Diagnosing pulmonary embolism: establishing and consolidating the role of spiral CT

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Diagnosis of Pulmonary Embolism with Spiral CT as a second procedure following scintigraphy in 627 Consecutive Patients with Suspected Pulmonary Embolism.
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European Radiology 2003; 13: 1501-1507.

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Abstract

Objective: *To evaluate, in a routine clinical settingthe role of spiral CT as a second procedure in patients with clinically suspected PE and abnormal perfusion scan.*

Methods: *We prospectively studied the role of spiral CT in 279 patients suspected of pulmonary embolism. All patients started their diagnostic algorithm with chest radiographs and perfusion scintigraphy. Depending on the results of perfusion scintigraphy patients proceeded to subsequent levels in the algorithm: stop if perfusion scintigraphy was normal; CT and pulmonary angiography if subsegmental perfusion defects were seen; ventilation scintigraphy followed by CT when segmental perfusion defects were seen; and pulmonary angiography in this last group when results of ventilation perfusion scintigraphy and CT were incongruent.*
Reference diagnosis was based on: normal perfusion scintigraphy, or high probability perfusion/ventilation scintigraphy in combination with abnormal CT, or pulmonary angiography. If pulmonary embolism was present, the largest involved branch was noted on pulmonary angiography, or on spiral CT-scan in case of a high-probability ventilation-perfusion scan and a positive CT-scan. A distinction was made between embolism in a segmental branch or larger, or subsegmental embolism.

Results: *Twohundred-and-seventynine patients had abnormal scintigraphy. In 27 patients spiral CT and/or pulmonary angiography was non-conclusive. Using spiral CT we correctly identified 117 of 135 patients with pulmonary embolism, and 106 out of 117 patients without pulmonary embolism. Sensitivity and specificity is therefore 87% and 91%. Prevalence of pulmonary embolism is 53%. Positive and negative predictive values are respectively 91% and 86%. In the high probability group, sensitivity and specificity increase to 97% and 100% with a prevalence of 90%. In the non-high probability group sensitivity and specificity decrease to 61% and 89% with a prevalence of 25%.*

Conclusion: *In a routine clinical setting current CT technology has limited value as a second diagnostic test because of low added value in patients with a high probability lungscan and low sensitivity in patients with non-high probability lungscan result.*

Introduction

Although various diagnostic algorithms in patients suspected of pulmonary embolism, have recently been evaluated and advocated, ventilation-perfusion scintigraphy is still the preferred initial test. [1] It usually is an initial though not a final study since a number of reports, including the Prospective Investigators of Pulmonary Embolism Data (PIOPED), have shown that only a small number (33%) of patients will have an unequivocal diagnosis following ventilation-perfusion scintigraphy.[2] Additional tests are needed for the remaining majority (67%) with an inconclusive, or non-high probability scintigraphy.

Spiral computed tomography (CT) is one of the additional tests which have been introduced recently. Studies evaluating spiral CT have yielded contradictory results.[3] Van Erkel et al have calculated that spiral CT is marginally cost effective for any sensitivity.[4] However, when sensitivity dropped below 85%, conventional strategies without spiral CT had a lower mortality. Many groups have reported sensitivities for PE which were well above this threshold of 85% [5-9], while others have disputed this.[10]

The purpose of this study was to determine, in a prospective multicenter study, the utility of spiral CT as a second procedure following ventilation-perfusion scintigraphy, in routine clinical practice.

