^{67}Ga FOR TUMOR SCANNING

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Studies of the biological behaviour of gallium isotopes date back to Dudley, et al (*1,2*), Bruner and Brucer (*3,4*), and Hayes, et al (*5,6*). The clinical use of ^{67}Ga in tumor scanning is based upon initial observation of Edwards and Hayes (*7*) that ^{67}Ga is concentrated in human neoplasms. This affinity of carrier-free ^{67}Ga has been proven in a variety of human and animal tumors by a number of authors (*8–25*). The reports of Edwards, et al (*7,11–13*) deserve special attention; these authors have reviewed 107 scans in 84 patients with a great number of different neoplasms (*12*).

This publication summarizes the experiences of four European University Centers in visualizing the distribution of ^{67}Ga-citrate in 246 patients with different neoplasms and non-neoplastic diseases. Our clinical investigations were preceded by biological studies in animals. In addition, we have estimated the radiation dose using a whole-body counter for the determination of whole-body retention of ^{67}Ga. Preliminary results were communicated recently (*21*).

PRODUCTION OF ^{67}Ga AND CHARACTERISTICS

Galiium-67 was produced in the cyclotron* by the irradiation of zinc with protons: ^{67}Zn(p,n)^{67}Ga and ^{68}Zn(p,2n)^{67}Ga. At the same time large amounts of short-lived ^{66}Ga and ^{65}Ga are formed. Five days after bombardment the product contains no ^{65}Ga, less than 0.5% ^{66}Ga, and less than 0.04% ^{65}Zn per 1 mCi ^{67}Ga. The amount of copper is less than 5 μg/ml. These data apply to the solution that is injected; 1 ml of it (pH 6–8) contains 1 mCi ^{67}Ga, 1.6–2.5 mg sodium citrate, and 9 mg benzyl alcohol in isotonic solution of sodium chloride.

Gallium-67, which has a physical half-life of 78 hr, decays by electron capture followed by the emission of four main gamma rays of 0.093, 0.184, 0.296, and 0.388 MeV (*26*).

METHODS AND TECHNICAL EQUIPMENT

Each patient received intravenously 2–3 mCi ^{67}Ga-citrate in the described solution. Scans were usually performed 2 and 3 days after injection. In selected patients distribution of the ^{67}Ga was visualized up to 7 days. We used a 5-in. scanner or a Dynapix; for visualizing processes near the surface a fine-focusing collimator was applied, and for deeply situated lesions a coarse-focusing collimator was used. According to the scanner's technical possibilities, measurements were performed differentially (296-keV gamma-transition) or integrally (lower window at 250 keV). In two patients without and in one patient with malignancy the retention of ^{67}Ga was followed with a whole-body counter up to 44 days.

RADIATION DOSE INVESTIGATIONS

The radiation dose from ^{67}Ga depends especially on its distribution in the organism and its effective half-time in certain organs. In order to gather information on this subject we carried out studies on 60 male Wistar-rats weighing 140 gm. After intravenous injection of 8 μCi ^{67}Ga we examined the kinetics of the radioactivity in the whole body as well as in plasma, kidneys, liver, spleen, intestine, colon, pancreas, adrenal glands, testes, lungs, heart, skeletal muscle, rib cartilage, and bone (femur). In the whole body the effective half-time of ^{67}Ga is 73.5 hr, whereas the biological half-time is 53.1 days. Figure 1 shows the kinetics of the whole-body radioactivity.

