CLINICAL EVALUATION OF ^{67}Ga-CITRATE SCANNING

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In 1969 Edwards and Hayes noted on a skeletal scintiscan the accumulation of ^{67}Ga-citrate in the neck lymph nodes of a patient with Hodgkin's disease (*1*). Since then ^{67}Ga-citrate has been shown to accumulate sufficiently in a variety of tumors to allow for their visualization (*2–8*). The actual mechanism of uptake of ^{67}Ga-citrate by the tumor tissue is still unknown although some postulates based on animal experiments have been proposed (*9,10*).

This paper describes our experience in the visualization of the distribution of ^{67}Ga-citrate in 149 patients with a variety of neoplasms and inflammatory lesions.

TABLE 1. RESULTS OF ^{67}Ga SCANS

Diagnosis	No. of case	Scintigram (+)	(±)	(−)
Lung cancer (primary)	19	18	0	1
Lung cancer (metastatic)	10	5	3	2
Lung cancer (post-irradiation)	6	2	0	4
Pulmonary tuberculosis (active)	10	5	5	0
Pulmonary tuberculosis (inactive)	15	0	1	14
Bacterial pneumonia	7	2	3	2
Virus pneumonia	4	1	0	3
Lung abscess	1	1	0	0
Sarcoidosis	2	2	0	0
Silicosis	2	2	0	0
Breast cancer	16	8	2	6
Benign mammary tumor	19	1	1	17
Maxillary cancer	8	8	0	0
Esophagus cancer	4	1	0	3
Stomach cancer	4	0	1	3
Colon cancer	6	2	0	4
Hepatoma (primary)	2	1	1	0
Hepatoma (metastatic)	2	1	0	1
Pancreas cancer	4	0	2	2
Thyroid cancer	4	1	0	3
Osteosarcoma	2	2	0	0
Malignant lymphoma	2	2	0	0
Benign tumor of submandibular gland	2	0	0	2
Phlegmonous appendicitis	1	1	0	0
Sialoadenitis	4	4	0	0
Ameloblastoma	1	0	0	1

MATERIALS AND METHOD

Gallium-67 decays by electron capture with a half-life of 78 hr, yielding no beta rays. The gamma-ray energies are 93, 184, 296, and 388 keV, respectively. The moderate energies of the 184- and 296-keV gamma rays are suitable for use with a commercially available scanner or with a scintillation camera. The ^{67}Ga used in this investigation was supplied by the Philips-Duphar Cyclotron and Isotope Laboratory.

About 1.5–2.0 mCi of carrier-free ^{67}Ga-citrate was administered to the patients after mixing it with 200 mg of sodium-citrate. Forty-eight hours after administration, a scintigram was taken with a Toshiba universal scintillation scanner (3 × 2-in. crystal) attached to a 19-hole honeycomb collimator with a focal length of 15 cm.

The ^{67}Ga-citrate was administered to 149 patients whose lesions were a variety of benign, malignant, and inflammatory lesions of the lung, mammary gland, stomach, esophagus, colon, pancreas, liver, maxillary sinus, salivary gland, and thyroid gland.

RESULTS

Results are shown in Table 1.

Lung. All except one of the 19 primary lung cancer cases showed a positive scan. In the one case the size of the tumor in the resected specimen was 2.0 × 1.5 cm and showed a nodular adenocarcinoma histologically. The smallest pulmonary cancerous lesion detected by scintigram was 2.0 × 1.7 cm in size. It was also a nodular adenocarcinoma. Analysis of ten metastatic pulmonary cases (three mammary cancers, two thyroidal cancers, one pancreatic cancer, three maxillary cancers, and one rectal cancer) revealed that the metastatic lung cancers showed

