancy potential rating (MPR) on a scale of 1, benign; 2, indeterminate; or 3, malignant.

^{99m}Tc depreotide SPECT reviews were performed by two senior consultant nuclear medicine physicians (KH and MR), who have clinical and research experience. All reviews were by agreement and no participant data (name, patient ID or clinical data) were visible to the readers. Only a written description of the location of the lesions was given prior to the assessment. Images were graded positive if there was an increase in uptake in the area of the pulmonary lesion compared with the surrounding normal lung tissue. Otherwise they were graded negative.

Definitive pathological diagnoses were obtained in 75% (105/140) of the cases mainly by biplane fluoroscopy-guided or ultrasound-guided fine-needle aspiration biopsy. In the majority of the procedures material was obtained by biplane fluoroscopy-guided fine-needle aspiration biopsy. Ultrasound-guided biopsies were performed

when appropriate and CT-guided biopsies were performed in very few cases. 96% (67/70) of the malignant diagnoses and 54% (38/70) of the non-malignant diagnoses were pathologically verified. Malignant diagnoses were based on cytology or histopathology and non-malignant diagnoses were verified by additional coarse needle aspiration biopsies. In this manner three separately obtained non-malignant diagnoses were accepted. All tissue specimens were examined by a specialised lung pathologist (UB), who characterised the specimens with regard to the presence and type of lung cancer. The remaining 25% (35/140) were not suitable for invasive procedures for various reasons (*e.g.* nodule size <10 mm, poor compliance, severe comorbidity etc.). These participants were instead followed by regular interval CT scans according to the international standard. Follow-up was done at 3, 6, 12 and 24 months, or longer if necessary [12], but ceased if lesions resolved entirely during the follow-up period. Median follow-up (25th to 75th percentile) was 18 months (range, 6–42 months).

Statistical methods

Descriptive statistics were used for baseline characteristics. Normality was tested with histograms and quantile-quantile (QQ) plots.

CT MPRs were applied on an ordinal scale of 1, 2 or 3, with higher values indicating disease, and tabulated

Table 2. CT malignancy potential ratings (MPRs) and reference standard ($n=140$)

MPR	Reference standard	
	Malignant	Benign
Malignant	53 (77%)	10 (14%)
Indeterminate	14 (20%)	40 (56%)
Benign	2 (3%)	21 (30%)
Total	69 (100%)	71 (100%)
Fisher's exact $p<0.001$		

Table 3. ^{99m}Tc depreotide single photon emission CT (SPECT) grades and reference standard ($n=140$)

SPECT grade	Reference standard	
	Malignant	Benign
Positive	65 (94%)	30 (42%)
Negative	4 (6%)	41 (58%)
Total	69 (100%)	71 (100%)
Fisher's exact $p<0.001$		

Table 4. Overall comparison of CT and ^{99m}Tc depreotide single photon emission CT (SPECT) classification probabilities, predictive values and overall diagnostic accuracy ($n=140$)

	CT (%)	SPECT (%)
Prevalence	49 (41–58)	49 (41–58)
Sensitivity	97 (90–100)	94 (86–98)
Specificity	30 (19–42)	58 (45–69)
PPV	57 (48–66)	68 (58–78)
NPV	91 (72–99)	91 (79–98)
Accuracy	84 (76–89)	76 (68–83)

NPV, negative predictive value; PPV, positive predictive value. Diagnostic test variables derived from Tables 2 and 3. Results are shown as estimates and 95 confidence intervals.

against a reference standard outcome at multiple cut-offs [13]. Sensitivity was prioritised and the CT MPR 2 and 3 were treated as malignant test results. ^{99m}Tc depreotide SPECT grades were applied as either positive (malignant) or negative (benign) test results. A side-by-side comparison was done; sensitivity, specificity, positive predictive values (PPVs) and negative predictive values (NPVs) were tabulated; and overall diagnostic accuracies were estimated as the areas under the empirical receiver operating characteristic (ROC) curves [14]. 95% confidence intervals (CI) were computed applying binomial exact methods.

The validity of the ^{99m}Tc depreotide SPECT results was examined for all three CT MPRs separately to assess

whether ^{99m}Tc depreotide SPECT scan was beneficial for any subgroup of patients in a clinical examination algorithm.

We used the licenced statistical software package STATA/IC 10 (StataCorp LP, College Station, TX).

Results

Baseline characteristics

60 males and 80 females with a mean age of 64 years (range, 34–83 years) participated in the study. 137 participants had a mean smoking history of 31 pack-years [standard deviation (SD), 17] [1]. Three participants refused to answer.