According to our results, the effective half-time of ^{67}Ga in the organs examined is in the same range

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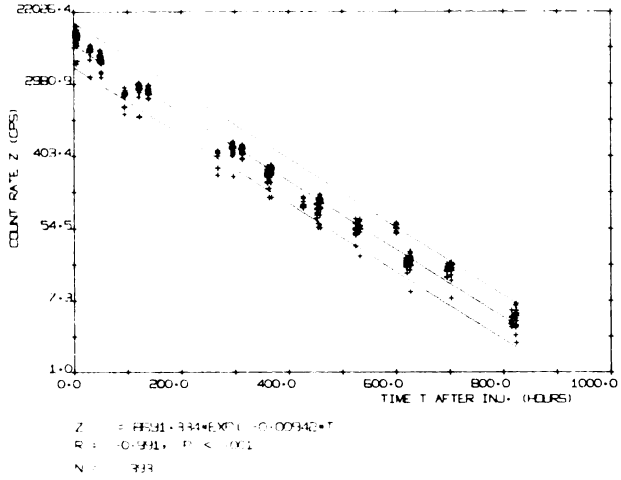

FIG. 1. Kinetics of whole-body radioactivity (M ± 2σ) after intravenous injection of ^{67}Ga in rats.

TABLE 1. ABSORBED DOSES FOR SEVERAL TARGET ORGANS

Target	Absorbed dose (mrad/mCi)	
	Inhomogeneous distribution	Homogeneous distribution
Total body	250	320
Gonads*	190	410
Total skeleton	820	370
Kidneys	900	360
Spleen	1,280	340
Liver	1,330	370

* Calculated for uterus because absorbed fractions for the gonads have not been published.

(52.7–71.7 hr) due to the physical half-time of ^{67}Ga (78 hr), although its biological half-time in the organs varies between 162 and 850 hr. As ^{67}Ga accumulates especially in skeleton, liver, kidneys, and spleen, the absorbed dose for man was calculated from the data in MIRD publications (*27,28,29*) for certain targets considering the observed inhomogeneous distribution in the rat. They were compared with the absorbed dose for a homogeneous distribution of ^{67}Ga in the total body (*30*). Both the biological date (distribution-factors, biological half-time) and the way of calculating the absorbed doses are to be published elsewhere (*31*).

It can be concluded from the data in Table 1 that in the case of ^{67}Ga a knowledge of its distribution is essential for correct absorbed-dose calculations and that the assumption of a homogeneous distribution may only be used as a first approximation.

RESULTS OF WHOLE-BODY COUNTING

We measured the ^{67}Ga retention of a reduced dose (2.5 μCi) in two tumor-free patients with a whole-body counter. During the observation time (14 days), the counting rate (corrected for the physical decay) could well be approximated by a single exponential function. Biological half-times of 14 and 22 days were observed. This is in general agreement with the value published in *ORAU 110* (*30*). For one tumor patient we measured a retention of about 95%, 44 days after injection.

Another interesting result of this extended measurement (up to 75 days) was the observation of radioactive contamination of ^{67}Ga with some ^{65}Zn (Fig. 2). Corrected for time of injection, the ratio is 40 nCi ^{65}Zn/mCi ^{67}Ga.

The biological half-time of zinc was estimated to be 70 ± 10 days. The resulting body burden of ^{65}Zn is on the order of 2–5 mrad/mCi ^{67}Ga assuming a uniform zinc distribution. The dose to the critical organ (liver) may be higher, but in any case it will be small compared with the dose from ^{67}Ga.

CLINICAL INVESTIGATIONS

In our series 246 patients were studied. Of these patients 151 had a malignant tumor diagnosed histologically. Histological verification was made on the primary tumor in 102 and on a metastasis in 34, of which 17 were without clinically diagnosed localization of the primary tumor. In 16 cases a positive cytological diagnosis (with or without the indication of the tumor type) was accepted for diagnosis. In 32 patients we had only a clinical diagnosis of malignancy. In the 136 patients with a histological confirmation of the diagnosis the ^{67}Ga-scan was positive in 100 patients; in the 32 patients without histological confirmation the scan was positive in 15 (Table 2).

