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⁶⁷Ga SCANNING IN THE STAGING OF MALIGNANT LYMPHOMA

D.A. Turner, A. Gottschalk, P.B. Hoffer, P.V. Harper, E. Moran and J.E. Ultmann

Department of Radiology (Section of Nuclear Medicine), Department of Medicine,
Department of Surgery of the University of Chicago and the Argonne Cancer
Research Hospital (operated by the University of Chicago for the United States
Atomic Energy Commission)
Chicago, Illinois 60637, U.S.A.

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48 patients have been evaluated with gallium-67 (⁶⁷Ga) whole body scanning as part of a protocol for the staging of Hodgkin's disease. 38 of these patients have subsequently undergone laparotomy, for the purpose of staging, as well as selected superficial lymph node biopsies. Histological confirmation of sites of Hodgkin's disease was also available for 9 patients with involvement of "special sites", i.e. sites other than lymph nodes, spleen or liver, and for one patient with Hodgkin's disease in the liver.

The results of the scans were compared with the presence of disease as determined by histological examination of the biopsy specimens and radiographic examination of the chest. In the 38 patients subjected to laparotomy, ⁶⁷Ga scanning correctly identified 45 of 67 (67%) confirmed sites of disease. While the method was very reliable in the detection of disease above the diaphragm, accuracy in the abdomen was poor.

Gallium-67 scanning was particularly useful in patients with disease in "special sites." Since the ⁶⁷Ga scan was the only non-invasive study that indicated the presence of tumor in three such cases, it was crucial in the evaluation of these patients.

Gallium-67 scanning is recommended as a useful supplementary examination in the evaluation of patients with Hodgkin's disease. It may identify sites for biopsy which might otherwise be overlooked.

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GALLIUM-67 SCANNING IN THE STAGING OF HODGKIN'S DISEASE*

D. A. Turner,[†] A. Gottschalk, P. B. Hoffer,[‡] P. V. Harper,
E. Moran and J. E. Ultmann

From the Departments of Radiology (Section of Nuclear Medicine),
Surgery, and Medicine of the University of Chicago and the
Argonne Cancer Research Hospital,[§]
Chicago, Illinois 60637 U.S.A.

Since the initial observation of Edwards and Hayes that gallium-67 (⁶⁷Ga) localizes in soft-tissue neoplasms, numerous reports concerning the use of ⁶⁷Ga-citrate as a tumor scanning agent have appeared in the literature [1].

This communication presents data from an ongoing evaluation of the use of ⁶⁷Ga scanning in the staging and management of patients with Hodgkin's disease. The report is concerned primarily with a series of patients who have undergone ⁶⁷Ga scanning prior to staging laparotomy and biopsy of selected superficial lymph node sites. Additional patients in whom the clinical diagnosis of lymphoma has been confirmed by biopsy before scanning also will be discussed. Some of the data presented here have been published elsewhere [2,3].

The physical properties of ⁶⁷Ga are acceptable for radionuclide scanning in humans. It has a half-life of 78 h, decaying by electron capture with the following discrete photon emissions: 93 keV (40%), 184 keV (24%), 296 keV (22%), and 388 keV (7%) [4]. These energies are suitable for imaging with scintillation cameras as well as with rectilinear scanning devices.

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[‡]Scholar in Radiological Research of the James Picker Foundation.

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The total-body radiation dose from ^{67}Ga is estimated to be 0.34 rads/mCi [1].

The mechanism by which ^{67}Ga accumulates in neoplastic and other tissues remains unknown, although it is believed to localize in a lysosome or lysosome-like organelle [5]. When carrier-free ^{67}Ga -citrate is injected intravenously, ionic ^{67}Ga is rapidly bound to transferrin and other plasma proteins [6]. It leaves the blood with a half-life of about 12 h and accumulates in kidney, liver, marrow, spleen, lung, bone, and adrenal gland [7]. It also localizes at sites of inflammation [8,9,10]. In addition, it has been reported that ^{67}Ga is concentrated by the breasts of patients with gynecomastia, and that it accumulates in the breasts of pre-lactating and lactating females, a phenomenon we have also observed [11,12]. We have occasionally seen ^{67}Ga activity in the breasts of females who were neither pregnant nor lactating.