Materials and methods

Patients

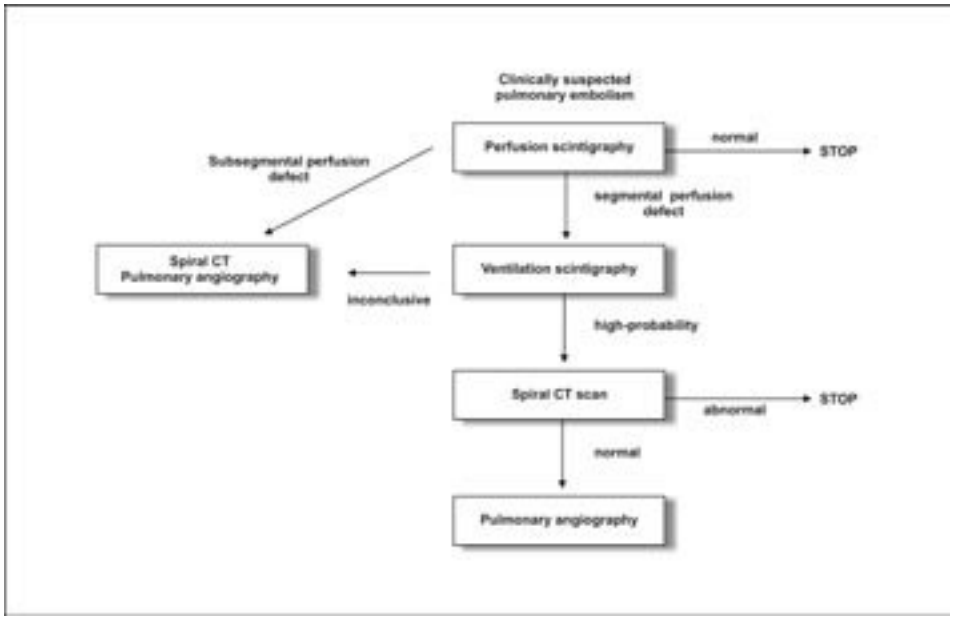
All 1162 patients from the six participating hospitals (four academic and two general), referred for tests to diagnose or exclude pulmonary embolism between the period May 1997 and March 1998 were eligible. The protocol was approved by the six local medical ethical committees and by the research committee of the National Health Insurance Council who subsidized the study. Inclusion criteria were: clinical suspicion of pulmonary embolism as decided by the referring physician based on his or her judgement of signs and symptoms such as pleuritic or non specific chest pain, and dyspnea. Exclusion criteria were: anticoagulant treatment at the time of screening for more than 24 hours, one or more diagnostic tests for pulmonary emboli already performed, younger than 18 years of age, and pregnancy as indicated by the patient. The initial tests had to be performed within 24 hours after the initial suspicion of pulmonary embolism, and all diagnostic tests had to be completed within 48 hours. The study was designed in such a way that patients with contra-indications for spiral-CT and/or conventional pulmonary angiography were not initially excluded from participation in the study.

Study design

All patients started their diagnostic algorithm (figure 1.) with perfusion scintigraphy in combination with chest radiography. A normal perfusion scintigram was considered to be enough evidence to exclude pulmonary embolism, and no further tests were performed. In patients with a segmental perfusion defect ventilation scintigraphy was obtained. Patients with subsegmental perfusion defects did not have ventilation scintigraphy, because there was no possibility of these scans becoming high-probability. Subsequently all patients with perfusion defects underwent spiral CT scanning and in case of a non-high probability ventilation-perfusion scintigraphy result pulmonary angiography was added as reference. Pulmonary angiography was also added as reference when the CT-scan was normal in case of a high-probability ventilation-perfusion scintigraphy. Patients with an inconclusive scintigraphic result, in whom CT findings were not verified by pulmonary angiography (protocol violators) were excluded. Therefore a normal perfusion scintigraphy, a pulmonary angiography or a combination of a high probability ventilation perfusion scan result and an abnormal CT-scan result were taken as gold standard.

The responsible radiologist or nuclear physician in each participating center interpreted all test results. The diagnosis pulmonary embolism was used as reference diagnosis when pulmonary angiography was positive or when the

Figure 1. Diagnostic algorithm



combination of high-probability ventilation-perfusion scintigraphy with positive CT occurred. In the case of a negative pulmonary angiography or normal perfusion scintigraphy pulmonary embolism was considered to be absent.
If pulmonary embolism was present, the largest involved branch was noted on the pulmonary angiography, or on the spiral CT-scan in case of a high-probability ventilation-perfusion scan and a positive CT-scan. A distinction was made between embolism in a segmental branch or larger, or subsegmental embolism.

