GALLIUM-67-CITRATE SCANNING FOR THE LOCALIZATION AND STAGING OF LYMPHOMAS

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One-hundred-eight ^{67}Ga-citrate scans were evaluated in Hodgkin's and non-Hodgkin's lymphomas for staging, diagnosis of recurrence, and for determining the results of treatment. Accuracy as confirmed by comparing the scans with pathologic material or roentgenologic and clinical findings was found to be 83%. Known lymph node involvement was diagnosed correctly in 87% but accuracy was only 48% for extranodal areas. Bone lesions were diagnosed correctly in 83% compared with only 48% of lesions of the lungs and liver. Scans were 75% accurate in 28 patients scanned for initial staging. False negatives were present in 12%; recurrent tumor in an area of prior radiation therapy appeared to be the most common cause. There were 5% false positives. Gallium scanning is a useful adjunct to other methods of detecting lymphoma.

The recent unequivocal improvement in the response to treatment of both Hodgkin's disease and other lymphomas is due to the development of better methods of radiation therapy and the introduction of combinations of effective chemotherapeutic agents (*1,2*). The improvement is predicated, however, on accurate staging of the disease prior to selection of therapy. Lymphangiograms revealed a high incidence of unsuspected abdominal lymph node disease (*3*) and bone marrow biopsies have shown superiority over aspirates in defining dissemination to that area in Hodgkin's disease (*4*).

The staging laparotomy (*5*) has proved its value (*6*) in the localization of occult splenic and hepatic disease in both Hodgkin's disease and non-Hodgkin's lymphoma (*7*). The need for such surgery has been questioned by those favoring aggressive radiotherapy for all Stage I, II, and III disease (*8*) and by those concerned about serious infections following splenectomy in children (*9,10*).

The search for an accurate, relatively noninvasive staging technique has recently led to evaluating the precision of scanning with ^{67}Ga-citrate (*11–13*). This method has proved to be a harmless and accurate means of detecting and localizing tumors of many types (*14–19*) and has shown particular avidity for lymphomas (*13*). Its use in the staging of lymphoma, following the response after treatment and confirming recurrence or new areas of involvement with correlation of clinical and anatomical findings in a large group of patients, forms the basis of this report.

METHODS

Carrier-free ^{67}Ga-citrate was obtained from Diagnostic Isotopes, Inc. It has a convenient half-life of 78 hr and decays by electron capture with principal gamma emissions ranging from 93 keV to 388 keV. The average administered dose was 3.0 mCi given intravenously with an estimated total-body radiation dose of less than 1.0 rad (*20*).

Since the normal colonic radiogallium activity imposes considerable difficulty in the interpretation of abdominal scans, each patient was given a combination containing 30 ml of Milk of Magnesia and 5 ml of cascara sagrada every night for three consecutive nights following the i.v. administration of ^{67}Ga-citrate (*21*). The scans were obtained at 72 hr after injection using a rectilinear scanner with high-energy, 5-in focusing collimators. Simultaneous anterior and posterior views were obtained of the neck, chest, abdomen, and pelvis.

One-hundred-eleven patients with various histologic types of lymphoma were referred to the Department of Nuclear Medicine at the Roswell Park Memorial Institute for ^{67}Ga-citrate scanning. A pre-

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TABLE 1. DIAGNOSIS, STAGE, AND PURPOSE OF SCAN FOR 116 ^{67}Ga-CITRATE STUDIES IN LYMPHOMA

	HD*	HL†	DLL‡	NLL‖
Stage at scan				
I	5	5	1	0
II	12	3	2	1
III	16	6	5	0
IV	33	16	10	1
Purpose of scan				
Primary staging	16	7	4	1
Recurrent disease	27	14	5	1
Effect of therapy	23	9	9	0

* Hodgkin's disease.
† Histiocytic lymphoma.
‡ Diffuse lymphocytic lymphoma.
‖ Nodular lymphocytic lymphoma.

liminary report of some of these cases has appeared elsewhere (*22*). There were 60 males and 51 females ranging in age from 5 to 89 years with a median of 40 years. Sixty-two patients had Hodgkin's disease (HD), 29 histiocytic lymphoma (HL), 18 diffuse lymphocytic lymphoma (DLL), and 2 nodular lymphocytic lymphoma (NLL). A total of 118 studies was done on this group; two studies were discarded because of technical inadequacies. Of the remainder, 28 were for staging, 47 for diagnosis of recurrence, and 41 to follow the progress of treatment (Table 1). The complete clinical records of all the patients were reviewed as were all the scans by two of the authors (SA and KLP). X-rays and colloid scans of liver, spleen, and bone were compared when performed.

