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Diagnostic value of ^{67}Ga-scintigraphy in chest surgery

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Fogh, J., Bertelsen, Sv., and Schmidt, A. (1974). *Thorax*, **29**, 26–31. **Diagnostic value of ^{67}Ga-scintigraphy in chest surgery.** Gallium-67 (^{67}Ga) has a high affinity for malignant tissue. The diagnostic value of ^{67}Ga-scintigraphy for differentiating between malignant and benign disease was studied in 109 patients with lesions of the chest discovered by radiological examination. Histological diagnoses were obtained in all the patients after the study was concluded.

All the patients with sarcoidosis showed intense uptake of ^{67}Ga in their lesions. The diagnostic specificity for the rest of the material was 94%, the diagnostic sensitivity 76%, and the prevalence 76%.

^{67}Ga-scintigraphy appears to be a valuable addition to thoracic diagnostic methods.

The problem whether a process discovered in the lungs, mediastinum or pleura by radiological examination should be considered as potentially malignant or benign is often presented to the chest surgeon.

In the case of mediastinal lesions this problem is fairly easily solved. Hilar lymph node enlargements often have a characteristic radiological appearance, and a histological diagnosis may usually be obtained from a biopsy of lymph nodes in the neck or by mediastinoscopy. In other types of mediastinal lesions, exploratory surgery will usually be carried out owing to the risk of compression and the high incidence of malignancy. Hence a histological diagnosis of mediastinal lesions will generally be obtained.

Infiltrative lesions in the lungs, on the other hand, more often present diagnostic problems. Conventional methods frequently fail to reveal the nature of such lesions, and an exploratory thoracotomy may be a major operation involving severe risk, especially to patients with impaired pulmonary function. However, it may often be necessary to carry out an exploratory thoracotomy which will eventually reveal the presence of a benign lesion. Obviously any additional examination which does not expose the patient to risk and which may help to disclose whether a pulmonary infiltrate discovered by radiographic examination is malignant or benign will be of great value.

Several authors have confirmed the observation by Edwards and Hayes (1969, 1970) that the radionuclide gallium-67 (^{67}Ga) when injected intravenously in carrier-free solution has a high and apparently specific affinity for malignant tissue. Hence it has been possible by means of ^{67}Ga-scintigraphy to visualize malignant tumours in various organs (Higasi *et al.*, 1969; Higasi *et al.*, 1970; Hör *et al.*, 1970; Vaidya, Chaudhri, Morrison, and Whait, 1970; Winchell *et al.*, 1970; Grebe, Steckenmesser, and Römer, 1971; Riccabona, Scholz, and Bauer, 1971; Fogh and Edeling, 1972; Langhammer *et al.*, 1972).

The purpose of the present work has been to estimate the diagnostic value of ^{67}Ga-scintigraphy for differentiating between malignant and benign tumours of the chest.

PATIENTS

One hundred and nine patients (73 men and 36 women between 22 and 71 years of age) with radiologically discovered lesions of the lungs, pleura, mediastinum, or chest wall were examined by ^{67}Ga-scintigraphy. The final diagnoses were not known at the time of examination.

Histological diagnoses were obtained in 102 patients at surgery and in seven cases at necropsy.

METHODS

Carrier-free ^{67}Ga (as gallium citrate), 2·3–2·8 mCi, was given intravenously in sterile isotonic solution[1].

[1]Philips-Duphar, Holland, DRN 3103

Disposable plastic syringes were used as carrier-free ^{67}Ga tends to adhere to glass.

Scintigraphy was carried out 48 or 72 hours after injection. The ratio between ^{67}Ga-concentration in the tumour and surrounding tissues (target/non-target ratio) is maximal after a couple of days.

Gallium is excreted with the faeces. In order to reduce 'background counts' from the intestines a laxative was given (Perilax^{R}, 2 tablets daily) in the interval between ^{67}Ga-administration and scintigraphy.

The patients were examined by means of a rectilinear scanner (Picker Nuclear Magna Scanner 500) equipped with a 5×2 in NaI-crystal and a 31-hole focussing collimator (No. 2112, focal distance 3 in).

The spectrometer was set to accept photons between 150 and 330 KeV. The results were stored on magnetic tape (Nukab Memonukleograph) and a series of reproductions with different subtraction levels was made for each of the studies.

Scintigraphy was carried out in at least two projections and lasted approximately one hour. In a number of cases, the scintigraphy was performed on outpatients awaiting admission to hospital.

^{67}Ga has a physical half-life of 78 hours and emits gamma rays with energies of 93, 184, 296, and 388 KeV. The universal radiation dose to a patient from 2·5 mCi ^{67}Ga has been calculated to less than 1 rad, and the dose to critical organs (that is, liver, kidneys, testes, and bone) to less than 2 rads (Popham, Taylor, and Trott, 1970; Vaidya *et al.*, 1970).

