⁵⁷Co-bleomycin and ⁶⁷Ga-citrate in detecting and staging lung cancer

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ABSTRACT In the investigation of suspected lung cancer bleomycin labelled with cobalt-57 and gallium-67 labelled with citrate are currently used to detect the primary tumour and to establish the presence of metastases in the lung hilum and mediastinum. A comparative study of these radiopharmaceuticals was performed in 63 patients with proved lung cancer. ⁵⁷Co-bleomycin showed the primary tumour in 58 patients (92%) and ⁶⁷Ga-citrate in 34 (54%) ($p < 0.01$). The average tumour-to-lung ratio was 3.4 with ⁵⁷Co-bleomycin and 1.5 with ⁶⁷Ga-citrate. Proved metastases in the hilum or the mediastinum were visualised with ⁵⁷Co-bleomycin scintigraphy in 16 out of 18 patients (89%) and with ⁶⁷Ga-citrate scintigraphy in only eight (45%) ($p < 0.01$). These results indicate that ⁵⁷Co-bleomycin scintigraphy is more suitable for detecting and staging lung cancer than is ⁶⁷Ga-citrate. ⁵⁷Co-bleomycin is valuable in the detection of peripheral lesions, in which a pathological diagnosis is difficult to achieve, since a positive scintigram indicates malignancy. When ⁵⁷Co-bleomycin scintigraphy suggests hilar or mediastinal metastases mediastinoscopy should be carried out; but when no metastases are apparent it is reasonable to proceed directly to thoracotomy without mediastinoscopy.

In patients with a peripheral lesion on the chest radiograph a diagnosis is often difficult to establish. Cytological examination of the sputum is not always conclusive.¹ Furthermore, it is frequently not possible to obtain a biopsy specimen to provide a histological diagnosis.² When the diagnosis of bronchial carcinoma is established, staging is of the utmost importance. Patients with cancers other than small-cell are traditionally considered suitable for surgical removal of the affected lobe or lung only in the absence of hilar and mediastinal metastases,³ although lately a more aggressive approach has sometimes been advocated.^{4,5} The mediastinum can be evaluated by mediastinoscopy; but because of the morbidity it causes this is not considered a minor surgical procedure, and only part of the mediastinum can be explored this way. A non-invasive method that reduces the need for mediastinoscopy would be highly desirable.⁶ Scintigraphy using gallium-67-citrate and bleomycin labelled with cobalt-57 has been reported to be useful in establishing the

malignant nature of a lesion seen on the chest radiograph.^{7,8} Furthermore, both radiopharmaceuticals are in use for the detection of lymph-node metastases in the hilum and mediastinum.^{9,10}

It has been suggested that ⁵⁷Co-bleomycin is more suitable than ⁶⁷Ga-citrate for the detection of primary lung cancer,¹¹⁻¹³ but no comparative study of the detection of metastases in the hilum or mediastinum has been published to our knowledge. In this paper we present evidence that ⁵⁷Co-bleomycin is superior to ⁶⁷Ga-citrate for both purposes.

Methods

The criteria for selection of patients included (a) the need to investigate a peripheral lesion of unknown origin seen on the chest radiograph and (b) the need to detect possible metastases in the hilum and mediastinum. Most patients were referred because of a small symptomless lesion on a chest radiograph from a mass screening programme.

Scintigraphy was performed in 93 patients. Informed consent was obtained. Of these patients, 23 were excluded because of lack of histological confirmation. Of the remaining 70 patients, 63 were

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men and seven were women. The age range was 44–83 years (mean 63 years). In 63 patients a diagnosis of malignant lung tumour was made. There were 41 patients with squamous-cell carcinoma, 11 with large-cell anaplastic carcinoma, seven with adenocarcinoma, two with small-cell anaplastic carcinoma, and one with basal-cell carcinoma. A patient with carcinoid tumour was also included. In eight patients a benign lesion was found at operation or after careful follow-up; one of these had both a benign and a malignant lesion. In all patients with a malignant tumour the hilum and the mediastinum were evaluated by a surgical procedure or at necropsy within 10 weeks of scintigraphy.