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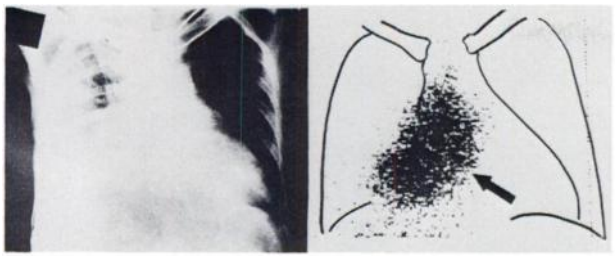

FIG. 1. Case 1. Pulmonary carcinoma. Chest x-ray shows mass extending from right hilar region with atelectasis of right lower lobe. Scintigram taken 48 hr after administration of 2.0 mCi of ^{67}Ga-citrate reveals considerable uptake corresponding to shadow in chest x-ray (indicated by arrow). Location and size of tumor are more easily detectable on ^{67}Ga-citrate scan than on chest x-ray.

a lower uptake of ^{67}Ga-citrate than did the primary lung cancers. On histologic examination, although the number of analyzed cases was small, there was a greater uptake of ^{67}Ga in seven cases of undifferentiated carcinoma than in three cases of squamous cell carcinoma and three cases of adenocarcinoma. Occasionally location and size of tumor were more easily detectable on the ^{67}Ga-citrate scan than on chest x-ray (Fig. 1). It is of interest that pulmonary carcinomas with a positive scan became negative when effectively treated with ^{60}Co radiation (Figs. 2 and 3).

Active pulmonary inflammations, such as tuberculosis, pneumonia, lung abscess, and pleurisy, also showed positive scans. However, after treatment the scan became negative (Fig. 4). In the cases of sarcoidosis and silicosis, positive scans were obtained when the lesions were thought to be in a proliferative stage (Fig. 5). Representative Cases 1 to 6 are shown in Figs. 1–5, respectively.

Mammary gland. Six negative scans were obtained among the 16 cases of breast cancer. All the T_1 cases (using TNM classification) were negative. Three out of 12 cases of T_2 were negative. Therefore the minimal detectable size in breast cancer was approximately 2 cm in diam. In the analysis of nine papillary and seven scirrhous adenocarcinoma, histological studies demonstrated no relationship between the types of cancer and the scintigram.

There was one false positive case among 19 cases of benign tumors, including six fibroadenomas and 13 cystic tumors. This case was accompanied by inflammation. Representative Cases 7 and 8 are shown in Fig. 6.

Maxillary sinus. All eight cases of cancer of the maxillary sinus showed strongly positive scans. Representative Cases 9 and 10 are shown in Fig. 7.

Other organs. It was rather difficult to obtain positive scintigrams in cases of cancer of stomach, esophagus, intestine, and pancreas. Among the four cases of stomach cancer, three cases were negative and one case was inconclusive. In the resected specimens of those stomach cancers showing a negative scan, the radioactivity of ^{67}Ga was 2.0–3.2 times greater than that of the unaffected surrounding stomach tissue. Two out of six cases of colon carcinoma were positive. The bladder and bowels had to be evacuated prior to the performance of the abdominal scans. One out of two primary hepatomas was positive. One out of two metastatic hepatoma cases was also positive.

The liver defect seen on the ^{198}Au-colloid scan corresponded to the area of increased uptake of the ^{67}Ga scan. All three cases with papillary adenocarcinoma of thyroid gland were negative while one case