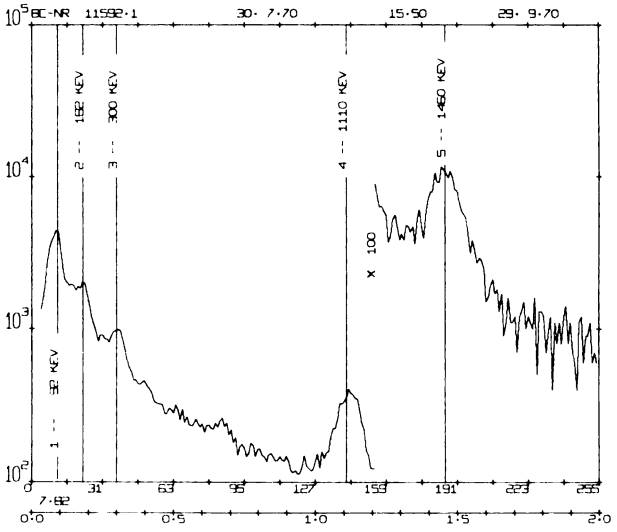

FIG. 2. Gamma-ray spectrum of whole-body counting 44 days after i.v. administration of 2.5 mCi ^{67}Ga.

TABLE 2. ^{67}Ga ACCUMULATION IN PATIENTS WITH MALIGNANT DISEASES

	Total		Morphologically verified	
	No. patients	^{67}Ga accumulation	No. patients	^{67}Ga accumulation
Respiratory tract (bronchi)	72 (70)	64 (62)	61 (59)	55 (53)
Thyroid	8	7	7	6
Metastases (unknown primary tumor)	17	15	17	15
Melanoma	11	8	10	8
Digestive tract	33	14	26	12
Urinary tract	7	1	5	1
Genital tract	6	2	5	2
Breast	9	3	2	1
Deep connective tissue	5	1	3	0
Sub total	168	115	136	100
Malignant disease RHS	35	22	35	22
Total	203	137	171	122

In two patients malignancy was dubious (aggressive fibromatosis, carcinoid in bronchus), and five patients had benign tumors. Four patients had undergone radical surgical treatment without clinical signs of recurrence of tumor or of metastasis; they showed no abnormal ^{67}Ga accumulation. Malignant disease of the reticulo-histiocytic system, either local or generalized, was present in 35 patients. Benign nontumorous disease was present in 32 patients.

In Table 2 we summarize the results of the ^{67}Ga studies in 203 patients with various malignant diseases. Of interest was the detection of a primary bile duct carcinoma until then unknown in a patient with a tumor in the lung-hilus and liver. In one patient with a gastric carcinoma the preoperative scan was negative; the scan of the resected stomach was positive. In a primary carcinoma of the liver the ^{67}Ga accumulation could not be distinguished from hepatic accumulation of the ^{67}Ga normally seen.

Table 3 summarizes the findings in malignant reticulo-histiocytic diseases. The high numbers of positive scans found in Hodgkin's disease and lymphosarcoma were impressive.

Table 4 gives the ^{67}Ga uptake related to previous therapy. We regarded patients as "treated" who recently, up to 6 months prior to ^{67}Ga scanning, received

1. radiotherapy with a minimum dose of 1,200–1,500 rads (all neoplasms included).
2. radiotherapy with at least 500 rads (in case of all reticulo-histiocytic malignancies).
3. recent adequate chemotherapy or hormonetherapy.

"Untreated" patients were those not recently treated or those with tumor recurrence after treatment. In attempting to compare the ^{67}Ga uptake in untreated and treated cases we find that the figures are not adequate to allow a conclusion at this moment.

Table 5 lists the results in relation to morphological types of bronchial carcinomas. Galium-67 concentration was found in 50 of 54 cases of various histological types.