Imaging studies

Chest radiographs were preferably made erect and in two directions (posterior-anterior and left lateral). If this was not possible an anterior-posterior radiograph was made in bed.
Perfusion scintigraphy was performed after intravenous administration of 0,03 mCi/kg Tc-99m-labeled macro-aggregated serum albumin (Mallinckrodt, Petten, The Netherlands). Perfusion images were acquired with a minimum of 200,000 counts per view in at least four views: anterior, posterior, left anterior oblique and right anterior oblique views. Ventilation studies were performed using Krypton-81m (Mallinckrodt, Petten, The Netherlands) via Rb-Kr generator (Cygne-Amersham) in a single breath. A minimum of 200,000 counts was required for views in the same four directions as the perfusion scintigraphies. Gamma-camera and collimator depended on local availability. (Siemens Orbiter 3700 Digitrac, Siemens Medical Systems, Iselin, N.J.USA; ADAC Vertex and Argus, ADAC Laboratories Europe B.V., Maarsen, The Netherlands; Toshiba GCA501 and GCA9015a, Toshiba Medical Systems Division, Tokyo, Japan; Varicam Elscint Inc. Hackensack N.J., USA; collimators used MEAP, LEHR, MEHR and LEGP).
Spiral CT scanners had to be capable of scanning at least 16 centimeters contiguously (Siemens Somatom plus 4 and Somatom 6, Siemens Medical Systems, Erlangen, Germany; Elscint (Elscint, Haifa, Israel); Philips SR7000 and SR8000, Philips, Best, The Netherlands). Scanning was performed using a 5mm table speed and 3mm slice thickness. First the level of the aortic arch was determined on the scout view. Sixteen centimeters caudally the starting point was identified. The scanning process was then started from this position in a cranial direction, 20 seconds after intravenous injection of 900 mg/s of iodine for 40 seconds, either by injection of one hundred milliliters of nonionic contrast agent with 35% iodine content (Iomeron 350, Bracco Byk Gulden, Konstanz Germany) at an injection rate of 2,5 mL/sec or by injection of 120 mL of nonionic contrast agent 30% iodine content (Ultravist 300, Schering, Berlin, Germany) at an injection rate of 3,0 mL/sec. The scan was performed during a single breath

hold, although shallow breathing was allowed in very dyspnoeic patients. Images were reconstructed at 2mm intervals.
Pulmonary angiography was performed by introducing a 7.1F Grollmann catheter (Cook, Eindhoven, The Netherlands) in a femoral vein under local anesthesia. The left and right main pulmonary artery were selectively catheterized in turn, and angiographic images were digitally acquired in antero-posterior and left anterior oblique views while injecting contrast material. Depending on the patient and the anticipated cardiac output a protocol of 15 ml/sec (total 30ml) or 20ml/sec (40 ml total) was used. Occasionally additional images were obtained in areas of special interest matching the perfusion images. Interpretation was done on a viewing station.

Image analysis

Ventilation-perfusion scintigraphies were interpreted in conjunction with the chest radiographs using the revised PIOPED criteria [11] and were classified as normal, inconclusive (non-high), or high probability.
The CT-scans were interpreted by the at the time responsible radiologist in each participating center. CT and ventilation-perfusion scintigraphy were not independent tests. The observers were blinded to the detailed results of ventilation-perfusion scintigrams, but were aware of the presence of abnormal scintigraphic test results. The radiologist responsible was allowed to make minor adjustments to the protocol such as adding a few seconds to the scanning delay time in cardiac compromised patients and taking additional slices or small volumes in difficult areas. Likewise the radiologist was also allowed to make occasional multiplanar reconstructions in problematic areas.
A workstation allowing cine mode viewing with various window and level settings was always used. Standard settings were window width 350 HU, window level 50HU for mediastinal structures and pulmonary vasculature and window width 1500 HU, window level –500HU for comparison of opacified lung vasculature and anatomical relation to bronchi and lung parenchyma. Of all CT-scans with the final diagnosis of pulmonary embolism, the largest involved branch of the pulmonary vasculature was noted and categorized in 2 categories: segmental or larger artery involved, or subsegmental artery pulmonary embolism.
For the detection of pulmonary embolism on CT, the previously described criteria [7] were used. Pulmonary embolism was considered to be present if in the case of a well opacified scan there was an intraluminal filling defect on more than one slice. A filling defect could be seen as a complete occlusion of the vessel, an eccentric partial filling defect or a partial central filling defect surrounded by contrast agent.

A CT-scan was considered negative if in the case of a good quality scan no filling defects could be seen. A scan was considered to be equivocal when insufficient opacification of vessels or imaging artefacts were observed.
The interpretation of the angiograms was also done on a viewing station. For the detection of pulmonary embolism the diagnostic criteria described by Sagel and Greenspan[12] were used. If present, the largest branch involving pulmonary embolism was noted and as with CT-scan analysis categorized in 2 categories.