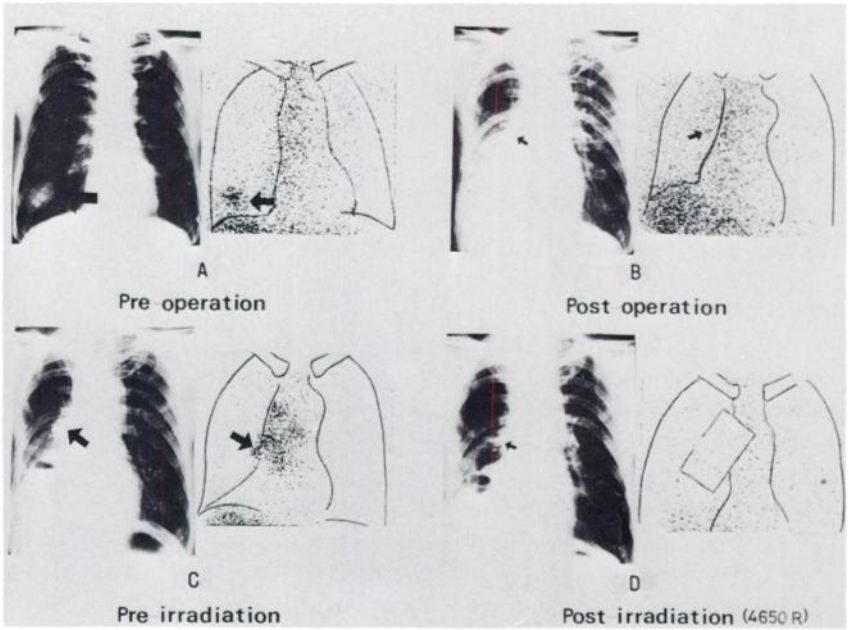

FIG. 2. Case 2. Pulmonary carcinoma. Chest x-ray (A) shows nodular shadow in right lower lobe (indicated by arrow). Scintigram taken 48 hr after administration of 2.0 mCi of ^{67}Ga-citrate reveals positive scan corresponding to shadow on chest x-ray. Postoperative chest x-ray (B) and ^{67}Ga scintigram (B) were obtained 6 months after operation. Scintigram reveals questionable lesion in right hilar region (indicated by arrow). Chest x-ray (C) and ^{67}Ga scintigram (C) were taken 1 month later. Scintigram revealed definite lesion in right hilar region. Chest x-ray (D) and ^{67}Ga scintigram (D) obtained after ^{60}Co irradiation. Uptake of ^{67}Ga in tumor of right hilar region is diminished after radiotherapy.

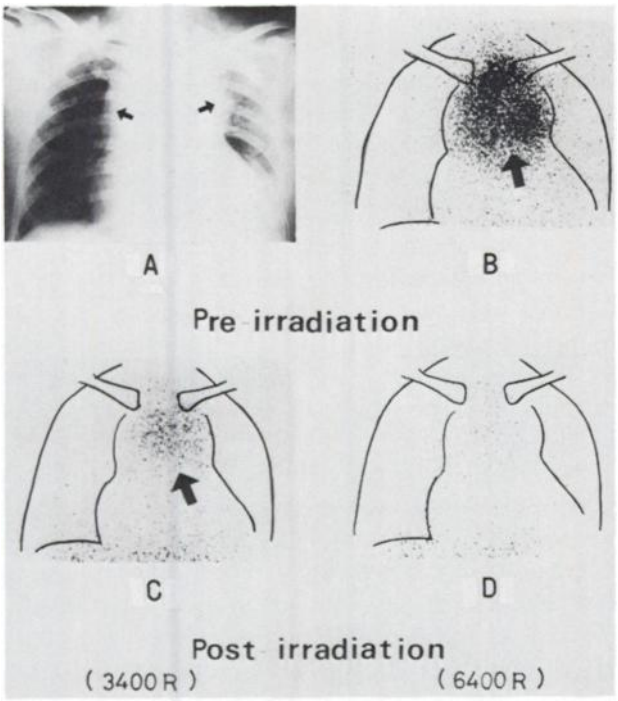

FIG. 3. Case 3. Malignant thymoma. Chest x-ray (A) shows widened mediastinum. Gallium-67 scintigram (B) reveals hot area corresponding to shadow on chest x-ray. Gallium-67 scintigrams (C and D) were taken during and after ^{60}Co radiotherapy. Uptake of ^{67}Ga-citrate decreased in proportion to radiation dose.

with undifferentiated carcinoma was positive. Although the number of analyzed cases was small, as far as the benign tumors were concerned, the two cases of mixed tumors of the submaxillary gland and the ameloblastoma of mandible were negative.