TABLE 3. ^{67}Ga ACCUMULATION IN MALIGNANT DISEASE RHS

	No. patients	^{67}Ga accumulation
Hodgkin's disease	17	14
Lymphosarcoma	5	4
Reticulosarcoma	7	3
Follicular lymphoma	3	0
Chron. lymph. leukemia	1	0
Chron. myel. leukemia	1	1
Plasmacytoma	1	0
Total	35	22

TABLE 4. ^{67}Ga ACCUMULATION IN RELATION TO PREVIOUS THERAPY

	Untreated patients		Treated patients	
	No. patients	^{67}Ga accumulation	No. patients	^{67}Ga accumulation
Respiratory tract (bronchi)	64 (62)	58 (56)	8 (8)	6 (6)
Thyroid	5	5	3	2
Metastases (unknown primary tumor)	15	14	3	2
Melanoma	11	8	—	—
Digestive tract	27	12	6	2
Urinary tract	6	1	1	0
Genital tract	5	2	1	0
Breast	3	3	6	0
Deep connective tissue	4	1	1	0
Sub total	140	104	28	11
Malignant disease RHS	24	17	11	5
Total	164	121	39	16

TABLE 5. ^{67}Ga UPTAKE OF 54 BRONCHIAL CARCINOMAS WITH DIFFERENT MORPHOLOGY

Tumor type	No. patients	^{67}Ga accumulation
Adenocarcinoma	2	2
Colloid carcinoma	1	1
Squamous cell carcinoma	18	18
Oat cell carcinoma	11	10
Anaplastic carcinoma	13	11
No type, cytology only	9	8
Total	54	50

The frequency of ^{67}Ga accumulation in various organs for four distinct histological tumor types has been summarized in Table 6. Remarkable is the low portion of ^{67}Ga uptake in adenocarcinomas due to the fact that positive scans were found only in one of eight patients with a colon carcinoma (see discussion). We disregarded 54 patients with histologic tumor types other than those referred to in this table.

Finally Tables 7 and 8 give the ^{67}Ga uptake in nonmalignant diseases studied in 39 patients.

TABLE 6. ^{67}Ga UPTAKE IN FOUR DIFFERENT TUMOR TYPES AND THEIR LOCALIZATIONS

Tumor type	Organ	No. patients	^{67}Ga uptake
Adenocarcinoma	Bronchus	2	2
	Thyroid	1	1
	Unknown primary tumor	2	1
	Stomach	10	7
	Colon	9	1
	Prostate	1	1
	Ovary	1	1
	Total	26	14
Squamous cell carcinoma	Bronchus	18	18
	Unknown primary tumor	2	2
	Tonsil	1	1
	Esophagus	2	1
	Uterus (cervix)	1	0
	Total	24	22
Oat cell carcinoma	Bronchus	11	10
Anaplastic carcinoma	Bronchus	13	11
	Thyroid	2	2
	Unknown primary tumor	3	3
	Stomach	1	1
	Breast	2	1
	Total	21	18

TABLE 7. ^{67}Ga ACCUMULATION IN DUBIOUS MALIGNANT AND BENIGN TUMORS

	No. patients	^{67}Ga accumulation
Dubious malignant tumors		
Aggressive fibromatosis	1	0
Carcinoid (bronchus)	1	0
Total	2	0
Benign tumors		
Thyroid cyst	2	0
Hepatoma	1	1
Epidermoid cyst	1	0
Pericardial cyst	1	0
Total	5	1

TABLE 8. ^{67}Ga ACCUMULATION IN 32 NONMALIGNANT DISEASES

	No. patients	^{67}Ga accumulation
Sarcoidosis		
Recent	4	4
Old	3	0
Pulmonary tuberculosis		
Primary	1	1
Secondary/tertiary	4	0
Chronic pulmonary disease		
Lipiodol infiltrate	1	1
Cystic disease	1	1
Kaplan syndrome*	1	0
Fibrosis	1	1
Pleural adhesions	1	0
Paragoniasis	1	1
Acute pulmonary disease		
Inflammatory	2	0
Embolic	2	0
Pneumothorax	1	0
Hepatic cirrhosis	4	0
Chronic gastric disease		
Ulcer	2	0
Gastritis	2	1
Chronic colitis	1	0
	32	10

* Rheumatic lungs affection.

