

Combined use of ^{99m}Tc -labelled macroaggregates of albumin and ^{75}Se -selenomethionine in the diagnosis of lung cancer

MAIR CRITCHLEY, H. J. TESTA,
and T. B. STRETTON

Departments of Medical Physics and Medicine, Manchester Royal Infirmary

Critchley, M., Testa, H. J., and Stretton, T. B. (1974). *Thorax*, 29, 421–424. **Combined use of ^{99m}Tc -labelled macroaggregates of albumin and ^{75}Se -selenomethionine in the diagnosis of lung cancer.** A two-stage isotope technique has been used in 30 patients with radiographic evidence of circumscribed pulmonary lesions in an attempt to establish the nature of the underlying pathological process. The test was carried out as a 'blind' procedure without knowledge of the findings of investigations other than the plain chest radiograph. An initial scan was performed with ^{99m}Tc -labelled macroaggregated albumin. The view showing the lesion most clearly was selected and a second scan was obtained after an intravenous injection of ^{75}Se -selenomethionine. Scans were interpreted by comparison of the 'cold area' on the technetium scan with the corresponding area on the selenomethionine scan. Accumulation of ^{75}Se -selenomethionine at the site corresponding to the lesion is described as a positive result and absence of accumulation as negative. The findings suggest that there is selective uptake of ^{75}Se -selenomethionine by primary bronchogenic carcinoma; in the few patients with secondary carcinomas and non-malignant disease investigated so far, the lesion has failed to concentrate ^{75}Se -selenomethionine.

The radiographic appearance of a pulmonary opacity does not always indicate the nature of the underlying pathological process. Radioactive isotopes have the advantage that they may be injected intravenously and detected externally, with very little disturbance to the patient. They may be attached to molecules or aggregates and used to display areas of poor perfusion, thereby localizing the site of a lesion. Or they may be incorporated in substances which are concentrated within a lesion so that the site of disease appears on a scan as a 'hot area'. The diagnostic value of the selective uptake of radioactive substances by tumours has already been established in respect of other tissues of the body.

Isotopes previously used as potential diagnostic agents in lung cancer have included ^{197}Au and ^{203}Hg -labelled chlormerodrin (Sodee, 1964; Sodee and Clifton, 1964; Gotta, Degrossi, and Pecorini, 1970). Chlormerodrin concentrated 15–20% more in squamous-cell carcinoma than in normal tissue (Mallard, 1971), but there was

an appreciable uptake by vascular adenomas and by some inflammatory lesions (Sodee, 1964; Gotta *et al.*, 1970). ^{75}Se -selenite has been recommended as an alternative agent (Cavalieri, Scott, and Sairenji, 1966) and in three patients with primary lung tumours the lesions were easily localized, whereas in two patients with pneumonia and a lung abscess there was no accumulation of the isotope within the lesion. ^{75}Se -selenomethionine has been used in a series of five patients with primary bronchogenic carcinoma, the lesion being successfully detected in four patients (Jovanović and Bouckaert, 1969); the use of this agent in other pulmonary conditions was not reported. Subsequently, ^{67}Ga -citrate was introduced and appeared to have advantages with its short half life, suitable gamma ray emission, and small radiation dose, but while there was no difficulty in distinguishing malignant from benign lung tumours, it proved difficult to differentiate neoplastic from inflammatory lesions (Higasi *et al.*, 1972).

The purpose of this paper is to present results obtained with a dual isotope technique utilizing ^{99m}Tc -technetium-labelled macroaggregated albumin (^{99m}Tc -MAA) followed by ^{75}Se -selenomethionine in an attempt to differentiate primary lung cancer from other pathological conditions.