⁵⁷Co-bleomycin was prepared as follows. Into 3 mCi (111 MBq) ⁵⁷Co-chloride in 1 ml HCl (0.1 mol/l) was stirred 7.5 mg bleomycin or the bleomycin-A2 fraction (supplied by Lundbeck) in 1.0 ml 1.8% NaCl solution and subsequently 2 ml 0.1 mol/l Na-acetate (pH 5.6). The pH of the product was 4–6. Filtration (0.22 µm pore size) was performed under aseptic conditions. The radiopharmaceutical was injected only when the amount of free ⁵⁷Co²⁺ was less than 3%, measured with instant thin-layer chromatography.

All patients were first injected intravenously with 1 mCi (37 MBq) ⁵⁷Co-bleomycin. Scintiphotos were made 24 hours later. Subsequently 3 mCi (111 MBq) ⁶⁷Ga-citrate (obtained from New England Nuclear and Byk Mallinckrodt CIL BV) was injected intravenously and usually 48 hours later scintiphotos were obtained.

Scintigraphy was performed with a large-field gamma camera. During the ⁵⁷Co-scintigraphy a low-energy, parallel-hole collimator was used. A preset count of 50 k and a preset time of 10 minutes were used. During the ⁶⁷Ga-scintigraphy a medium-energy parallel-hole collimator was used. The 296-keV and 184-keV photopeaks were used. A preset count of 400 k and a preset time of 10 minutes were selected. Anterior and posterior views of the thorax were obtained and other views if necessary.

All scintigrams were reviewed as unprocessed analogue pictures by several of the authors without knowledge of the pathological diagnosis and a consensus interpretation was made. The results of the scans were expressed as positive, equivocal, or negative. Scintigrams were also accumulated in a computer system in 64 × 64 frame mode. Tumour-to-lung uptake ratios were calculated from the digital pictures with the following technique. A rectangular region of interest was chosen around the tumour. A lower display level was set to visualise the tumour only and the mean count per channel in the visible part of the region was calculated. This was divided by the mean count per channel of a similar

Table 1 Detection of primary tumours in 63 patients with proved lung cancer

Scintigraphy result	⁵⁷ Co-bleomycin	⁶⁷ Ga-citrate
Positive	58	34
Equivocal	1	9
Negative	4	20

rectangular region of interest in the corresponding area of the opposite lung.

Results

PRIMARY TUMOUR

⁵⁷Co-bleomycin was clearly superior in detecting primary tumours (table 1). There was a sensitivity of 92% with ⁵⁷Co-bleomycin scintigraphy and of 54% with ⁶⁷Ga-citrate scintigraphy (equivocal scintigrams are considered negative). This difference is significant (sign test, $p < 0.01$). In 55 patients tumour-to-lung ratios were calculated. The tumour-to-lung ratio with ⁵⁷Co-bleomycin scintigraphy was 3.4 ± 1.7 (mean $\pm$ SD) and with ⁶⁷Ga-citrate scintigraphy 1.5 ± 0.9 . The mean difference between these ratios in individual patients is significant (Student's *t* test, $p < 0.01$).

The size of the lesions, measurable on the chest radiographs in 57 patients, influenced the scintigraphy results. The mean diameter of the lesions measured was 3.7 cm (range 1.0–8.3 cm). The diameters of the tumours in the patients with false negative ⁵⁷Co-bleomycin scintigrams were 3.7, 1.7,

Fig 1 Relation between diameters of the primary tumours and negative, equivocal, and positive results of ⁶⁷Ga-citrate scintigraphy.

Fig 2 Chest radiograph of a 66-year-old man presented with a coin lesion (diameter 1.7 cm) in the right lung, discovered at a routine chest x-ray examination; cytological examination of the sputum was suggestive of squamous-cell carcinoma (Papanicolaou grade 4). The lesion could not be seen at bronchoscopy.

1.2, and 1.0 cm. The diameter of the tumour in the patient with an equivocal ^{57}Co -bleomycin scintigram was 2.5 cm. The relation between tumour size and the results of the ^{67}Ga -citrate scintigrams is shown in fig 1.

Tumours smaller than 3 cm were seldom visualised with ^{67}Ga -citrate. An example of a small tumour seen on a chest radiograph and on the ^{57}Co -bleomycin but not the ^{67}Ga -citrate scintigram is illustrated in figs 2 and 3.

The pathological diagnoses of the tumours in the four patients with false-negative ^{57}Co -bleomycin scans were carcinoid tumour, squamous-cell carcinoma, adenocarcinoma, and large-cell anaplastic carcinoma. No relation between the histological type of the tumour and the scintigraphy results was noted for either radiopharmaceutical.