To determine the accuracy of the procedure, confirmation of the findings on the gallium scans was made primarily by direct pathologic examination of tissue obtained by biopsy, laparotomy, or postmortem examination within 1 month of the scan from areas of positive uptake or from areas suspected of disease but where no abnormality was detected by scanning. If no tissue was available for pathologic examination at the time of the scan, unequivocal x-ray or palpatory evidence of disease was accepted as confirming the scan in patients with previous histologically confirmed lymphoma. Disappearance of a positive area on a subsequent gallium scan after specific antilymphoma therapy was also considered as acceptable confirmation of the scan.

These principles led to the following definitions: a true positive (TP) was an area of abnormal uptake confirmed by direct pathologic, radiologic, or palpatory examination of the area in question and in which there was no evidence of inflammation or infection; a true negative (TN) was an area that showed no abnormal uptake and was confirmed to be free of tumor by other means; a false positive (FP) was an area of abnormal uptake either not confirmed to be tumor by histologic examination or lacking correlation with x-ray on palpatory findings; a false negative (FN) was an area with a lack of abnormal uptake shown to contain tumor by direct examination or by x-ray and palpatory findings.

In 8 of 116 studies, there was insufficient pathologic data or clinical followup for evaluation; therefore only the remaining 108 studies were utilized for analysis.

RESULTS

Lymph node areas. Lymph node uptake was seen in 71 of the 108 scans. When lymph node-bearing tissue was considered alone, there was 87% accuracy in detecting tumor (Table 2). The accuracy in lymphocytic lymphomas seems somewhat better than that for HD or HL. Eleven false negatives and three false positives were seen; the latter all occurred in patients with HL.

Extranodal areas. The uptake of ^{67}Ga by non-lymph node tissues involved with lymphoma appeared to be less predictable than in lymph nodes; only 29 of the 108 scans showed abnormal uptake in visceral organs or bone. Fifty-six studies were performed in patients with known Stage IV disease. There was one false positive and no false negatives among 14 studies obtained in patients known to be free of

TABLE 2. DISTRIBUTION OF ^{67}Ga-CITRATE IN LYMPH NODE-BEARING TISSUE

	Diagnosis											
	HD				HL				LL†			
Area	TP	TN	FP	FN*	TP	TN	FP	FN	TP	TN	FP	FN
Above diaphragm	18	—	—	—	5	—	2	—	5	—	—	—
Below diaphragm	6	—	—	—	7	—	—	—	7	—	—	—
Both regions	14	—	—	—	5	—	1	—	1	—	—	—
No nodal uptake	—	15	—	8	—	6	—	2	—	5	—	1

* TP, true positive; TN, true negative; FP, false positive; FN, false negative.
† Lymphocytic lymphoma.

TABLE 3. DISTRIBUTION OF ^{67}Ga-CITRATE UPTAKE IN VISCERAL AREAS

	Diagnosis											
	HD				HL				LL			
Area	TP	TN	FP	FN	TP	TN	FP	FN	TP	TN	FP	FN
Lung	7	—	1	3	—	—	1	1	—	—	1	—
Bone	5	—	—	1	4	—	—	1	1	—	—	—
Liver	4	—	—	4	—	—	—	1	—	—	—	—
Spleen	—	—	—	1	—	—	—	1	—	—	—	1
Bone marrow	—	—	—	2	—	—	—	1	—	—	—	1
Chest wall	—	—	—	3	—	—	—	1	1	—	—	1
Intestine	—	—	—	1	—	—	—	1	—	—	—	1
Other	2	—	—	—	1	—	—	1	—	—	—	1

visceral disease at the time of the scan. Among the remaining 42 studies, 53 extranodal areas known to contain active disease were evaluated in terms of the number of true and false positives and negatives in a given area (Table 3). The scanning procedure was most sensitive for detecting bone lesions, being 83% accurate. Lung and liver lesions were correctly diagnosed in 48% of the cases. Involvement of the spleen, bone marrow, chest wall, and intestine was missed by the scan in nearly all of the patients. Lymphomatous involvement of the pericardium and paraspinal tissues in two patients with HD and of the uterus in one with HL was diagnosed accurately.

Three false positives occurred in pulmonary tissue. In one case of DLL, a pulmonary abscess was found at autopsy; in one case with HL, the postmortem failed to explain the abnormal uptake. In the remaining patient with HD, a striking uptake involving the entire right lung was noted (Fig. 1). The chest x-ray film showed only a slight haziness at both lung bases and a residual mediastinal mass but no tumor in the right lung. Radiation pneumonitis or a viral infection were postulated as possible causes of the abnormal uptake. A scan done 2½ months later (Fig. 1) when the patient was in relapse showed uptake only in the area of recurrence but none in the right lung.