In the inflammatory group all cases of chronic sialoadenitis as well as the one case of phlegmonous appendicitis were positive. Representative Case 11 is shown in Fig. 8.

DISCUSSION

Our previous experiments using microautoradiograms revealed that ^{67}Ga-citrate was taken up by the tumor cell (*3*). Hayes and others reported similar results (*9*). However, the mechanism of uptake of ^{67}Ga-citrate into the tumor cells is still unknown. Edwards and Hayes (*4*) felt some substance with an affinity for gallium must be present in higher concentration in the tumor tissue than in other tissues. From the result of our recent experiments, we would like to postulate that uptake is more likely due to differences in the permeability of tumor cell membrane from that of the normal one. Thus after injecting stable gallium-citrate into Ehrlich tumor-bearing mice, the tumor cells were examined by high-resolution electron microscopy. The injected gallium was noted to be associated with the electron dense cytoplasmic granules. These granules appear to represent lysosomes. The detailed account of the gallium-binding granules will be published in another paper.

As Hayes and others (*11*) have reported, when stable carrier gallium was administered simultaneously with a carrier-free ^{67}Ga-citrate, its uptake into bones was excellent while the uptake by the tumor, the liver, and other organs was poor. This is also true in the whole-body autoradiogram of the mice (LAF_1) bearing Furth's mastocytoma as seen in Fig. 9. As to the uptake mechanism of ^{67}Ga-citrate in the cells, there seems to be a difference between the tumor and the bones. The ^{67}Ga-citrate bound with serum protein would be taken up by the tumor and liver cells, while the free ^{67}Ga would be more likely bound to apatite in bone. When carrier-free ^{67}Ga-citrate was injected into mice, its excretion in the feces was larger in amount than that in urine. However, when ^{67}Ga-citrate containing a small amount of carrier of stable gallium-citrate was injected, its excretion in the urine was more rapid and larger than that in feces (*10*). The author would like to interpret this result as follows: the larger amount of free ^{67}Ga-citrate which was not bound with serum protein in blood is destined to be excreted by the kidney.

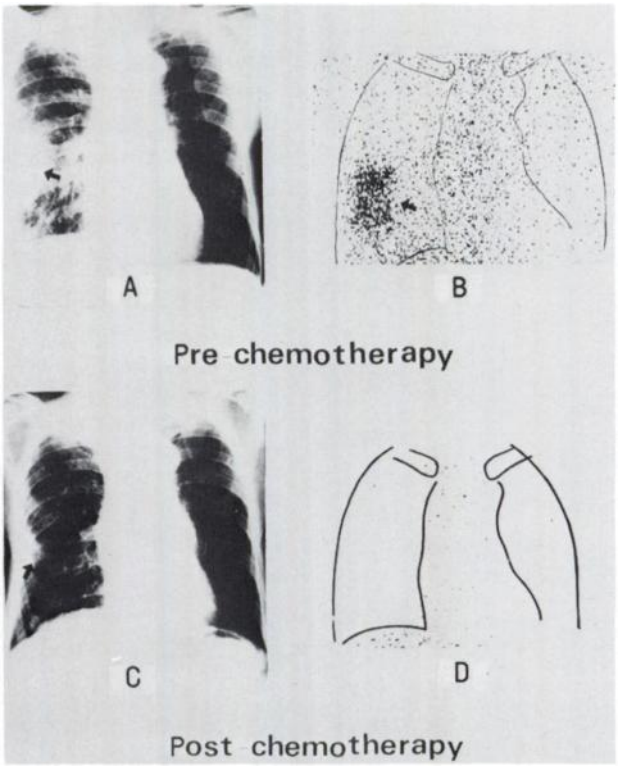

FIG. 4. Case 4. Pulmonary tuberculosis. Chest x-ray (A) taken before chemotherapy shows productive shadow in right lower lobe. Gallium-67 scintigram (B) reveals positive scan corresponding to shadow in chest x-ray picture (indicated by arrow). Chest x-ray (C) and ^{67}Ga scintigram (D) were taken at time of completion of chemotherapy. Concentration of ^{67}Ga is greatly reduced due to effective treatment.