HILUM AND MEDIASTINUM

Eighteen patients proved to have metastases in hilum or mediastinum. The results of scintigraphy in this group and in the 45 patients without metastases are presented in table 2. In the detection of these metastases the sensitivity of the ^{57}Co -bleomycin scintigraphy was 89% and of the ^{67}Ga -citrate scintigraphy 44%, a significant difference (sign test, $p < 0.01$). The specificity of the ^{57}Co -bleomycin scintigraphy was 98% and of ^{67}Ga -citrate scintigraphy 91% (equivocal scintigrams are considered false positive). This difference is not significant (sign test).

BENIGN LESIONS

Eight patients proved to have a benign lesion. The nature of their lesions and the scintigraphy results are presented in table 3. Three had false-positive results from ^{57}Co -bleomycin scintigraphy but none from ^{67}Ga -citrate scintigraphy.

Fig 3 Negative ^{67}Ga -citrate scintigram (left) and positive ^{57}Co -bleomycin scintigram (right) with tumour-to-lung ratio of 2.4 and appreciable uptake of radioisotope also in the mediastinum (same patient as in fig 2). Both are posterior views. At mediastinoscopy enlarged lymph nodes were found, and the biopsy specimen showed squamous-cell carcinoma.

Table 2 Detection of metastases in hilum and mediastinum with ⁵⁷Co-bleomycin and ⁶⁷Ga-citrate scintigraphy

Group	No of patients	⁵⁷ Co-bleomycin scintigraphy			⁶⁷ Ga-citrate scintigraphy		
		Positive	Equivocal	Negative	Positive	Equivocal	Negative
With hilar tumour	18	16		2	8		10
Without hilar tumour	45		1	44	2	2	41

Table 3 Diagnoses and scintigraphy results* of eight patients with benign lesions

Patient No	Diagnosis	⁵⁷ Co-bleomycin	⁶⁷ Ga-citrate
1	Active tuberculosis	+	—
2	Pneumonia	+	—
3	Lung infarction	+	—
4†	Chondroma	—	—
	Scar tissue	—	—
5	Metaplasia	—	—
6	Pneumonia	—	—
7	Pneumonia	—	—
8‡	Bronchopathia osteoplastica	—	—

* + indicates positive scintigram and — negative scintigram.

† This patient had two different benign lesions.

‡ This patient also had squamous-cell carcinoma.

Discussion

Clinical staging of lung cancer is important for several reasons¹⁵—firstly, to aid the selection of the most effective treatment; secondly, to assist in determining prognosis; and, thirdly, to allow comparison of end-results reported from different sources.

⁶⁷Ga-citrate is widely used for this purpose; ⁵⁷Co-bleomycin is used on a smaller scale. After the first paper on the use of ⁶⁷Ga-citrate as a tumour-seeking agent¹⁶ initially encouraging results in detecting lung cancer were reported. In 1217 patients, collected from different publications, a sensitivity of 91% was found.¹⁷ Later it became evident that a negative scan could not be relied on in the case of lesions less than 3 cm in diameter.⁷ The detection of mediastinal metastases proved disappointing, possibly because of the high uptake normally seen in this region.¹⁸ Recently it was stated that the detection of hilar and mediastinal tumour extension with ⁶⁷Ga-citrate is still highly controversial.⁶ A considerable number of false-positive¹⁹ and false-negative scintigrams has been reported.²⁰ Possibly a higher dose, up to 10 mCi (370 MBq),²¹ more refined equipment such as a tomographic system,²² injection of iron,^{23 24} or injection of desferoxamine mesylate after ⁶⁷Ga-citrate injection²⁵ would improve the sensitivity. Another disadvantage of ⁶⁷Ga-citrate is its rather poor specificity—it is concentrated in benign lesions such as inflammation²⁶ and sarcoidosis lesions.²⁷

⁵⁷Co-bleomycin has proved to be useful in the

detection of lung cancer. A sensitivity of 98% was found in one series⁸ and in another 96%.²⁸ In 112 patients with mediastinal tumour invasion no false negatives were encountered.⁸ The specificity of ⁵⁷Co-bleomycin has not been investigated thoroughly. The long half life of ⁵⁷Co (270 days) has restricted its use largely to those patients suspected of having a neoplasm. It is known, however, that in inflammatory conditions, especially active tuberculosis, positive scintigrams are sometimes seen.^{8 28} Now that ⁵⁵Co, a positron-emitting radioisotope with a half life of 18 hours, is available as a label for bleomycin,²⁹ a prospective study in non-neoplastic diseases should be carried out to determine the specificity of Co-bleomycin.