Statistical analysis

Statistical analyses were performed using statistical software (SPSS Inc. , Cary, NC). Data management and these analyses were performed by a specially assigned group of biostatisticians and epidemiologists. Sensitivity and specificity (including their 95% confidence intervals) for CT were calculated. In addition the sensitivity for CT was calculated separately for both the subsegmental and segmental or larger pulmonary embolisms.

Results

Of 1162 patients suspected to have pulmonary embolism, 179 did not meet our criteria. Sixteen patients were below the age of 18, 11 were pregnant, in six there was an indication to treat immediately with thrombolytic therapy at the time of screening (one of these six patients was also below the age of 18), 43 patients had diagnostic tests performed prior to start of the study protocol. One hundred-and-four patients could not be included in the study because the diagnostic work-up could not be started within 24 hours after screening due to logistic problems during weekends and holidays. Informed consent was obtained from 627 patients out of the remaining 983 eligible patients (64%).
In 101 patients the study protocol was not completed because not all imaging studies were performed within 48 hours due to the following reasons: logistic problems or hardware down time (17 patients), withdrawal of informed consent (12 patients), withdrawal by the treating physician (21), medical reasons (28 patients) such as contrast allergy, deterioration or withdrawal by the treating physician because of alternative diagnosis (18 patients). In five patients the reason for not completing the protocol is unknown (table 1).
Ultimately 526 patients with a mean age of 51.2 years were included. Male to female ratio was 0.66. Only 18% were in-patients, 82% were out-patients. Eighty-three patients (16%) had had a venous thrombo-embolic event in the past. Median duration of symptoms was 3 days. The characteristics of a sample of 141 consecutive patients who were excluded during 2 months of the study

were evaluated for comparison with all 526 study patients. The group of patients included had no different male to female ratio, frequency of comorbidity, or risk factors for pulmonary embolism such as immobilization, previous trauma or surgery, use of oral contraceptives, familial risks or inherited blood disorders, as compared to the excluded group.

Table 1. Patients screened for the study.

Patients screened		1162
Excluded	Age < 18 years	16 *
	Pregnancy	11
	Indication for immediate thrombolytic therapy	6 *
	Objective diagnostic work-up already started elsewhere	43
	Logistic reasons (weekend, holidays)	104
Eligible patients		983
Informed consent		627
Incomplete study protocol	Withdrawal of informed consent	12
	Medical reasons (cardiac arrhythmia)	28
	Alternative diagnosis / incomplete protocol	18
	Withdrawal by treating physician	21
	Technical reasons (time constraints, machine breakdown)	17
	Unknown reasons	5
Final diagnosis		526

**) one patient was < 18 years and received thrombolytic therapy*

Of the 526 patients available for complete analysis, 247 (47%) had a normal perfusion scintigraphy. The findings in the entire group with abnormal scintigraphies and the findings in two subgroups (high probability ventilation-perfusion scintigraphy versus non-high probability ventilation-perfusion scintigraphy) are shown in table 2.

Entire population

Twohundredseventynine patients had an abnormal perfusion scintigram. Results could not be analyzed in 27 patients. In 19 of these patients CT was equivocal (inconclusive), in seven patients pulmonary angiography was non-conclusive, and in one patient both CT and angiography were non-conclusive. When compared to

Table 2. CT compared to gold standard for the entire study population, the high-probability group and the non-high-probability group.

Entire population

	PE +	PE -	Total
CT +	116	12	128
CT -	17	107	124
Total	133	119	252

Prevalence 53%, sensitivity 87%, specificity 90%, PPV 91%, NPV 86%.

High probability group

	PE +	PE -	Total
CT +	94	-	94
CT -	3	11	14
Total	97	11	108

Prevalence 90%, sensitivity 97%, specificity 100%, PPV 100%, NPV 78%.