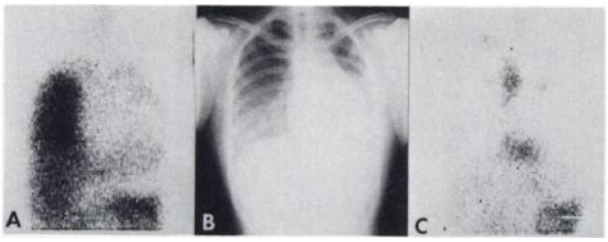

FIG. 1. (A) Scan shows diffuse, intense uptake in right lung with slight uptake at apex and base on left. Chest film (B) shows anterior mediastinal mass with haziness at both bases suggestive of interstitial process. No pulmonary tumor corresponding to area of intense uptake is seen. Scan done 2½ months later (C) shows no uptake in lungs. Mediastinal and hilar uptake is present and was consistent with clinical picture of relapse.

Staging. Gallium scans were carried out in conjunction with staging workups in 16 Hodgkin's and 12 non-Hodgkin's lymphoma patients.

In 13 of the 16 cases with HD, the gallium scan agreed with the other findings in the staging workup, including laparotomy in 3. Of the remaining three in disagreement, the scan failed to show a large mediastinal mass that was shrinking from recent emergency radiotherapy in one; in the second, the scan readily demonstrated a pulmonary lesion but failed to show any activity in involved lymph nodes; in the third, a mediastinal and a chest wall mass failed to show uptake.

In 8 of the 12 cases of non-Hodgkin's lymphoma, the gallium scan agreed with the staging workup, including laparotomy in 2. Of the remaining 4 in disagreement, one underwent laparotomy and was found to have negative nodes, spleen, and liver but a positive bone marrow; a second patient showed abnormal uptake in abdominal nodes but not in a mediastinal mass demonstrated by tomography; a third showed mediastinal node uptake with negative abdominal nodes although these were clearly involved as shown by lymphangiography; the last case showed a mediastinal uptake that had no chest x-ray counterpart. This patient was placed in Stage I, treated with radiation to the involved area only, and did not show any sign of mediastinal disease during followup.

Accuracy. Assessment of the overall accuracy of the scans was made on the basis of pathologic, roentgenologic, and clinical information (e.g., chest films, barium contrast procedures, lymphangiograms, or various combinations of these). The findings from these procedures were in complete agreement with the gallium scan in 71 of the 108 studies. Confirmation by direct pathologic examination was available in 64 studies. Examination of tissue confirming active disease from one area plus radiologic or palpatory findings or both in other areas correlated with the scan completely in the remaining 44.

The accuracy of the scans by diagnostic category

TABLE 4. DISTRIBUTION OF ACCURACY OF 116 ^{67}Ga-CITRATE STUDIES ACCORDING TO DIAGNOSIS

Result	Diagnosis			
	HD	HL	DLL	NLL
True positive	42	18	9	1
True negative	11	4	5	0
False positive	1	3	1	0
False negative	7	4	2	0
Insufficient data	5	1	1	1

is seen in Table 4. The total of true positives and true negatives was 90 of 108 scans for an overall correlation of 83%. The degree of accuracy was 85% for HD, 79% for HL, and that for DLL plus NLL was 83%. The interpretation of the scans was in error in 17%.

An attempt was made to discover the sources of error in those diagnosed incorrectly. Of the five false positives, there was one case of DLL in which the scan indicated a lung abnormality. A pulmonary abscess without associated tumor was found at autopsy. Abnormal uptake appeared in the mediastinum in two cases of HL and in the lung of a third case. In the latter, postmortem examination revealed no pathological findings. Subsequent followup of the remaining two patients has revealed no mediastinal lymphoma; no antitumor therapy has been directed to the mediastinum in either case. The patient with HD and false-positive pulmonary uptake has been described before.

Seven patients with HD showed false negatives. The histologic type was mixed cellularity in three and nodular sclerosing in the other four. All but one of the patients had received radiation therapy from 1 to 6 months prior to the scan at doses from 3,500 to 4,000 rads to the anatomic areas in which relapsing disease was diagnosed. The remaining patient had received chemotherapy 1 week prior to the scan but still had physical and roentgenologic evidence of disease. Three patients with HL and two with DLL had received radiation therapy to the areas of false-negative findings within 6 months of the scan. One patient with HL with a completely negative scan was found to have bone marrow involvement at laparotomy; he had received no prior therapy.

Three patients were categorized as having true-positive scans but showed areas of false negativity. One patient with HD had no nodal uptake but demonstrated lung and liver involvement; she had received prior total nodal irradiation. A second patient with HL had uptake in involved abdominal nodes but mediastinal adenopathy failed to show the tracer. A third patient with DLL showed uptake in the mediastinal nodes but not in abdominal nodes. Neither had received prior therapy.

