

LUNG CANCER DIAGNOSIS WITH ^{67}Cu : PRELIMINARY RESULTS

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Carrier-free ^{67}Cu , injected intravenously as citrate, is concentrated in malignant tumors. This accumulation is intense enough to allow the use of a gamma camera. This uptake by tumors, however, is not specific. As with the other substances used at present, progressive inflammatory lesions also concentrate radioactivity. Interest in ^{67}Cu lies in the possibility of distinguishing between malignant and inflammatory lesions as a result of the difference in uptake kinetics. Should the results reported be confirmed, ^{67}Cu might possibly be used as a routine test in lung cancer detection.

Many substances have been proposed for the scintigraphic detection of lung cancer. Among these, three are more widely used: $^{197}\text{HgCl}_2$ (1-3), ^{67}Ga -citrate (3-7), and ^{57}Co -bleomycin (8). Their increased uptake by the malignant tumor tissue enables one to distinguish malignant from benign tumors, but progressive inflammatory lesions and some diseases such as sarcoidosis also display an increased uptake and may be mistaken for a cancer. This lack of specificity decreases their value and has not encouraged the development of a detection test for lung cancer with any of these substances.

The ideal substance for lung cancer detection should display an absolute specificity for malignant tumors or at least be able to differentiate between malignant tumors and other lesions through differences in kinetics.

Among the molecules we studied systematically, carrier-free ^{67}Cu , as citrate, appeared quite interesting.

MATERIALS AND METHODS

Copper-67 is a beta and gamma emitter with a half-life of 58 hr. It is produced carrier-free by neutron bombardment of ^{67}Zn -enriched zinc (89.55%)

by the $^{67}\text{Zn}(n,p)^{67}\text{Cu}$ reaction. Actually, because of the contamination of the zinc target by natural copper, its specific activity ranges about 500 mCi/mg on injection. It decays by beta emission and emits two main gamma rays at 92 keV (23%) and 184 keV (40%). The amount of ^{64}Cu present in this preparation ranges about 10% of ^{67}Cu activity at the time of injection.

Each patient is given 1 mCi of ^{67}Cu -citrate (from CEA and Radiochemical Center, Amersham) intravenously. Systematically, three scans are taken 1, 4, and 24 hr after injection with a Pho/Gamma III camera. For each scan, the storage time is 15 min.

The data obtained with the gamma camera are processed with an Inter technique Tridac digital scintigraphy unit. The Tridac memory has a capacity of 16 K with four 4 K subgroups. A Multi-8 computer enables us to "normalize" the scans so as to take into account the nonuniform response of the camera crystal. Only the images of the Tridac oscilloscope are used.

Nine patients were investigated. Five of them were affected with primary bronchial cancer; the proof of cancer was obtained by histological examination of biopsy or surgically removed tumor. There were two patients with evolving lung tuberculosis. The other two were affected respectively with mediastinal lymph node, tuberculosis, and lung abscess "cooled" after protracted antibiotic therapy.

After scan normalization in two patients, uptake intensity was assessed by determining the uptake ratio, (activity in tumor area/activity in normal symmetrical area), the surface area of the two areas selected being the same. From the first results obtained in normal individuals, it appears that the

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values of this ratio in excess of 1.50 are pathological. This value can only be used provisionally until the definitive limit values are determined.

The dose of radiation absorbed in the liver, which can be regarded as the critical organ since it binds from 20 to 30% of injected ^{67}Cu , is about 0.02 rads/ μCi , i.e., twice as low as that absorbed with an equal radioactivity of colloidal ^{198}Au .

RESULTS

Normal individuals. The ^{67}Cu uptake by normal lung parenchyma is low, above all after the sixth hour. The mediastinal area is clearly visible on the scans taken at 1 hr, and especially its lower third which appears as a triangle, the base of which is the diaphragm and probably involves cardiac area. This mediastinal image is almost completely faded as early as the 24th hour. Hepatic uptake is prolonged, decreasing quite slowly in the course of time.

Primary lung cancer. We examined five patients with primary lung cancer (Table 1). In all of them, we observed an intense uptake in tumor area (Figs. 1, 2). This image was already visible 1 hr after injection and even more between 4–6 hr. However, the most interesting scans are those obtained after 24 and 48 hr because the physiological uptake

by mediastinal and pulmonary tissue is very low at that time and the limits of the image of the tumor are more definite.

The uptake ratio was measured in two of the five patients with primary lung cancer. In both cases, it was high as early as 1 hr and retained approximately the same value after 24 hr and in one case after 48 hr. The five cancers studied were squamous cell carcinomas.