Clinical studies show that lung cancer readily results in a positive scintigram. On histologic examination, the undifferentiated carcinomas showed markedly positive scintigrams. It seems that ^{67}Ga-citrate was less readily taken up by squamous cell and adenocarcinomas than by undifferentiated carcinomas. Cobalt-60 therapy decreased the uptake of ^{67}Ga-citrate by the malignant tumor. As seen in Fig. 3, with an increase of dose of the ^{60}Co irradiation, the accumulation of ^{67}Ga-citrate into the tumor diminished. The same clinical results have been reported by Edwards (*4*) and Vaidya (*12*). The relation between the radiation dose and the accumulation of ^{67}Ga is still obscure. However, the uptake of ^{67}Ga by tumor seemed to decrease in proportion to the radiation dose (Fig. 3). Therefore it seems that the accumulation of ^{67}Ga-citrate in the tumor cells is related to cell function. Furthermore, in some cases it was possible to anticipate the appearance of metastatic lesions by using the ^{67}Ga scintigram before it became visible roentgenographically (Fig. 2B).

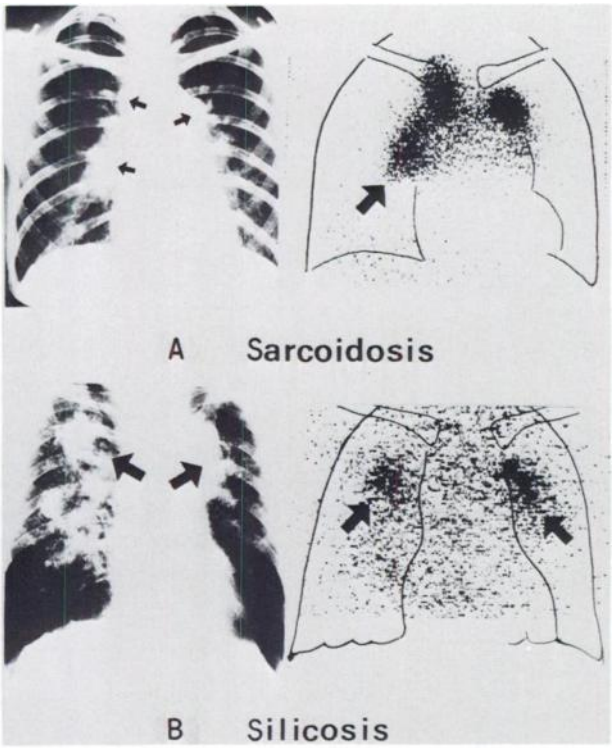

FIG. 5. Case 5, sarcoidosis, and Case 6, silicosis. Chest x-ray (A) of sarcoidosis shows enlargement of hilar regions bilaterally. Gallium-67 scintigram reveals strongly positive scan corresponding to shadows on chest x-ray. Chest x-ray (B) of silicosis shows proliferative and nodular shadow in upper lung fields bilaterally. Gallium-67 scintigram reveals positive scan corresponding to shadow on chest x-ray.

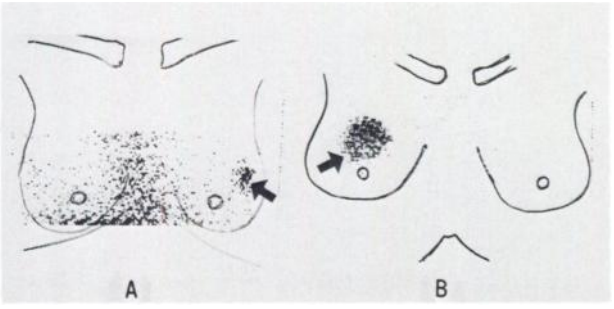

FIG. 6. Cases 7 and 8. Breast carcinoma. Gallium-67 scintigrams (A and B) are strongly positive (indicated by arrow). As seen in second scintigram (B) uptake by liver and vertebrae is slight when compared with uptake of ^{67}Ga-citrate by tumor. In Case 7 (A) patient was operated 5 days after administration of ^{67}Ga-citrate. Radioactivity in cancer tissue was 9.4 times higher than that in surrounding unaffected breast tissue.