RESULTS

LUNG LESIONS At operation or/and necropsy of 65 patients with lung lesions, 51 were found to have malignant tumours. Forty-four patients suffered from primary lung cancers and seven patients from pulmonary metastases. One patient with primary lung cancer had metastases to the chest wall. The results of ^{67}Ga-scintigraphy of these patients are given in Table I. Nearly all the primary lung cancers (43 of 44) were visualized prior to surgery by ^{67}Ga-scintigraphy (=^{67}Ga-positive). On the other hand, half of the metastatic processes (4 of 7) were not disclosed by scintigraphy (=^{67}Ga-negative). The diameter on the chest film of all four ^{67}Ga-negative malignant processes was less than 20 mm. All ^{67}Ga-positive infiltrates were larger than 20 mm.

TABLE I
MALIGNANT LESIONS IN THE LUNG

	No.	^{67}Ga+[1]	^{67}Ga−
Primary, malignant lesions ..	44	43	1
Secondary, malignant lesions ..	7	4	3

[1] ^{67}Ga+ = accumulation of ^{67}Ga in the pathological process.

TABLE II
BENIGN LESIONS IN THE LUNG

	No.	^{67}Ga+	^{67}Ga−
Interstitial pneumonias	9	4[1]	5
Bronchial adenoma	1		1
Lung abscesses	2		2
Tuberculosis	1		1
Aspergilloma	1	1	

[1] One patient developed cancer of the lung 14 months later.

In 14 patients surgery revealed benign infiltrates. The histological diagnoses and the results of ^{67}Ga-scintigraphy in these cases are given in Table II. It is remarkable that four of nine cases of interstitial pneumonia were ^{67}Ga-positive. Control examination 14 months after surgery disclosed that one of the four patients who had shown ^{67}Ga-uptake in interstitial pneumonia had developed a malignant tumour at the site of the original infiltrate. Most, if not all, of the infiltrate had been removed for microscopic studies at the first operation on this patient. Before the second operation, which revealed an extensive anaplastic tumour penetrating into the mediastinum, ^{67}Ga-scintigraphy once more showed accumulation at the site of the lesion.

MEDIASTINAL LESIONS Twenty-eight patients had mediastinal lesions. The results of ^{67}Ga-scintigraphy and the histological diagnoses are listed in Table III. All patients with sarcoidosis displayed massive accumulation of ^{67}Ga in the nodes. The same was seen in patients with malignant lymphogranulomatosis. However, the ^{67}Ga-scintigram appeared normal in one patient with Hodgkin's disease who was being treated with vinblastine (Velbe) at the time of examination. One of seven thymomas was ^{67}Ga-negative. This was a well-defined, stalked thymoma of lymphocytic type. The other six thymomas showed significant accumulation of ^{67}Ga at scintigraphy. Four of these were encapsulated, and two had penetrated their capsules and infiltrated the surrounding tissue.

TABLE III
LESIONS IN THE MEDIASTINUM

	No.	^{67}Ga+	^{67}Ga−
Lymphogranulomatosis (malignant)	7	6	1[1]
Sarcoidosis	7	7	
Thymoma	6	5	1[2]
Lymph node metastasis	1	1	
Reticulum cell sarcoma	3	3	
Benign (goitre, lymph nodes, cysts)	4		4

[1] Patient was undergoing prolonged chemotherapy.
[2] Thymoma of lymphocytic type.

PLEURAL AND CHEST WALL LESIONS Sixteen patients had lesions in the pleura or chest wall. As shown in Table IV, all histologically benign processes in the pleura were ^{67}Ga-negative while the malignant were positive.

TABLE IV
LESIONS IN PLEURA OR CHEST WALL

	No.	^{67}Ga+	^{67}Ga−
Pleural lesions			
Malignant	5	5	
Benign	5		5
Chest-wall lesions			
Malignant	5	5	
Benign	1		1

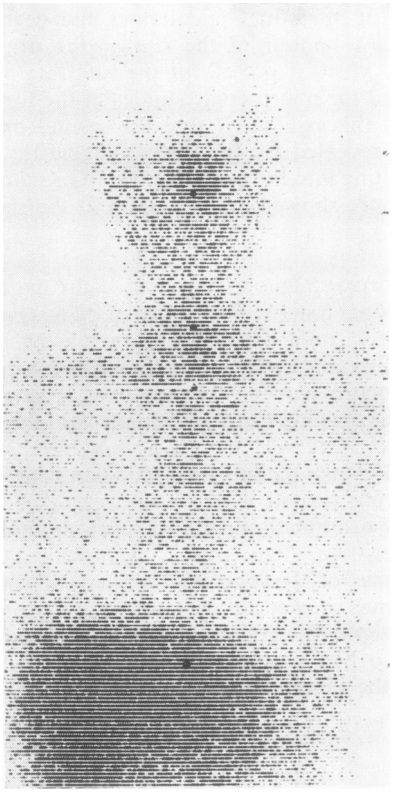


FIG. 1. *Normal ^{67}Ga-scintigram of the chest (anteroposterior view). Uptake in liver and breastbone are normal findings.*