In Patient MAR (Table 1), the cancer involved the right lung, and ^{67}Cu uptake in this area was clearcut. In this patient, chest x-rays disclosed a second opacity at the middle part of the left lung. Known for several years, the latter radiographic image remained unchanged and was indicative of a stable lesion; no increased ^{67}Cu uptake was observed in this area at early as well as at late stages. The difference in ^{67}Cu uptake in the area of the two radiographic opacities observed in this patient is worth noting.

In Patient ANS (Table 1, Fig. 2), the surgical operation and the histological examination of operative specimens established extension of cancer to mediastinal lymph nodes. On the scans this was easily detectable; the image was clearly demarcated from that of the rounded right supradiaphragmatic lung tumor.

TABLE 1. RESULTS OF ^{67}Cu SCANS

Patient	Gamma camera scans		Uptake ratio			
	+	—	1 hr	4 hr	24 hr	48 hr
Primary lung cancers						
TOM	Quite advanced left lung cancer	Differentiated squamous cell carcinoma	+			
CAT	Right upper lobe cancer	Differentiated squamous cell carcinoma	+			
ANS	Right middle lobe cancer with invasion of mediastinal lymph nodes	Differentiated squamous cell carcinoma	+			
MAR	Hilar cancer partially obstructing left lower lobar bronchus. Unexplained left lung opacity	Differentiated squamous cell carcinoma	+	—		
LAM	Left lower lobe cancer and presently stabilized bilateral lung tuberculosis	Differentiated squamous cell carcinoma	+	—		
Patients with inflammatory lesions						
DJE	Cavitary progressive left apical tuberculosis		+			
LEN	Progressive noncavitary tuberculosis of whole left lung		+			
BAL	Mediastinal lymph node tuberculosis		+			
VAL	Cooled lung abscess					

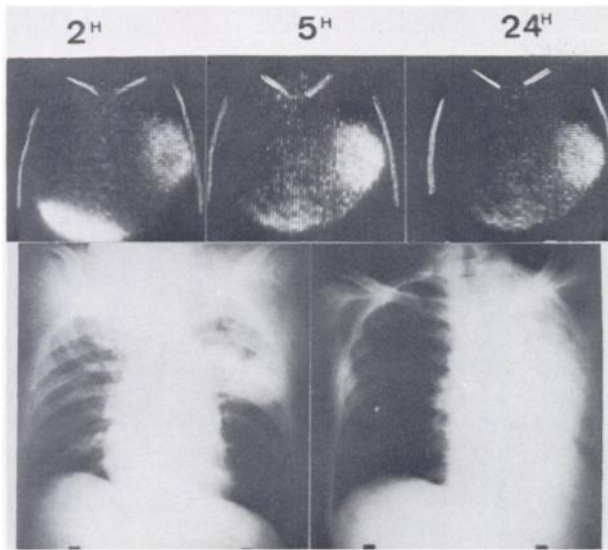


FIG. 1. Patient TOM with primary left lung cancer. Uptake of ^{67}Cu (1 mCi of ^{67}Cu -citrate) is intense as early as second hour after injection. At time of examination, pleural effusion prevented us from seeing limits of tumor on lung x-rays (right x-rays). Left x-rays were taken few weeks before examination.

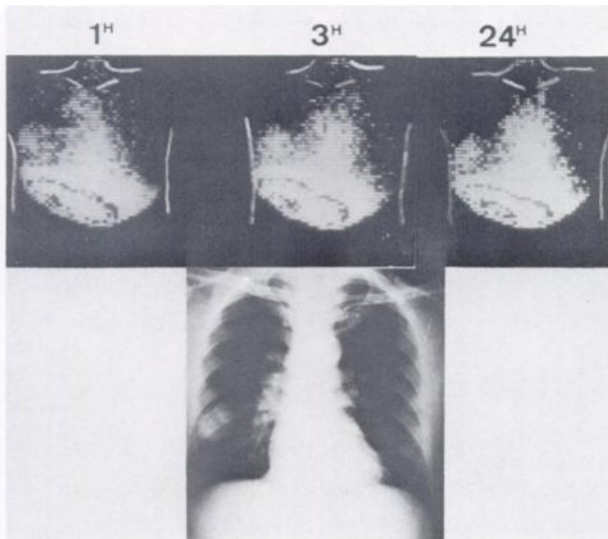


FIG. 2. Patient ANS with primary right lung cancer. Despite its location at right lung base, tumor is well delineated by ^{67}Cu -citrate.