1. MATERIALS AND METHODS

Since August 1, 1970, all previously untreated patients with biopsy-proven Hodgkin's disease seen at the University of Chicago Hospitals and Clinics have undergone whole-body scanning with ^{67}Ga -citrate as part of a previously established protocol for the staging of Hodgkin's disease. Many patients suspected of having recurrent Hodgkin's disease have been evaluated similarly.

As of July 1, 1972, 38 patients, who had been evaluated by ^{67}Ga scanning, had undergone exploratory laparotomy for the purpose of staging. The staging laparotomy includes multiple excisional biopsies of lymph nodes (splenic hilar, porta hepatis, mesenteric, right and left aortic, and right and left iliac nodes), splenectomy, wedge biopsy of the liver, needle biopsies of the right and left lobes of the liver, and core biopsy of iliac bone [13,14]. Patients determined to be stage IV (see Table I) [15], and patients who had received chemotherapy (except prednisone) within four months preceding evaluation, were not subjected to staging laparotomy, and were therefore automatically excluded from this group.

In nine patients with disease involving "special sites" (sites other than lymph nodes, spleen, or liver), histological confirmation of the disease site was available. One patient had Hodgkin's disease in the liver, as demonstrated by percutaneous needle biopsy. None of these patients underwent complete staging laparotomy and will, therefore, receive separate consideration.

1.1 Scan method

Carrier-free ^{67}Ga -citrate was prepared initially in the Argonne Cancer Research Hospital's compact cyclotron (Cyclotron Corporation CS-15) by bombardment of natural zinc with 8-MeV deuterons [16]. Since April 1, 1972, however, a commercially available preparation of ^{67}Ga -citrate has been used.

Seventy-two hours prior to scanning, patients received 3.0 mCi of ^{67}Ga -citrate in a volume of less than 2 cm³ by intravenous injection.

The lumen of the colon normally contains considerable ^{67}Ga activity, which causes difficulty in the interpretation of ^{67}Ga scans of the abdomen (Fig. 1). Bowel preparation directed at elimination of this activity became increasingly vigorous as the study progressed. Initially, patients were prepared only with cleansing enemas just prior to scanning. Subsequently, 60 cm³ of castor oil were administered on the day before scanning. Recently we have subjected patients to repeated scanning after cleansing

enemas if any activity was seen in the colon. Activity not clearing on serial scanning after repeated enemas has been interpreted as being due to the presence of tumor.

All patients were scanned from head to knee with an Ohio Nuclear Model 84 radionuclide scanner, fitted with dual 5-in. detectors and 38H collimators (9 cm focal depth). Simultaneous anterior and posterior scans were made with the patient in the supine position. The upper detector was adjusted to a level 2 to 4 cm above the anterior surface of the patient's body. Scanning speeds of 650 to 750 cm/min were used, the entire scan taking 45 to 75 min.

The first 21 scans in this series were of a 20% window around the 296-keV photon emission of ^{67}Ga . Maximum information densities of 15 to 75 counts/cm² were obtained. Subsequent modification of our scanning instrument with three independent pulse height analyzers has made possible the simultaneous detection of the 93-keV, 184-keV and 296-keV photon emissions of ^{67}Ga . We have achieved maximum information densities of 240 counts/cm² in the last 17 cases of this series, without altering scanning speeds, by scanning 20% windows about these three photon emissions. The greatly improved quality of the scans afforded by the increased information density is illustrated in Fig. 2. A five-to-one minification readout was employed in all of the studies in this series.

1.2 Scan interpretation

The scans were interpreted by two of us (A.G. and P.B.H.) without knowledge of the patients' identities, clinical histories, or the results of other studies. Special attention was paid to the cervical, supraclavicular, axillary, mediastinal, paraaortic, iliac, and inguinal regions as well as the spleen, liver, and porta hepatis (see Figs. 3, 4, and 5). Abnormal activity in other areas was also recorded.

The scan results were compared with the presence of disease as determined by histological examination of the biopsy specimens. Supraclavicular and adjacent cervical nodes were tabulated as one area of involvement, as were paraaortic and mesenteric nodes ("paraaortic-mesenteric area").