DISCUSSION

Several early gallium-scanning studies included small numbers of lymphoma patients and demonstrated consistent uptake by these neoplasms (*11–19*). There have been three reports related to gallium scanning in Hodgkin's disease (*23–25*) and a recent report on this procedure in a large series of non-Hodgkin's lypmhomas (*26*). We have scanned 111 lymphoma patients and have accurately diagnosed the location of disease activity in 83% of them. The technique appears to be equally useful in all histologic types.

Uptake in lymph nodes appears to be the most consistent and the accuracy of the scan for detecting lymphoma in these areas was 87%. Kay and McCready reported a similar result in a series of 50 patients with HD (*24*). Johnston, et al (*25*) recently reported a series of 151 untreated patients with HD who underwent gallium scanning as part of a cooperative group study. True positive nodal uptakes were present in 83% of biopsied sites in the neck, 85% in the thorax, 64% in the axilla, and 50% in the abdomen. A similar cooperative study of 168 non-Hodgkin's lymphoma cases reported by Greenlaw, et al (*26*) yielded 53% TP in the neck, 66% in the thorax, 33% in the axilla, and 48% in the abdomen. Our method of reporting accuracy differs from that used by these two groups but we believe the figures to be comparable with the results of the present study. In contrast to our findings, however, Greenlaw's report indicated that the accuracy of the gallium scan in HL was superior to that of lymphocytic lymphosarcoma.

Extranodal uptake of ^{67}Ga-citrate accurately demonstrated tumor when there was bone involvement but precision was less in lung and liver lesions. Several unusual areas of soft-tissue involvement were also demonstrated but in most of these patients involvement was extensive and could easily have been detected by more conventional means.

Twenty-eight cases were studied at the time of initial staging and agreement with standard staging procedures was found in 75%. Gallium scanning is reliable for detecting lymph nodal involvement and gross organ involvement but it is unproven in detecting small foci of lymphoma. Laparotomy studies (*27*) have shown that occult disease may exist in the spleen in 20–50% and in the liver in 19% of patients with HD. Correlation of involvement with organ palpability, serum enzyme levels, and colloid scans of liver and spleen has been poor (*28–30*). Turner, et al (*23*) reported on 20 patients with HD

who underwent gallium scanning prior to staging laparotomy. The scan was correct in identifying tumor location in 79%. No liver or bone involvement was detected and the authors do not mention if any patients had these findings at surgery. Splenic involvement was correctly identified in four of seven scans thought to be positive. The group studies on HD (*25*) and non-Hodgkin's lymphoma (*26*) do not address themselves directly to the problems of the staging laparotomy. Fifty-nine of the HD patients underwent splenectomy, however, and 38 of the spleens contained disease (*25*). Fourteen scans were TP (37%) and 18 (47%) were FN. Of the 21 spleens showing no tumor, 19 scans were accurate in predicting this fact (90% TN). Although our results are similar to those of Turner's group, our series is hampered by the small number of patients undergoing laparotomy, making correlation with the presence of small foci of lymphoma difficult. None of our six patients who underwent splenectomy had splenic involvement and the scans in each case were correct. Splenic involvement was missed, however, in three other cases of diffuse involvement of the spleen in previously treated patients. Prior therapy may interfere with the recognition of ^{67}Ga-citrate tumor uptake in spleens despite the considerable splenic uptake found normally.

It is known that ^{67}Ga-citrate will localize in areas of inflammation (*31*) and this property has recently been proposed as a means of localizing occult sources of infection (*32*). Because of this, errors of interpretation in the form of false positives are likely in cancer patients. We found an incidence of FP of 4.7% in our studies but were unable to explain most of them. This appears to be the experience of the two large cooperative group studies as well (*25,26*).

The appearance of 11 false negatives in our group of lymphoma patients who had received prior irradiation is significant. Prior chemotherapy played a role in another case. It is possible that radiation or drug therapy or both may interrupt the blood supply of the tumor or the intracellular uptake of the radiopharmaceutical (*13*). In our experience, gallium scans have not been reliable in evaluating recurrent disease in previously radiated sites.

We conclude that scanning with ^{67}Ga-citrate is safe and will yield an overall accuracy of approximately 80% in the localization of lymphoma. The gallium scan was in agreement with other methods of staging in 75% of the cases. Its usefulness in those with small foci of disease in the spleen and liver is doubtful and needs further exploration. It appears that gallium scanning did not achieve the accuracy of the staging laparotomy for identification of abdominal involvement but it can serve as a useful adjunct to staging and may be of great value in the location of occult tumor, particularly in lymph nodes or bone.

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