Lesion size and distribution

The majority of the lesions in the study were of a moderate size (Table 1). Mean lesion size was 30 mm (SD, 17 mm). There was a distribution of 49% (69/140) malignant and 51% (71/140) benign lesions. Of the 69 malignant lesions, the distribution was 10% (7/69) small cell carcinomas, 13% (9/69) squamous cell carcinomas, 54% (37/69) adenocarcinomas, 1% (1/69) large cell carcinomas, and 22% (15/69) other or unclassified non-small cell carcinomas.

Figure 3. ^{99m}Tc depreotide single photon emission CT (SPECT) results stratified by CT results.

Table 5. ^{99m}Tc depreotide single photon emission CT (SPECT) results stratified by CT results

	SPECT (CT1) (n=23)	SPECT (CT2) (n=54)	SPECT (CT3) (n=63)
Prevalence	9% (1–28%)	26% (15–40%)	84% (73–92%)
Sensitivity	100% (16–100%)	71% (42–92%)	100% (93–100%)
Specificity	57% (34–78%)	68% (51–81%)	20% (3–56%)
PPV	18% (2–52%)	43% (23–66%)	87% (76–94%)
NPV	100% (74–100%)	87% (70–96%)	100% (16–100%)
Accuracy	79% (56–93%)	69% (56–82%)	60% (47–72%)

NPV, negative predictive value; PPV, positive predictive value; SPECT(CT1), ^{99m}Tc depreotide SPECT results when CT was benign; SPECT(CT2), ^{99m}Tc depreotide SPECT results when CT was indeterminate; SPECT(CT3), ^{99m}Tc depreotide SPECT results when CT was malignant.

Diagnostic test variables with estimates and 95% confidence intervals.

Overall results

CT and ^{99m}Tc depreotide SPECT produced similar results and all were highly significantly associated with malignancy. Thus, for CT, 77% of the malignant lesions were categorised as malignant, 20% as indeterminate and 3% as benign ($p<0.001$), and for ^{99m}Tc depreotide SPECT 94% of the malignant lesions were categorised as positive and 6% as negative ($p<0.001$). For CT the MPR ROC table was collapsed according to the predefined cut-off and a sensitivity of 97% (95% CI, 90–100%), a specificity of 30% (95% CI, 19–42%) and an overall diagnostic accuracy of 84% (95% CI, 76–89%) were estimated. For ^{99m}Tc depreotide SPECT a sensitivity of 94% (95% CI, 86–98%), a specificity of 58% (95% CI, 45–69%) and an overall diagnostic accuracy of 76% (95% CI, 68–83%) were estimated (Figures 1 and 2; Tables 2–4).

Sub-group analyses

^{99m}Tc depreotide SPECT results when CT was malignant

Sensitivity was 100% (95% CI, 93–100%), specificity was 20% (95% CI, 3–56%) and the overall diagnostic accuracy was 60% (95% CI, 47–72%).

^{99m}Tc depreotide SPECT results when CT was indeterminate

Sensitivity was 71% (95% CI, 42–92%), specificity was 68% (95% CI, 51–81%) and the overall diagnostic accuracy was 69% (95% CI, 56–82%).

^{99m}Tc depreotide SPECT results when CT was benign

Sensitivity was 100% (95% CI, 16–100%), specificity was 57% (95% CI, 34–78%) and the overall diagnostic accuracy was 79% (95% CI, 56–93%) (Figure 3; Table 5).

Discussion

We performed a prospective follow-up study and included 140 participants suspected of lung cancer. All participants underwent a contrast-enhanced MDCT scan with an additional non-contrast enhanced HRCT scan and a ^{99m}Tc depreotide SPECT scan. In the first part of the study overall results of CT and ^{99m}Tc depreotide SPECT were assessed individually and compared. For CT a three-category MPR was significantly associated with

malignancy. Thus, sensitivity was very high. However, participants with malignant and indeterminate lesions were treated alike; therefore, there was an expected trade-off in the form of a low specificity. When reviewing the ROC curve, overall diagnostic accuracy was high. For ^{99m}Tc depreotide SPECT a dichotomous grading system was significantly associated with malignancy with a very high sensitivity. However, for ^{99m}Tc depreotide SPECT specificity was higher. Interestingly though, when reviewing the ROC curve, overall diagnostic accuracy was lower than for CT. Statistically, this controversy reflects the

Figure 4. (a, b) Pulmonary lesions rated “malignant” by CT. Biopsies revealed a small-cell carcinoma and an adenocarcinoma. Both participants were female: a 60-year-old and 54-year-old, respectively. Both: C-425; W1400.