The "per cent error" figures in Tables II, III, and IV represent the rate at which the ^{67}Ga scans failed to detect histologically demonstrable sites of Hodgkin's disease, or incorrectly indicated the presence of disease where none existed. Expressed in this way, the error rate is independent of the ratio of histologically positive to histologically negative sites.

The "per cent accuracy" figures represent the rate at which a group of positive scans (or a group of negative scans) will correlate with histological findings. In contrast to the "per cent error" figure, these numbers are dependent on the ratio of histologically positive to histologically negative sites and therefore might be expected to vary significantly from one series to another. These data are included, however, because data are often used in this manner in clinical practice.

2. RESULTS

2.1 Thirty-eight fully staged patients

The overall results for the group of 38 fully staged patients are summarized in Table II. Of a total of 67 confirmed sites of disease, 45 were correctly identified and 22 were missed by the ^{67}Ga scan; this represents a false negative error rate of 33%. Two hundred twenty-eight sites were histologically free of disease. Fourteen of these sites were positive on the ^{67}Ga scans, a false positive error rate of 6%.

Separate consideration of each anatomical region yields a more useful assessment of the accuracy of ^{67}Ga scanning than the overall results above (see Table III). None of the 21 radiographically positive mediastinal areas were missed by the ^{67}Ga scans. There were two cases in which the scan was positive and the radiograph negative. We have considered these "false

positives" in our tabulation, although it is certainly possible, and in fact quite likely, that disease was present in the mediastinum in these cases in spite of the normal chest radiographs.

A total of 33 superficial lymph node sites were biopsied. Nineteen of these were positive by histological examination. The ^{67}Ga scans correctly identified 15 (79%). One of 14 sites negative on biopsy (7%) was positive on the scan.

Intra-abdominal lymph nodes were divided into three areas: portal, paraaortic-mesenteric, and iliac regions. Separate data from each of these regions are presented in Table III, and combined data from all three regions in Table IV. Only 5 of 22 lymph node sites containing Hodgkin's disease by histological examination were correctly identified by the scans, a false negative error rate of 77%. The false positive error rate was 5% for 130 histologically negative areas.

Since the spleen normally accumulates ^{67}Ga , we called the spleen abnormal only if the density of activity in the splenic bed was greater than or equal to that of the liver on the posterior view. Seven (78%) of nine spleens proven to harbor Hodgkin's disease by histological examination were positive on the ^{67}Ga scans. The false positive error rate was 17%, as 5 of 29 spleens in which no Hodgkin's disease was found were abnormal on the scans.

All liver biopsies and all technetium-99m sulfur colloid scans in this group of patients were negative. The ^{67}Ga scans of the liver were negative in all of these patients as well.

2.2 Patients with Hodgkin's disease in "special sites"

Patients in this group will be considered individually.

2.2.1 CASE 1. S.P. was admitted to the University of Chicago Hospitals and Clinics because of systemic manifestations suggestive of recurrent Hodgkin's disease. Extensive conventional diagnostic investigation revealed no evidence of recurrence. A ^{67}Ga scan, however, showed extremely high accumulation in the left upper quadrant of the abdomen, in spite of the fact that the spleen had been removed at a previous staging laparotomy two years earlier (Fig. 6). On the basis of the ^{67}Ga scan alone, the patient underwent a second laparotomy; at this time a large tumor mass in the splenic bed was disclosed.

2.2.2 CASE 2. K.M. developed pain in the right anterior chest wall while receiving radiotherapy for recurrent disease elsewhere. Physical and radiographic examinations were unrevealing. An area of high activity of ^{67}Ga was demonstrated in the region of her discomfort (Fig. 7). Biopsy demonstrated a focus of Hodgkin's disease between her ribs, for which she received additional radiotherapy. One year later, she began experiencing pain in her lower sternum after alcohol ingestion. A ^{67}Ga scan demonstrated prominent activity in this area, as did a fluorine-18 (^{18}F) bone scan. No additional biopsy was performed. Local radiotherapy was given, relieving her symptoms.

2.2.3. CASE 3. P.B. was admitted to the hospital, complaining of left posterior chest pain, weight loss, and anorexia, one year after radiotherapy for Hodgkin's disease, stage IB. A chest radiograph demonstrated only "pleural thickening." The ^{67}Ga scan showed abnormal activity in the left chest both anteriorly and posteriorly. At thoracotomy tumor was found along

the left inferior pulmonary ligament as well as in the left anterior chest wall, just lateral to the internal mammary artery.