MATERIALS AND METHOD

During the course of investigations to establish the nature of radiographically demonstrated opacities in the lungs, 30 adult patients received 25 $\mu\text{Ci}/\text{kg}$ of ^{99m}Tc -MAA by intravenous injection. After five minutes, anteroposterior, posteroanterior, right lateral, and left lateral views of the lungs were recorded sequentially using a gamma camera (Nuclear Enterprises MARK III). The pulmonary lesion appeared as a 'cold area'. The view showing this area most clearly was selected and, with the patient in the same position, a rectilinear scan was performed using a Picker Magna V Scanner. The anatomical landmarks of the thorax were carefully marked on this scan for purposes of localization. Each patient then received 3 $\mu\text{Ci}/\text{kg}$ of ^{75}Se -selenomethionine intravenously and one hour later a further rectilinear scan was performed using the same position and the same landmarks as previously. In three patients the lungs were also scanned 4 hours, 24 hours, and 48 hours after the initial injection but there was no improvement in the quality of these scans compared with those performed one hour after injection with ^{75}Se -selenomethionine.

The records were interpreted by comparing the 'cold area' seen on the technetium scan with the corresponding area on the selenomethionine scan. Accumulation of ^{75}Se -selenomethionine in a lesion was described as a positive and no accumulation as a negative result. The findings from bronchoscopy, tomography, and sputum cytology were not available to the observers who interpreted the scans.

RESULTS

The results obtained in 30 patients are summarized in the Table. All the patients had radiographic evidence of a localized lesion. The largest opacity measured 7×5 cm in the frontal plane and the smallest was 2 cm in diameter. Examples of ^{99m}Tc -MAA scans and ^{75}Se -selenomethionine scans are given in Figures 1 and 2.

Eighteen patients had positive selenomethionine scans. Fifteen had confirmatory histopathological evidence of primary bronchogenic carcinoma; nine patients had squamous-cell carcinoma, two adenocarcinoma, one oat-cell carcinoma, and three were undifferentiated. In two patients with positive scans we were unable to obtain histological proof of the diagnosis. Both patients died but necropsy was not performed. In each in-

TABLE
SUMMARY OF FINDINGS IN 30 PATIENTS STUDIED BY RECTILINEAR SCANNING AFTER INTRAVENOUS INJECTION OF ^{75}Se -SELENOMETHIONINE

Diagnosis	^{75}Se -Selenomethionine Scan	
	Positive	Negative
Primary cancer	15	1
Secondary cancer	0	3
Non-malignant lesion	2	7
Unconfirmed diagnosis	1	1
Thymoma	1	0

stance the natural history of the illness was consistent with the clinical diagnosis of a primary carcinoma of the lung. One other patient had an equivocal selenomethionine scan which was finally reported as positive; at operation the tumour was found to be a thymoma.

Twelve patients had negative selenomethionine scans. Of these, seven had clinically benign lesions; one patient had a hamartoma, two had tuberculosis, two had empyemas, one had bronchiectasis, and one had pneumonia. Three of the 12 had secondary carcinomas. One had a slowly growing undifferentiated tumour composed of spindle cells, and the site of the primary lesion was unknown. This patient had already received cytotoxic therapy at the time of scanning and was able and well enough to continue his work as a university professor. The other two patients had primary tumours of the large bowel with metastases in the lungs.

There was one false negative result. At operation this patient's squamous-cell carcinoma measured less than 2 cm in diameter. In the twelfth patient with a negative scan the precise nature of the pulmonary lesion remains unknown.

DISCUSSION

The value of colloids labelled with ^{99m}Tc and of ^{75}Se -selenomethionine in the diagnosis of primary hepatoma (Eddleston *et al.*, 1971) suggested to us the possible value of a dual isotope approach to the diagnosis of lung cancer.

Although lung scanning after the injection of ^{99m}Tc -MAA may demonstrate a tumour clearly the observation is non-specific in that any condition resulting in decreased perfusion will result in a 'cold area'. Nevertheless this preliminary procedure has proved to be important in choosing the best topographical projection for the subsequent selenomethionine scan.