Non-high probability group

	PE +	PE -	Total
CT +	22	12	34
CT -	14	96	110
Total	36	108	144

Prevalence 25%, sensitivity 61%, specificity 89%, PPV 65%, NPV 87%.
N=252 (complete data set without missing values and equivocal test results)

either a concordant high-probability ventilation-perfusion scintigraphy or abnormal pulmonary angiography, spiral CT correctly identified 117 out of 135 patients with pulmonary embolism, and 106 out of 117 patients without pulmonary embolism. Calculated sensitivity and specificity is therefore 87% and 91% respectively. Prevalence of pulmonary embolism in the group of patients that had a CT scan was 53%. Positive and negative predictive values are respectively 91% and 86% (table 2.).

High probability group

Perfusion- ventilation scintigraphy resulted in high-probability in 113 patients. CT was non diagnostic in two patients, angiography was non-diagnostic in three patients. In 94 of 108 patients spiral CT confirmed the presence of pulmonary emboli. CT was negative (discordant) in the remaining 14 patients. Angiography

was negative in eleven patients and positive for pulmonary embolism in three patients. There were thus eleven true- and three false negative CT diagnoses (table 2).

Non-high probability group

Ventilation-perfusion scintigraphy was inconclusive in 166 patients (32%) because of the presence of segmental perfusion defects matched by ventilation defects (76 patients), or because of subsegmental perfusion defects only (90 patients). In four patients pulmonary angiography was inconclusive and in 17 patients the CT scan result was inconclusive. Pulmonary angiography was positive for pulmonary embolism in two and negative in 15 of these 17 patients with non-conclusive CT scan results. In one patient both pulmonary angiography and CT scan were of insufficient non-conclusive quality. Thus in 144 patients CT was compared with angiography (table 2). There were 22 true positive, 96 true negative, 12 false positive and 14 false negative CT results.

Segmental analysis of CT-scan results

Pulmonary embolism was found in 135 patients out of 252 patients with conclusive CT-scans. A segmental analysis was available in all of these 135 scans. The results are summarized in table 3. In 111 patients pulmonary embolism was found in segmental or larger vessels: in 104 patients CT confirmed the presence of pulmonary embolism, in seven patients no pulmonary embolism was considered to be present. In 24 patients we found evidence of pulmonary embolism in subsegmental vessels. In 13 patients the CT-scan was considered positive for pulmonary embolism, the other 11 again were considered normal.

We also compared the result of the 18 false negative CT-scans (seven segmental and 11 subsegmental) with the initial result of ventilation-perfusion scintigraphy. Fifteen CT-scans were from patients with non-high ventilation-perfusion scintigraphy results. Only three were from patients with an initial high-probability result.

Table 3. Segmental analysis of the results of the spiral CT-scan compared to the final diagnosis.

Result	CT Normal	CT pulm embolism	Total
>Segmental	7	104	111
Subsegmental	10	12	22
Normal	107	12	119
Total	124	128	252

Discussion

The role of spiral CT in the diagnostic algorithm for pulmonary embolism is still controversial. It is likely that various strategies, depending on population characteristics, local expertise, and availability of diagnostic tests are appropriate. Our detailed description of the population and registration of patients who were excluded allows comparison with various other studies and indicates that our population is representative of a general unselected population. The prevalence of pulmonary embolism in this study-group (26%) was similar to that found in the PIOPED group (28%) and other studies[6] using conventional angiography as gold standard. The ratio of out vs in-patients was somewhat higher than reported before.[1,3] Also, we did not find any differences with regard to co-morbidity, risk factors for pulmonary embolism and demographic characteristics between patients who participated in the study and a random sample of consecutive patients that were excluded.

We evaluated the performance of spiral CT in a routine clinical situation, following an abnormal ventilation-perfusion scan result. Patients were, without selection, recruited in two academic and four general hospitals. The initial test was perfusion scintigraphy. Perfusion scintigraphy is a readily available robust uncontroversial technique with a high negative predictive value (87%) [11] that can be used to safely reduce considerably the volume of patients needing additional tests. In our population 47% of patients had a normal perfusion scintigram and did not require further testing for pulmonary embolism. The patients, who had perfusion abnormalities on the scintigram, were analyzed according to our predefined protocol using standard equipment and local expertise available at the time of analysis. The radiologists knew that scintigrams were not normal, but had no information regarding the category of scintigraphic findings.