2.2.4. CASE 4. W.W. had pain in the left knee for two months. Radiographs of the knee were normal. Chest radiographs demonstrated extensive infiltrates in the right lung. The ^{67}Ga scan revealed abnormal activity throughout the left chest as well as in the distal left femur and proximal left tibia. A ^{18}F bone scan also demonstrated abnormal activity at the latter two sites. At thoracotomy, extensive involvement of the entire right lung by tumor nodules was seen. Biopsy of the proximal left tibia confirmed the presence of tumor at that site as well.

2.2.5. CASE 5. S.T. was found to have an extrapleural mass along the left lateral chest wall on followup chest roentgenograms, eighteen months after radiotherapy for Hodgkin's disease. The lesion was positive on the ^{67}Ga scan. Thoracotomy confirmed the presence of tumor.

2.2.6. CASE 6. J.S. suffered acute spinal cord compression at the level of the third and fourth thoracic vertebrae as the result of histologically confirmed Hodgkin's disease. A ^{67}Ga scan two weeks previously had failed to demonstrate the spinal lesion, although it had demonstrated other tumor sites (Fig. 8).

2.2.7. CASE 7. B.K. developed large right and left cardiophrenic-angle masses, easily seen on the chest radiographs, one year after radiotherapy for Hodgkin's disease (Fig. 9). The ^{67}Ga scan was normal. At thoracotomy, the lesions proved to be tumor masses.

2.2.8. CASE 8. P.M., during routine staging for Hodgkin's disease, underwent left iliac crest bone marrow biopsy, which revealed tumor. The ^{67}Ga scan had been normal in this region.

2.2.9. CASE 9. A ^{67}Ga scan of N.W. failed to demonstrate Hodgkin's disease in the left iliac crest. Biopsy, however, showed the presence of the disease.

2.3 Patient with liver involvement proved by percutaneous needle-biopsy

A ^{67}Ga scan had been performed in only one such case, and was normal. A technetium-99m sulfur colloid scan of this individual, however, demonstrated numerous defects in the liver, substantiating extensive hepatic involvement.

3. DISCUSSION

Gallium-67 scanning is a useful supplementary examination in the management of patients with Hodgkin's disease. It may identify sites for biopsy which might otherwise be missed.

In our series, ^{67}Ga scanning was particularly important as a diagnostic adjunct in patients with Hodgkin's disease in special sites (i.e., sites other than liver, spleen, or lymph nodes). In three cases it was the only noninvasive study that indicated the presence of tumor. Therefore, it was crucial in the management of these patients.

Gallium-67 scanning is probably as reliable an index as radiography of mediastinal involvement by Hodgkin's disease. Certainly the two techniques are complimentary.

Gallium-67 activity accumulates in normal spleens. One would suspect, therefore, that the ^{67}Ga scan of an enlarged, though histologically lymphoma-free spleen might appear abnormal. In fact, four of the five false positive spleen scans occurred in patients with enlarged spleens. However, a ^{67}Ga scan of a spleen that weighed 481 g was normal in spite of the presence of Hodgkin's disease.

Larson and his associates [17] have reported a case in which focal involvement of the liver by Hodgkin's disease was detected on a ^{67}Ga scan as areas of radionuclide activity greater than that of the surrounding normal liver. The reliability of ^{67}Ga scanning in the detection of hepatic Hodgkin's disease cannot be determined from our series. Our only patient with confirmed liver involvement had a normal hepatic ^{67}Ga scan. On technical grounds, however, one would suspect that hepatic Hodgkin's disease might be difficult to detect against the background of the normal accumulation of ^{67}Ga by the liver. This factor probably played an important role in our failure to identify lymphoma in the porta hepatis of any of the seven patients in whom it was present.

Our results for abdominal lymph node sites have been particularly disappointing. This is due to the variable accumulation of ^{67}Ga activity by normal abdominal organs. Activity in the lumen of the colon has been an important source of confusion. Vigorous bowel preparation and serial abdominal scanning have reduced, but not entirely eliminated this problem. Gallium-67 activity normally accumulated by bone and marrow may either obscure the activity of involved lymph nodes adjacent to the spine or result in artifacts suggesting the presence of tumor. For example, the normal lumbar lordosis and the tomographic effect of a focused collimator may produce the artifactitious appearance of a tumor mass over the lower lumbar spine.