The results of the present study lead to the conclusion that ⁵⁷Co-bleomycin is superior to ⁶⁷Ga-citrate in the detection and staging of lung cancer. More primary tumours were visualised and the sensitivity was 92%, compared with 54% for ⁶⁷Ga-citrate. In comparative studies Grove *et al*¹¹ and Poulouse *et al*¹² found a sensitivity of 91% with ⁵⁷Co-bleomycin and 76% with ⁶⁷Ga-citrate in patients with lung cancer. The latter figure is better than our results. In the present study tumour-to-lung ratios for ⁵⁷Co-bleomycin were clearly better: 3.4 compared with 1.5 for ⁶⁷Ga-citrate. Bertrand *et al* compared tumour-to-lung ratios in 21 patients with lung cancer and found a ratio of 5.2 for ⁵⁷Co-bleomycin and of 2.1 for ⁶⁷Ga-citrate.¹³ Detection of hilar and mediastinal metastases proved more reliable with ⁵⁷Co-bleomycin in our study. In none of the few comparative studies that we know of were the hilum and mediastinum evaluated, yet these areas are of great clinical importance.

The size of the lesion plays an important part in its detection with radiopharmaceuticals. Patients with a large primary tumour, in whom a diagnosis could easily be established by other means, were excluded from this study. Patients with obvious clinical or radiological signs of hilar or mediastinal metastases were also excluded. They were subjected to mediastinoscopy without prior scintigraphy. In most of our patients the lesion was discovered on mass screening radiographs, when symptoms had not yet developed. As a result most of the patients studied had a small tumour. This may explain our unfavourable results with ⁶⁷Ga-scintigraphy. The

importance of the tumour size for the scintigraphy results is shown in fig 1.

The major drawback of ^{57}Co , its long half life, poses no threat to the patient since ^{57}Co -bleomycin is quickly excreted by the kidneys; but the urine should be collected for at least 24 hours and stored to prevent environmental contamination. Using ^{55}Co as label for bleomycin solves this problem. Our first results with ^{55}Co -bleomycin in the detection of lung cancer, with a positron camera, are promising.²⁹

We do not advocate that ^{57}Co -bleomycin should replace biopsy and histological diagnosis of the primary tumour; but in peripheral lesions, in which a pathological diagnosis is difficult to obtain, a positive scintigram is an indication of a malignancy. When hilar or mediastinal metastases are suggested by scintigraphy, mediastinoscopy is carried out. If mediastinoscopy provides histological evidence of metastases thoracotomy is not indicated. When no hilar or mediastinal metastases are shown on the scintigram (and in the absence of distant metastases) we consider that mediastinoscopy is not needed. We then proceed directly to thoracotomy.