^{75}Se -selenomethionine has the biological and metabolic properties of the natural amino-acid methionine and, when injected intravenously, is

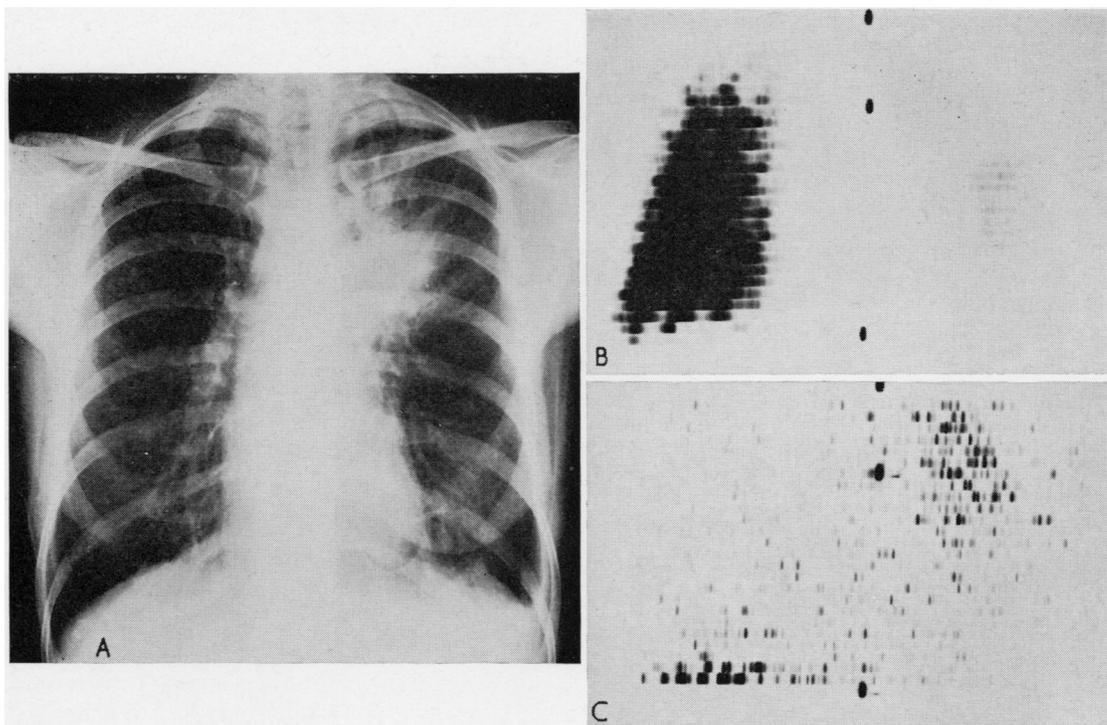


FIG. 1. Chest radiograph (A), ^{99m}Tc -MAA perfusion scan (B), and ^{75}Se -selenomethionine scan (C) in a patient with primary carcinoma of the left lung. The ^{99m}Tc -MAA scan shows impaired perfusion on the left side. The selenomethionine scan is positive, with increased uptake at the site of the lesion; the uptake of isotope at the right base is due to normal hepatic activity.

rapidly incorporated into newly synthesized protein (Awwad, Adelstein, Potchen, and Dealy, 1967). This is presumed to be the mechanism for the increased uptake of ^{75}Se -selenomethionine by primary bronchogenic carcinomas as demonstrated in the present study. Whether the amino acid passes to the tumour by the pulmonary or bronchial circulation is unknown. However, the apparent reduction in pulmonary arterial perfusion at and beyond the site of the lesion, as shown by ^{99m}Tc -MAA scanning, suggests that the ^{75}Se -selenomethionine may enter the tumour tissue via the bronchial circulation.

The seven patients with benign lesions and three with secondary carcinomas had negative selenomethionine scans. The poor uptake of ^{75}Se -selenomethionine by metastatic carcinoma is surprising and requires confirmation; if confirmed, it could presumably be due to a difference in metabolic rate as compared with primary carcinoma, or to differences in the blood supply. In this context it may be relevant that the

patient with an undifferentiated metastatic spindle-cell tumour and a negative result had received cytotoxic therapy before the lung scan was performed. However, it is evident that more observations are needed in patients with metastatic lung carcinoma and in those with benign lesions.