Progressive inflammatory lesions. Two patients were affected with progressive lung tuberculosis (Table 1). In both cases the initial uptake, observed 1 hr after injection, was intense. It decreased gradually in the course of time; after 24 hr it was no longer visible in Patient LEN while it was still visible, although quite faintly, in Patient DJE (Fig. 3). Unfortunately, the measurement of the uptake ratio was not feasible in either of these patients because their scans were not normalized.

A third patient (BAL, Table 1) was affected with mediastinal lymph node tuberculosis with volumi-

nous paratracheal lymphadenopathy, above all on the right side. A moderately increased ^{67}Cu uptake was observed in the area of radiographic lymph node lesions; it was poorly delineated and not intense but it was visible at early as well as at late stages. The uptake ratio was moderately increased with a maximum after 4 hr.

Treated inflammatory lesions. In a patient with recurrent lung abscess (VAL, Table 1) after protracted antibiotic therapy, no increased uptake was detected in the area of the focus visible on chest x-rays.

DISCUSSION

The systematic investigation of metal uptake by tumors led us to use ^{67}Cu -citrate for these studies. Its 58-hr half-life and its gamma radiations of moderate energy (92 and 184 keV) make ^{67}Cu an isotope especially suitable for the problems of scintigraphic detection, in particular with the gamma camera. The first results obtained show that its uptake by malignant lung tumors is high. Expressed as the uptake ratio (activity in tumor area/activity in symmetrical area), the increased uptake by malignant tumors is greater than that observed with $^{197}\text{HgCl}_2$ and seems to be of the same order of magnitude as that observed with ^{57}Co -bleomycin. It is intense enough to be detectable with a gamma camera fitted with a digital scanning system. The quality of images is comparable with that of the scans obtained with $^{197}\text{HgCl}_2$, ^{67}Ga -citrate, and ^{57}Co -bleomycin. It seemed to us that the very low mediastinal uptake observed with ^{67}Cu after the first hour enabled one to interpret more easily paramediastinal

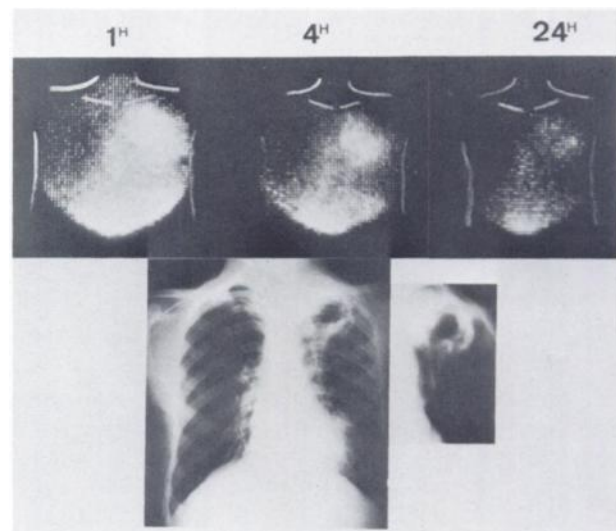


FIG. 3. Patient DJE with progressive (cavitary) tuberculosis of left apex. Uptake of ^{67}Cu by tuberculous lesions is only intense within a few hours of injection; it is much less after 24 hr.

images. A single patient showed a mediastinal image still visible after 24 hr; it corresponded to histologically malignant mediastinal lymphadenopathy.

Copper-67 uptake by progressive inflammatory lesions is intense. However, the course of ^{67}Cu uptake seems to be quite different in acute inflammatory lesions and in malignant lesions. It was intense at early stages in both types of lesions but clearly decreased after 24 hr in acute inflammatory lesions whereas it remained high in malignant lesions.

These preliminary results must be supplemented by a systematic investigation of ^{67}Cu uptake by benign tumors, secondary cancers, and less advanced primary cancers. Should it confirm the possibility of distinguishing between malignant and benign or inflammatory lesions, ^{67}Cu might be used profitably.

The cost of ^{67}Cu is still high: from \$200 to \$400/mCi. There is no doubt that this cost would be much lower if the demand for ^{67}Cu was to increase.

We attempted to replace carrier-free ^{67}Cu -citrate with carrier but with a high specific activity (about 20 mCi/mg). The results are quite inferior to those given by ^{67}Cu . Hepatic uptake is quite intense making the exploration of the lower half of both lungs difficult while the high energy of ^{64}Cu radia-

tion (511 keV) requires the use of special collimators.

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