DISCUSSION AND CONCLUSIONS

Several radionuclides and radiopharmaceuticals have been proposed for tumor scanning in past years. Gallium-67-citrate has been shown experimentally to concentrate in tumors of soft tissue and bone (*16, 17*). In *ORAU 110* (*30*) it is pointed out by comparative studies in animal tumors that ^{67}Ga-citrate is superior to ^{75}Se-selenomethionine, ^{203}Hg-chlormerodrin, and ^{125}I-albumin in absolute tumor concentration and in ratio of tumor-to-normal tissue concentration. This prompted us to review the results of tumor scanning with ^{67}Ga performed in four European Centers. We consider it worthy of emphasis that we observed striking tumor concentration of ^{67}Ga in 62 of 70 patients with bronchial carcinoma; in seven of eight patients with thyroid carcinoma; in eight of 13 patients with carcinoma of the stomach; in eight of 11 patients with malignant melanoma and in 15 of 17 patients with metastasis of unknown primary tumors. Furthermore it is remarkable that there was no dependence of ^{67}Ga accumulation on the histological type of tumor, neither for bronchial carcinoma nor for tumors elsewhere (Tables 5 and 6).

We could only surely recognize a positive scan in one out of eight carcinomas of the colon. According to the findings of Edwards and Hayes (*13*) and Winchell, et al (*25*) the detectability of malignan-

cies within the abdominal region is considerably hampered by physiological accumulation of ^{67}Ga in the intestine and liver. In studies of the abdominal region it is important to use laxatives to remove the ^{67}Ga from the intestines.

With their use and with serial scanning on different days we were able to diagnose one of the colon carcinomas and to differentiate the ^{67}Ga-uptake in this tumor from the changing localization of the activity in the intestine. In the other seven cases we could not interpret the scan due to inefficient cleaning of the bowel. We could confirm the usefulness of ^{67}Ga scanning in detecting malignant disease of the RHS (Table 3), which have been correctly diagnosed in 63% of the cases under our investigation.

Concentration of ^{67}Ga in tumors was found in untreated as well as in treated patients. Table 4 suggests a marked difference only in tumor localizations in the breast and in the RHS. Comparative control examinations before and after therapy are in progress (*32*).

We also studied the ^{67}Ga uptake in two doubtfully malignant and in five benign tumors (Table 7). We did not find ^{67}Ga uptake except in a histologically benign hepatoma, probably due to the physiological affinity of the liver for ^{67}Ga. The use of ^{67}Ga for the diagnosis of malignant thyroid tumors is supported by the absence of ^{67}Ga accumulation in two benign thyroid tumors.

In benign nontumorous lesions the ^{67}Ga uptake was infrequent except for early stages of sarcoidosis (Table 8). The uptake of ^{67}Ga in some nonmalignant processes might seem to be a limitation in the use of ^{67}Ga as a tumor-seeking scanning agent. However, this criticism is easily put in proper perspective if one remembers that clinically a single diagnostic procedure should not be considered as an absolute criterion. Therefore we consider ^{67}Ga to be a helpful tool in the clinical diagnosis of malignant diseases, especially so for bronchial carcinoma, thyroid carcinoma, gastric carcinoma, malignant melanoma, and malignant RHS disease.

SUMMARY

Gallium-67-citrate was administered to 246 patients. The highest percent of positives was found in patients with bronchial carcinoma, thyroid carcinoma, gastric carcinoma, malignant melanoma, and metastases of unknown primary tumors as well as in Hodgkin's disease. The series of patients analyzed according to histological classifications showed no dependence of ^{67}Ga accumulation on the morphological type of tumor.

Without the use of laxative and enemas the demonstration of ^{67}Ga accumulation in abdominal tumors is complicated by the physiological accumulation in the intestines.

The study of the ^{67}Ga accumulation in untreated and treated patients was not conclusive.

In 39 patients with nonmalignant disease ^{67}Ga accumulation in the lesion was found in 11, comprising four patients with recent sarcoidosis and one patient with primary tuberculosis. According to biological investigations and measurements of the whole-body retention, the total-body dose normally amounts to 250 mrad/mCi ^{67}Ga.

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