The two-stage isotope technique described is straightforward and atraumatic, and an investigation can be completed two and a half hours after the first intravenous injection. Although it was not possible to identify a lesion smaller than 2 cm in diameter, owing to the limits imposed by the degree of resolution of the scanning system and the physical characteristics of the isotope used, the results obtained in the first 30 patients indicate that the present approach has a potentially useful place in the diagnosis of lung cancer. It does not replace standard investigative procedures, but a particularly useful application of the method may be in the investigation of the asymptomatic patient who is found to have a 'coin' lesion on his chest radiograph.

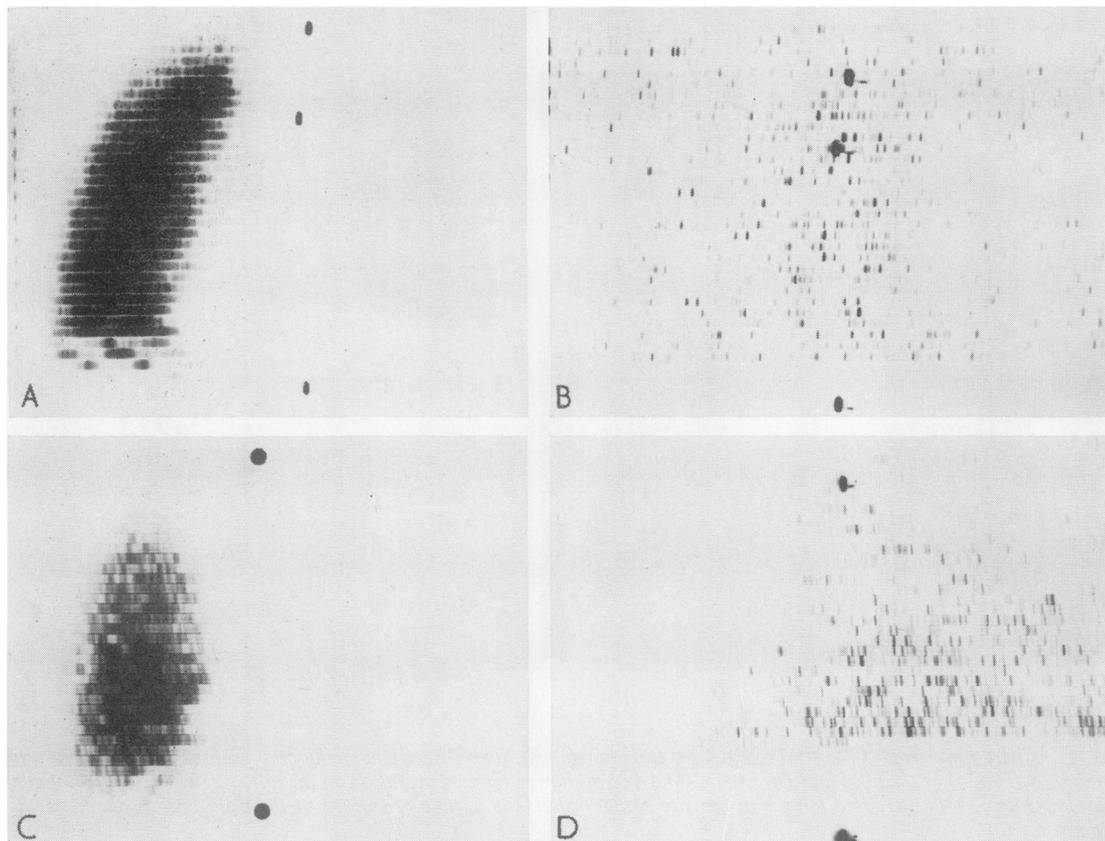


FIG. 2. ^{99m}Tc -MAA perfusion scan (A) and ^{75}Se -selenomethionine scan (B) in a patient with a left-sided empyema. Equivalent scans (C and D) in a patient with primary carcinoma of the left lower lobe. Both patients have impaired perfusion of the left lung. The ^{75}Se -selenomethionine scan (D) is positive in the patient with carcinoma but negative (B) in the patient with non-malignant disease.

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Requests for reprints to: Dr. T. B. Stretton, Manchester Royal Infirmary, Oxford Road, Manchester M13 3WL.