The sensitivity (87%) and specificity (91%) of spiral CT in our population relative to our gold standard is lower than that of many reports from specialized centers.[7,13] The sensitivity and specificity are, on the other hand, higher than some of the more skeptical reports.[9,10] Our sensitivity is similar to the threshold of a 85% sensitivity required to avoid higher mortality than conventional strategies not using CT . We think that the performance of spiral CT in our routine clinical setting is realistic. We consider our data as baseline, in view of the current technical multi detector ring CT revolution that is generally expected to result in better performance[14] although more prospective studies are clearly needed. Increased technical quality will probably even decrease the problem of not detected subsegmental emboli, which is the main cause of false negative CT results. In 24 of our 135 patients with pulmonary emboli, a subsegmental artery was the largest artery involved.

Eleven of these 24 patients (46%) had a false negative CT, while only seven out of 104 patients (7%) with involvement of at least a segmental artery had a false negative CT. When considering only the results of segmental pulmonary embolism our sensitivity increased to 94%. The clinical relevance of isolated subsegmental embolism, however, remains unclear. Some authors already mentioned that the detection of subsegmental PE in otherwise healthy patients might be less important.[15]

The accuracy of our algorithm can also be improved by implementing stricter quality control methods (CT scanning technique, educating radiologists)[16,17] and by adding additional tests. However, the design of a new algorithm is beyond the scope of our current study.

In view of our routine clinical setting we think that the performance of our algorithm with CT as a second line test is acceptable if we look at the entire population.

We were, however, disappointed with the added value of CT relative to the prevalence in the two subpopulations. The prevalence of pulmonary emboli in the group with high probability scintigrams was 90%. CT test results are accurate, but the gain in terms of sensitivity (97%), specificity (100%) and PPV (100%) can only be small. The NPV of 78% on the other hand is low. With CT we were able to identify eleven (10%) patients who did not have pulmonary embolism at the cost of three (3%) patients that had a true positive ventilation-perfusion scintigraphy, but a false negative CT. CT test results in this subpopulation are accurate with the exception of a relative high fraction of false negative results. We could not determine the potential impact of a known high probability scintigraphic test result on the accuracy of CT.[5,8]

The yield of CT in patients with a non-high probability scintigrams is more substantial in view of the prevalence of 25%, but test results of CT are poor in this group. Only the relatively high fraction of true negatives result in somewhat better specificity (89%) and NPV (87%). Many false negatives result unfortunately in unacceptable low sensitivity (61%) and PPV (65%).

Apart from studies determining sensitivities and specificities of spiral CT[7,8], several groups reported on the performance of CT in various specific clinical settings.[18,19] Ferreti at all reported a false negative rate for CT of 5.4% in a population of 164 with intermediate ventilation-perfusion scintigraphy in combination with normal duplex ultra sound of the legs.[3] Our 7.1% rate of false negatives for the entire population and 9.7% for the non-high probability scintigraphy group fit within their 95% confidence interval (1.3%-9.7%). There are obviously various differences, such as the use of ultrasound, and the use of clinical follow up as gold standard, that prohibit comparison of results in detail.

Our study design is similar to that used in the single center prospective study performed by van Rossum et al.[8] We believe our lower sensitivity and specificity relative to those reported by them (sensitivity 95% specificity 97%) show that the reported high results cannot be maintained in a routine clinical environment. Various gold standards have been used by previous researchers. We believe that our gold standard is acceptable in view of the power of concordance of two positive tests (spiral CT and high probability ventilation-perfusion scintigraphy), both with high positive predictive values[7,8], as well as the high predictive values of pulmonary angiography. Disadvantages of our definition of gold standard include the interobserver variability of pulmonary angiography (reaching 34%[20]), and the dependence of tests and gold standards upon each other. All current imaging techniques directly, or indirectly visualize the effects of occluded or non-occluded vessels. The quality of our gold standard, however, is similar to that used by others and because of practical and ethical reasons difficult to improve. The potential impact of angiographic interobserver variability on gold standard and subsequently on study results can be demonstrated by eliminating subsegmental emboli. When considering only the results of segmental pulmonary embolism our sensitivity increased to 94%.

This study shows that spiral CT in patients without a normal perfusion scintigram is an acceptable test. The sensitivity of 87% is within the previously calculated range that does not increase mortality.[4] There remain, however, problems with too many false negatives. We therefore conclude that in a routine clinical setting current CT technology has limited value as a second diagnostic test because of low added value in patients with a high probability lungscan and low sensitivity in patients with non-high probability lungscan result.

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