In summary, these data support the conclusion that ^{67}Ga scanning is a useful supplementary procedure in the management of patients with Hodgkin's disease. In an occasional case it will be the only noninvasive study that correctly identifies a tumor site. It must be stressed, however, that, since ^{67}Ga may localize in nonneoplastic tissue (e.g., at sites of inflammation), biopsy is required for definitive diagnosis.

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TABLE I. HODGKIN'S DISEASE: ANN ARBOR MODIFICATION OF RYE STAGING SYSTEM (1971)*

Stage I:	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (I_E).
Stage II:	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (II_E). Optional recommendation: Number of node regions involved indicated by subscript (e.g., $II_{(3)}$).
Stage III:	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of extralymphatic organ or site (III_E), or by involvement of the spleen (III_S), or both (III_{SE}).
Stage IV:	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement. The reason for classifying the patient as stage IV should be identified further by defining site by symbols.

*In Hodgkin's disease, all patients are subclassified A or B to indicate the absence or presence, respectively, of (1) unexplained weight loss of more than 10% of their body weight; (2) unexplained fever with temperatures above 38°; (3) night sweats.

TABLE II. OVERALL ACCURACY OF ^{67}Ga SCANNING IN THE STAGING OF HODGKIN'S DISEASE (295 Sites Evaluated)*

	Sites Histologically [†] Positive	Sites Histologically [†] Negative	Per cent Scan Accuracy
Scan positive	45	14	76
Scan negative	22	214	91
Per cent error of scan	33	6	

* In 38 patients undergoing staging laparotomy.

[†] Radiographically positive or negative in case of the mediastinum.

TABLE III. ACCURACY OF ⁶⁷Ga SCANNING BY INDIVIDUAL REGIONS*

III A. 38 Mediastinal Sites				III B. 33 Superficial Lymph Node Sites			
	Radiograph Positive	Radiograph Negative	Per cent Scan Accuracy		Histologically Positive	Histologically Negative	Per cent Scan Accuracy
Scan Positive	21	2	92	Scan Positive	15	1	94
Scan Negative	0	15	100	Scan Negative	4	13	77
% Error of Scan	0	12		% Error of Scan	21	7	
III C. 38 Portal Node Sites				III D. 38 Paraaortic-Mesenteric Regions			
	Histol. Pos.	Histol. Neg.	Per cent Scan Accuracy		Histol. Pos.	Histol. Neg.	Per cent Scan Accuracy
Scan Positive	0	0	-	Scan Positive	5	4	56
Scan Negative	7	31	80	Scan Negative	5	24	83
% Error of Scan	100	0		% Error of Scan	50	14	
III E. 76 Iliac Regions				III F. 38 Spleen Scans			
	Histol. Pos.	Histol. Neg.	Per cent Scan Accuracy		Histologically Positive	Histologically Negative	Per cent Scan Accuracy
Scan Positive	0	2	0	Scan Positive	7	5	58
Scan Negative	5	69	93	Scan Negative	2	24	92
% Error of Scan	100	3		% Error of Scan	22	17	
III G. 38 Liver Scans							
	Histologically Positive	Histologically Negative	Per cent Scan Accuracy		Histologically Positive	Histologically Negative	Per cent Scan Accuracy
Scan Positive	0	0	-	Scan Positive	0	0	-
Scan Negative	0	38	100	Scan Negative	0	38	100
% Error of Scan	-	0		% Error of Scan	-	0	

* For 38 patients undergoing staging laparotomy.

TABLE IV. ACCURACY OF ^{67}Ga SCANNING IN DETECTING HODGKIN'S DISEASE IN 152 INTRA-ABDOMINAL LYMPH NODE SITES (Portal, "Paraaortic-Mesenteric" and Iliac Regions Combined)*

	Sites Histologically Positive	Sites Histologically Negative	Per cent Scan Accuracy
Scan positive	5	6	46
Scan negative	17	124	88
Per cent error of scan	77	5	

* For 38 patients undergoing staging laparotomy.