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References

- Sackner MA. Bronchofiberscopy. *Am Rev Respir Dis* 1975;111:62-88.
- Mitchell DM, Emerson CJ, Collyer J, Collins JV. Fibreoptic bronchoscopy: ten years on. *Br Med J* 1980;281:360-3.
- UICC, eds. *Clinical oncology*. Berlin: Springer-Verlag, 1978:164.
- Rubinstein I, Baum GL, Kalter Y, Pauzner Y, Lieberman Y, Bubis JJ. Resectional surgery in the treatment of primary carcinoma of the lung with mediastinal lymph node metastases. *Thorax* 1979;34:33-5.
- Martini N, Flehinger BJ, Zaman MB, Beattie J jun. Prospective study of 445 lung carcinomas with mediastinal lymph node metastases. *J Thorac Cardiovasc Surg* 1980;80:390-9.
- Hoffer P. Status of gallium-67 in tumor detection. *J Nucl Med* 1980;21:394-8.
- DeLand FH, Bertram JL, Boyd C, et al. ^{67}Ga -citrate imaging in untreated primary lung cancer: preliminary report of cooperative group. *J Nucl Med* 1974;15:408-11.
- Nouel JP. *Fundamental and clinical studies of bleomycin. Gann monograph on cancer research No 19*. Baltimore: University Park Press, 1976:301-16.
- Lesk DM, Wood TE, Carroll SE, Reese L. The application of ^{67}Ga scanning in determining the operability of bronchogenic carcinoma. *Radiology* 1978;128:707-9.
- Rasker JJ, Beekhuis H, van de Wal AM, Homan van der Heide JN, Woldring MG. Cobalt-57-bleomycin scanning of hila and mediastinum in patients with bronchial carcinoma: a prospective study. *Thorax* 1976;31:641-9.
- Grove RB, Reba RC, Eckelman WC, Goodyear M. Clinical evaluation of radiolabeled bleomycin (bleo) for tumor detection. *J Nucl Med* 1974;15:386-90.
- Poulouse KP, Watkins AE, Reba RC, Eckelman WC, Goodyear M. Cobalt-labeled bleomycin—a new radiopharmaceutical for tumor localization. A comparative clinical evaluation with gallium citrate. *J Nucl Med* 1975;16:839-41.
- Bertrand A, Vaillant G, Robert J, et al. Étude comparative de la fixation de la bléomycine marquée au cobalt 57, du citrate de gallium 67 et du bichlorure de mercure 197 au niveau des lésions malignes ou bénignes intraparenchymateuses pulmonaires. *Rev Fr Mal Respir* 1975;3, suppl 1:243-8.
- Dixon WJ, Mood AM. The statistical sign test. *J Am Statist Ass* 1946;41:557-66.
- Carr DT. *Lung Cancer 1980* (Second world conference, Copenhagen). Amsterdam: Excerpta Medica, 1980:49-70.
- Edwards CL, Hayes RL. Tumor scanning with ^{67}Ga -citrate. *J Nucl Med* 1969;10:103-5.
- Kempken K, Langhammer H, Hör G, Pabst HW. Szintigraphische und klinisch-experimentelle Untersuchungen mit ^{67}Ga an 142 Bronchialkarzinomen. *Nuklearmedizin* 1978;17:47-52.
- Bekerman C. *Gallium-67 imaging*. New York: John Wiley and Sons, 1978:113-31.
- Alazraki NP, Ramsdell JW, Taylor A, Friedman PJ, Peters RM, Tisi GM. Reliability of gallium scan chest radiography compared to mediastinoscopy for evaluating mediastinal spread in lung cancer. *Am Rev Respir Dis* 1978;117:415-20.
- DeMeester TR, Golomb HM, Kirchner P, et al. The role of gallium-67 scanning in the clinical staging and preoperative evaluation of patients with carcinoma of the lung. *Ann Thorac Surg* 1979;28:451-64.
- Bekerman C, DeMeester TR, Skinner DB. *Medical radionuclide imaging*. Vol 2. Vienna: International Atomic Energy Agency, 1977:351-61.
- Hauser MF, Gottschalk A. Comparison on the Anger tomographic scanner and the 15" scintillation camera in gallium imaging. *J Nucl Med* 1977;18:603 (abstract).
- Smith FW, Dendy PP, Pocklington T, Dawson AA, Foster MA, Mallard JR. A preliminary investigation of ^{67}Ga -citrate distribution in hyperferraeic patients. *Eur J Nucl Med* 1980;5:327-32.
- Hoffer P. Gallium: mechanisms. *J Nucl Med* 1980;21:282-5.
- Hoffer PB, Samuel A, Bushberg JT, Thakur M. Desferoxamine mesylate (Desferal): a contrast-enhancing agent for gallium-67 imaging. *Radiology* 1979;131:775-9.
- Lavender JP, Lowe J, Barker JR, Burn JL, Chaudhri MA. Gallium 67 citrate scanning in neoplastic and inflammatory lesions. *Br J Radiol* 1971;44:361-6.

- ²⁷ Langhammer H, Glaubitt G, Grebe SF, *et al.* ⁶⁷Ga for tumor scanning. *J Nucl Med* 1972;13:25–30.
- ²⁸ Rasker JJ, van de Poll MAPC, Beekhuis H, Woldring MG, Nieweg HO. Some experience with ⁵⁷Co-labeled bleomycin as a tumor-seeking agent. *J Nucl Med* 1975;16:1058–69.
- ²⁹ Nieweg OE, Beekhuis H, Paans AMJ, *et al.* Detection of lung cancer with ⁵⁵Co-bleomycin using a positron camera: a comparison with ⁵⁷Co-bleomycin and ⁵⁵Co-bleomycin single photon scintigraphy. *Eur J Nucl Med* 1982;7:104–7.