Figure 5. (a, b) Pulmonary lesions rated “indeterminate” by CT. Biopsies revealed two adenocarcinomas. Both participants were female, a 72-year-old and 49-year-old, respectively. Both: C-425; W1400.

limited information obtained by a rigid dichotomous grading system, and the result is likely to represent an underestimation of the “true” diagnostic accuracy of ^{99m}Tc depreotide SPECT. In the second part of the study ^{99m}Tc depreotide SPECT results were stratified by CT results. These results lead us to conclude that a ^{99m}Tc depreotide SPECT examination may be useful for the group of patients rated malignant by CT. These patients need further examinations and ^{99m}Tc depreotide SPECT correctly identified all truly diseased patients, albeit with a high number of false positives (Figures 4 and 6a,b; Table 5). Conversely, while previous studies have focused on the benefit of ^{99m}Tc depreotide SPECT for the group of patients with indeterminate lesions, our subgroup analysis could not confirm these results. Although this group of patients represent a substantial diagnostic problem, our study had only a moderate sensitivity reflecting unacceptable high numbers of false negatives, which were later identified as an SCLC and regular adenocarcinomas (Figures 5 and 6c,d; Table 5). Owing to

Figure 6. (a, b) The same lesions as in Figure 4. Both lesions were rated positive by ^{99m}Tc depreotide single photon emission CT (SPECT) and thereby represent true positives. (c, d) The same lesions as in Figure 5. Both lesions were rated negative by ^{99m}Tc depreotide SPECT and thereby represent false negatives. This illustrates a major issue; ^{99m}Tc depreotide SPECT is both highly sensitive and specific when it comes to highly suspicious lesions. However, sensitivity drops significantly when it comes to indeterminate lesions.

the limited number of patients with benign lesions, we considered it inappropriate to make any conclusions regarding these.

Conclusively, both CT and ^{99m}Tc depreotide SPECT made valuable contributions to the evaluation of pulmonary lesions. However, ^{99m}Tc depreotide SPECT results were not superior to CT results and did not contribute further to the diagnostic work-up. Furthermore, with regard to indeterminate lesions, ^{99m}Tc depreotide SPECT sensitivity was too low.

There are multiple strengths to our study. Firstly we designed a prospective follow-up study and carried out an extensive blinding procedure. Secondly, GCP rules and regulations were followed and we were thereby able to achieve high validity of our data and thirdly, we included 140 consecutive participants, thereby making our single-centre study one of the largest ever published on this issue. Finally, we compared participants with non-participants on several demographic parameters and found no discrepancies.

Recently, the most influential ^{99m}Tc depreotide SPECT studies have been meta-analyses, in which CT, ^{99m}Tc depreotide SPECT, 18-FDG PET and MRI are considered equally accurate when characterising solitary pulmonary nodules [3]. Although the part of the meta-analysis regarding ^{99m}Tc depreotide SPECT rests on a limited number of studies and patients, the results closely resemble ours [3] and thereby support our overall results of non-superiority.

A number of different approaches are used when confronted with the risk of lung cancer or the discovery of a pulmonary lesion. While most institutions offer selected patients an MDCT scan of the chest and upper

abdomen, some institutions engage in screening studies, typically applying low dose CT to a large patient population with varying degrees of success [15, 16] and debatable benefits for the patient [17]. Also the use of 18-FDG PET for the characterisation of pulmonary lesions is growing [18]. However, although a number of studies have established 18-FDG PET is superior to CT, with regard to characterising pulmonary lesions, the modality suffers from both false positive and false negative results, and whereas false positive lesions may be considered annoying, false negatives are detrimental. These considerations mean there is no simple recommendation for the use of 18-FDG PET in the work-up of pulmonary lesions. Still, new options keep emerging, *e.g.* perfusion CT [19].

We began this study to compare the established imaging modality, CT, to the new and rather expensive modality ^{99m}Tc depreotide SPECT. Based on our preliminary report we hoped to achieve both higher sensitivity and specificity, and we were especially interested in the results for indeterminate lesions. However, after finishing the study we must conclude that ^{99m}Tc depreotide SPECT is difficult to recommend because the results were not superior to CT results and did not contribute further to the diagnostic work-up. Furthermore, with regard to indeterminate lesions, ^{99m}Tc depreotide SPECT sensitivity was too low.

Conclusion

While CT remains the workhorse of lung cancer diagnostics, ^{99m}Tc depreotide SPECT, being both expensive and time-consuming, has no place in a standard clinical examination algorithm.

Acknowledgments

SWH, HHM, FR, KH and MR were involved in the conception and design of the study. TRR included the participants. SWH created the dataset. SWH, HHM, FR, KH and MR performed the analysis and data interpretation. SWH drafted the article. All authors were involved in the critical revision of the manuscript and gave final approval of the version submitted. SWH is guarantor.

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