DISCUSSION

Conventional scintigraphic methods have so far been based mainly on accumulation of a specific radionuclide in normal tissue of a single organ. Tumours or other processes have therefore generally been pictured as areas devoid of activity ('holes' in the scintigram). The reports by Edwards and Hayes in 1969 and 1970 showed that ^{67}Ga has a high and apparently rather specific affinity for malignant tissue in a number of different organs. This opened new aspects in tumour diagnosis. A study of patients with lesions in the chest is especially useful for an evaluation of the validity of ^{67}Ga-scintigraphy because relatively little scattered radiation from ^{67}Ga-accumulating organs, such as intestines, liver, or bones, will disturb the results (see Fig. 1 which shows normal distribution of ^{67}Ga).

Very few of the reports on ^{67}Ga-scintigraphy published so far have dealt with sufficiently large numbers of patients to allow an evaluation of the diagnostic value of this method. Hör *et al.* (1970) found ^{67}Ga-uptake in 103 (67%) of 153 histologically verified malignant tumours and in 9 (43%) of 27 benign tumours. Grebe *et al.* (1971) found gallium uptake in 50 (64%) of 78 malignant tumours and in one (9%) of 11 benign lesions. Riccabona *et al.* (1971) found abnormal ^{67}Ga-uptake in 54 (95%) of 57 cases of malignant lesions and in one (8%) of 13 patients with non-malignant tumours. The two latter reports, however, do not clearly define how the final diagnoses were obtained. Langhammer *et al.* (1972) have examined 246 patients with ^{67}Ga-scintigraphy. Seventy-seven of these patients had diseases of the chest. The authors found a diagnostic specificity of 92%, a diagnostic sensitivity of 65%, and a prevalence of malignant diseases of 89%[1], which is in accordance with our results.

The conclusion of our studies is that ^{67}Ga has a high affinity for malignant tumour tissue so that most of these tumours may be visualized by ^{67}Ga-scintigraphy. However, we did find, as others did before, that certain benign processes also accumulate ^{67}Ga. Thus, shortly after our investigations had started it became evident that massive accumulation of ^{67}Ga is regularly observed in the lymph nodes of Boeck's sarcoidosis.

Among 31 patients with benign lesions in the chest, an abnormal ^{67}Ga-scintigram was observed in 12 (39%). If Boeck's sarcoidosis, which is generally diagnosed quite easily, is omitted from the material, 24 patients with benign lesions remain, and among these, five showed abnormal ^{67}Ga-uptake (21%). Similar observations have been made

[1]Diagnostic specificity=percentage for whom a positive reaction is true
Diagnostic sensitivity=percentage for whom a negative reaction is true
Prevalence=percentage of malignant disease in the tested population

by other authors (Dige-Petersen, Heckscher, and Hertz, 1972; Higasi *et al.*, 1969, 1970; Hör *et al.*, 1970; Riccabona *et al.*, 1971). If the patients with sarcoidosis are omitted, the diagnostic sensitivity, specificity, and prevalence of the method can be calculated to 76%, 94%, and 76% respectively (as shown in Table V). Thus, if an abnormal ^{67}Ga-accumulation is observed in the chest, there is a 94% probability that the process is malignant. The diagnostic accuracy in cases of malignancy is accordingly very good.

TABLE V

TOTAL MATERIAL
(PATIENTS WITH SARCOIDOSIS NOT INCLUDED)

	No.	^{67}Ga+	^{67}Ga−
Malignant	78	72	6
Benign	24	5	19
Total	102	77	25

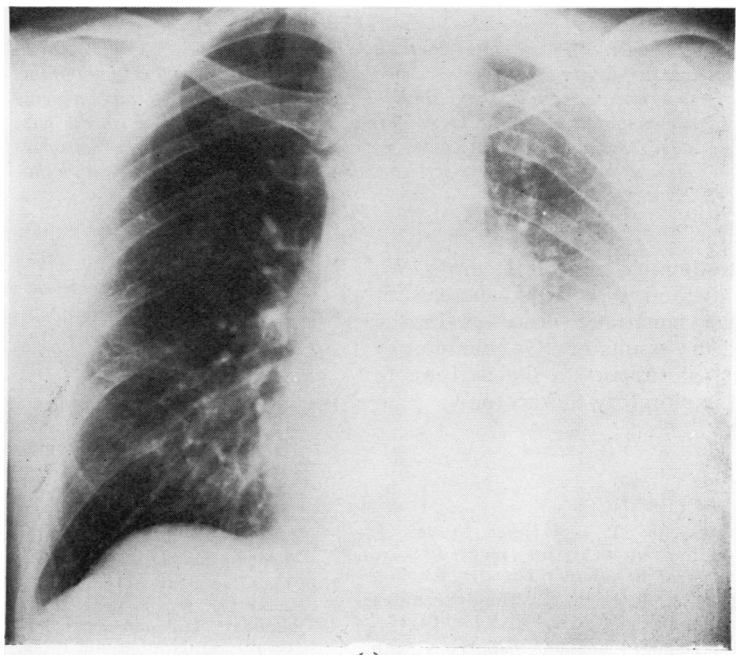
Diagnostic specificity: 72/77 ~ 94%
Diagnostic sensitivity: 19/25 ~ 76%
Diagnostic prevalence: 78/102 ~ 76%