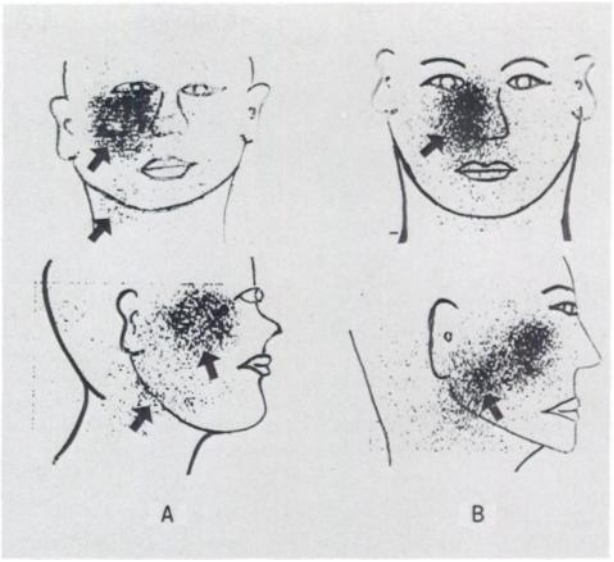

FIG. 7. Case 9 and Case 10. Cancer of maxillary sinus. Anterior and lateral ^{67}Ga scintigrams are shown in A and B. In anterior scintigram (A) accumulation in center of tumor is less noticeable. It may be due to central necrosis. In lateral scintigram (B) infiltration to upper pharyngeal region is well demonstrated.

In Fig. 1 it is obvious that when the uptake of ^{67}Ga-citrate into the tumor is greater, the uptake into the liver is smaller. The mechanism of uptake of ^{67}Ga-citrate into the tumor would be different from that of the liver. In addition, ^{67}Ga-citrate was obviously taken up by the active inflammatory lesion of the lung (Fig. 4). Examination of the microautoradiograms of the inflammatory lesions of the animal experiments showed that ^{67}Ga-citrate was distributed in the infiltrating neutrophil leucocytes. In the cases of sarcoidosis and silicosis, ^{67}Ga-citrate was taken up by the active granulomatous lesions (Fig. 5). This uptake would be due to phagocytosis of histiocytes in the granuloma. When the inflammatory lesion responded to chemotherapy, there was a disappearance of leucocytes and lymphocytes with a concomitant drop in ^{67}Ga-citrate concentration. The uptake of ^{67}Ga-citrate by the inflammatory lesion is largely dependent on its stage of activity.

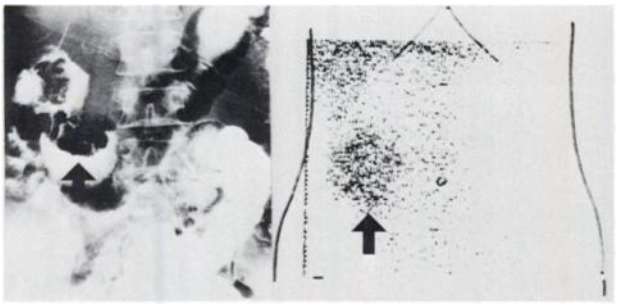

FIG. 8. Case 11. Carcinoma of colon. X-ray of colon shows large filling defect in transverse colon due to carcinoma. Gallium-67 scintigram is strongly positive in region corresponding to filling defect of x-ray. This patient was operated 10 days after administration of ^{67}Ga-citrate. Radioactivity in cancer tissue was 2.2 times higher than that in surrounding unaffected colon tissue.