The high prevalence for malignant diseases in the present study impairs the statistical evaluation of the method as a means of differentiating between benign and malignant processes of the chest.

As stated, four malignant lung tumours in our series did not accumulate ^{67}Ga sufficiently to be seen by scintigraphy. They were one primary tumour and three metastatic processes, all shown to be of a diameter less than 18-29 mm on chest radiography. The failure to visualize these four lesions may be due partly to the limited resolution of the detector used for scintigraphy, but the problem is probably more complicated, as ^{67}Ga-uptake in tumour cells presumably depends on a number of factors such as cell metabolism or inflammatory reactions. Hence it has been observed that necrotic areas within a tumour do not accumulate ^{67}Ga and that malignant tumours which primarily accumulated ^{67}Ga lose this ability following deep *x*-ray therapy or chemotherapy (Edwards and Hayes, 1970; Fogh and Edeling, 1972).

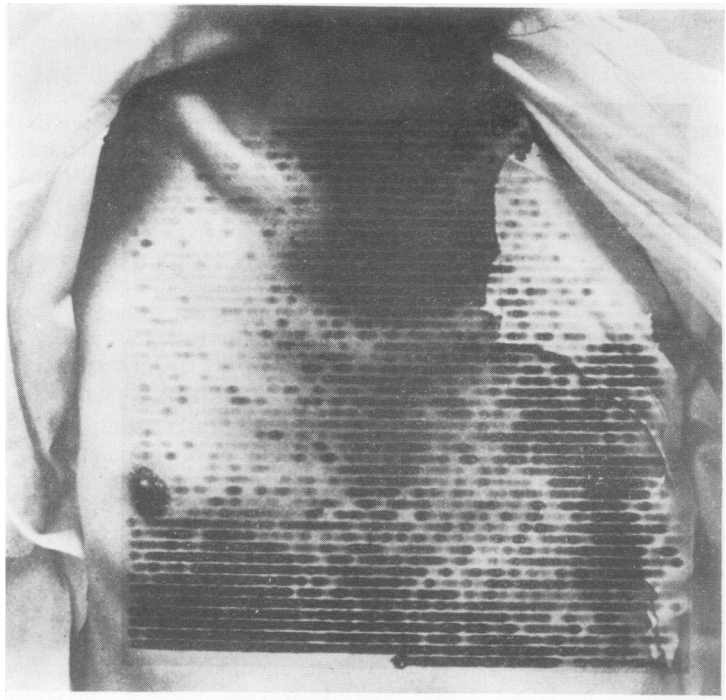
In the present study of 109 patients with histologically verified diagnoses, ^{67}Ga-scintigraphy of malignant conditions has proved to have a high diagnostic accuracy. In cases of benign lesions, the method has been less specific and thus has not fulfilled the expectations of obtaining a means of differentiating between malignant and benign processes. However, the present material is not large enough to allow an evaluation of the validity of the method concerning various benign processes. It will be necessary to collect a larger series of benign lesions.

It seems evident that ^{67}Ga-scintigraphy is a valu-



(*a*)

FIG. 2. *Legend overleaf.*



(b)

FIG. 2. *A 57-year-old man presented with a left-sided pleural effusion. (a) A chest radiograph showed some thickening of the left pleura but the film was obscured by pleural effusion despite aspiration of 700 ml of liquid. The exudate contained no tumour cells. Bronchoscopy and mediastinoscopy were normal. (b) ^{67}Ga scintigraphy (scintigram superimposed on a photograph of the patient) revealed pathological accumulation along the lower part of the lateral chest wall on the left side. The patient died suddenly before scheduled surgery. Necropsy showed thrombosis of the left coronary artery and mesothelioma of the left pleura.*

able supplement to thoracic surgical diagnosis. We have found the method especially valuable for revealing unknown metastatic processes in the chest (Fig. 2) and the results of ^{67}Ga-scintigraphy have quite often lent support to the decision to perform or avoid exploratory thoracotomy.

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