Because ^{67}Ga-citrate accumulates in inflammatory lesions as well as tumor tissue, it is evident that gallium is not specific for the metabolism of tumor cells. Biologic function of the gallium which has been taken up by the cell is also obscure.

Clinically it is possible to differentiate malignant tumors from benign ones with the aid of scanning. It is, however, difficult to differentiate malignant tumors from inflammatory lesions. At present it is still difficult to obtain positive scintigrams in cases of cancer of the stomach, pancreas, esophagus, intestine, and liver. According to the whole-body autoradiograms of the tumor-bearing mice (Fig. 9), ^{67}Ga-citrate accumulates in the normal skeleton, liver, and mucous membranes of the stomach and intestines. Therefore it may be difficult to demonstrate the cancerous lesion of these organs as positive scintigrams. On the other hand, ^{67}Ga-citrate is poorly taken up by the normal lung and muscles so that a positive scintigram may be obtained in cancers of lung and breast.

That ^{67}Ga-citrate accumulates in malignant tissues is well known. Although the mechanism is unknown it is possible that when this mechanism is elucidated, a good tumor-seeking radiopharmaceutical will be produced. Further studies in this are necessary.

SUMMARY

Gallium-67-citrate scintiscans was performed in 149 cases with a variety of malignant, benign, and inflammatory lesions. Gallium-67-citrate was noted to be valuable in the diagnosis of cancers of lung, breast, and maxillary sinuses. At present, however, it is rather difficult to obtain positive scintigrams in cases of the stomach, pancreas, esophagus, and liver.

The following conclusions could be drawn from this study. (A) ^{67}Ga scanning was useful in establishing the extent of lesions as well as the presence of undetected metastases. (B) By using a ^{67}Ga scintigram, it is possible to detect cancerous lesions which are not visible roentgenographically. (C) ^{67}Ga scanning is useful for the determination of the irradiation area in radiotherapy, the evaluation of the effectiveness of the treatment, and the susceptibility of tumor cells to irradiation.

The major problem remains the accumulation of ^{67}Ga-citrate by inflammatory and granulomatous lesions, therefore making the differentiation between malignant tumor and these two groups difficult.

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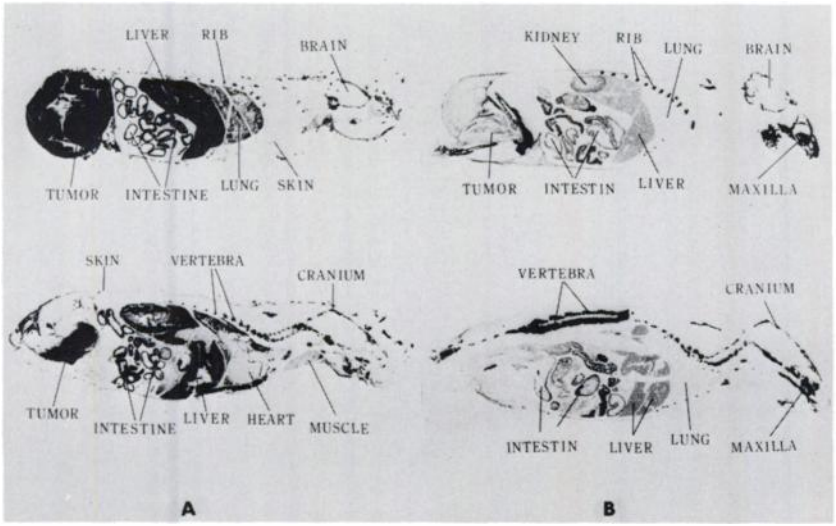

FIG. 9. Whole-body autoradiogram (A) of mouse bearing Furth's mastocytoma was taken 48 hr after administration of 150 μCi of carrier-free ^{67}Ga-citrate. Whole-body autoradiogram (B) was taken 48 hr after administration of 150 μCi of ^{67}Ga-citrate containing carrier dose of 2 mg stable gallium-citrate under identical conditions. Note excellent skeletal definition in (B) compared with (A).

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