Early Detection of Lymphoma Recurrence with Gallium-67 Scintigraphy

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Early detection of tumor relapse in lymphoma patients is often a difficult diagnostic problem. CT, which detects a mass, often cannot differentiate between fibrosis or relapsed tumor. For this reason, we have studied the value of ^{67}Ga scintigraphy in the diagnosis of tumor recurrence. The sensitivity of ^{67}Ga scintigraphy in the detection of lymphoma recurrence was studied at an average interval of 8.7 mo following treatment in 32 patients who developed recurrent lymphoma. Its specificity was studied in 36 patients with no recurrence who were in continuous clinical remission. At the time of appearance of relapse, the sensitivity of whole-body ^{67}Ga imaging was 95% and the specificity 89%. In 12 events of recurrence in 10 patients, ^{67}Ga scintigraphy was abnormal at sites that later proved to be regions of relapse. In these patients, scintigraphy demonstrated recurrence an average of 6.8 mo before the appearance of clinical symptoms, findings on clinical examination or abnormality on CT or chest x-rays. Gallium-67 scintigraphy, which permits screening of the whole body for recurrence in a single study, was of particular value in evaluating lymphoma recurrence, since 27% of the recurrences were located exclusively in sites different from the original sites of disease. Gallium-67 scintigraphy appears to be a sensitive and specific test for restaging patients with lymphoma recurrence.

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Early diagnosis of recurrence of lymphoma is of value for successful treatment (*1–5*). Diagnosis of relapse is usually assessed by clinical symptoms and laboratory and radiographic findings which occur when the disease has progressed significantly (*6*). Even at recurrence, restaging procedures, such as bone marrow biopsy, chest radiograph and CT, have a low sensitivity of 21%–55%. Only physical examination has an adequate sensitivity of 80% (*6*), but it is limited only to external regions of the body.

In recent years, ^{67}Ga scintigraphy has proven to be of value in the assessment of treatment response of patients with lymphoma (*7–14*). The use of high doses (*15*) and modern SPECT equipment (*7,10*) make ^{67}Ga scintigraphy effective in differentiating uptake in regions with disease from uptake in normal tissue. Gallium-67 scintigraphy is now routinely employed in many centers in the clinical management of lymphoma patients.

The role of ^{67}Ga scintigraphy in the diagnosis of recurrence has not been systematically evaluated, although nine of ten patients who had ^{67}Ga studies in the study by Weeks et al. (*6*) had positive scintigraphy during recurrence. Gallium-67 scintigraphy during follow-up, immediately after treatment, has been used to determine if a patient has achieved complete response or for prediction of survival (*8–13*), but not for diagnosis of recurrence. Gallium-67 scintigraphy's role in the diagnosis of recurrence is the subject of this present study.

MATERIALS AND METHODS

The patients included in this study are part of an ongoing prospective protocol assessing the value of ^{67}Ga scintigraphy in patients with lymphoma. Sixty-eight patients with initially ^{67}Ga-avid tumors, who achieved a complete clinical response after treatment were included in the study. They fulfilled the criteria used to make or exclude the diagnosis of recurrence. Fourteen other patients were excluded for not adhering to the protocol or when not all necessary diagnostic material was available.

Recurrence was diagnosed by abnormal symptoms, abnormal findings on physical examination and abnormal laboratory tests. Indications of recurrence on CT included signs of new disease in initial or new sites of lymphoma or progress of disease when in a residual mass. In two patients, diagnosis of recurrence was based on chest x-rays. All patients had whole-body ^{67}Ga studies. Studies were performed at an average interval of 8.7 mo after treatment in all patients with Hodgkin's and nonHodgkin's lymphoma who had achieved continuous clinical remission. Indications for the evaluation of patients were routine follow-up studies, studies performed when the patients developed symptoms or studies obtained when patients were concerned for some reason and sought medical help.

Thirty-two patients had a clinical relapse on 41 occasions at the time of evaluation, based on a combination of clinical, laboratory and imaging evidence. Forty-one ^{67}Ga studies supplied true-positive and false-negative results, indicating the sensitivity of scin-

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tigraphy. Eighteen of these patients were female and 14 male, with an average age of 38.8 yr (range 7–69 yr). Seventeen patients had Hodgkin's lymphoma (HD) and 15 had nonHodgkin's lymphoma (NHL). In the NHL group, four had high-grade lymphoma, eight had intermediate grade and three had low-grade disease. The criteria used to determine abnormal gallium scans have been previously described in detail elsewhere (*10,13*). Only scans with intense abnormal uptake, clearly separated from normal structures, were considered to be positive studies. Vague symmetrical uptake on both sides of the lower mediastinum in some patients was considered to be nonspecific and was not regarded as representing disease. Diffuse bilateral lung uptake of ^{67}Ga following therapy was also considered nonspecific and not indicative of disease recurrence. Studies were done up to 14 days after injection in order to determine if abdominal uptake was in the intestine or in recurrent disease. The need for meticulous imaging techniques and artifact recognition has been previously discussed (*10,13*). Gallium-67 scans were considered true-positives when they showed one or more abnormal sites in a patient diagnosed by a combination of clinical, laboratory and other imaging criteria to have a recurrence.

Data from 36 patients who remained by clinical, laboratory and radiological criteria in continuous clinical remission at the time of scintigraphy, provided the true-negative and false-positive imaging results indicating specificity. Nineteen of these patients were female and 17 were male, with an average age of 31.3 yr (4–69 yr). Twenty-seven patients had HD and nine had NHL. In the NHL group, five had high-grade, three had intermediate grade and one had a low-grade lymphoma. To enlarge the database for determination of specificity and to include patients with shorter remission than those who did not develop recurrence, we also included results from 11 of 32 patients in the clinical recurrence group, prior to recurrence, during clinical remissions which lasted an average of 14.9 mo. Specificity determinations were therefore based on evaluation of 53 examinations in a total of 47 patients. If several negative ^{67}Ga studies were performed during a continuous clinical remission, they were all considered as one true-negative result.

For scintigraphy, adult patients received 8 mCi (296 MBq) of ^{67}Ga-citrate intravenously; children received 75 μCi (2.77 MBq) per kg body weight. Scintigraphy was performed in all patients at 48 hr and 7 days after injection. When colonic activity was seen after 7 days, subsequent images were obtained with a delay of up to 14 days. Images were performed with a large or very large, rectangular field of view digital SPECT camera or a dual-headed camera (Apex 415 ECT, SP-6HR ECT, Helix, Elscint, Haifa, Israel) with triple energy peaks of 93, 184 and 300 keV and a parallel-hole, medium-energy gallium collimator. For planar scintigraphy, anterior and posterior views were obtained and 500–1000K counts were accumulated for each view. When the dual-headed camera was used, whole-body scanning was done in one pass for 20 min (Fig. 1) at 48 hr and for 26 min at 1 wk. The studies done 1 wk after injection did not include the legs.

SPECT imaging was performed following the planar study. The data acquisition protocol included a 360-degree rotation, with 60 projections 6 degrees apart: 3.5–8 $\times$ 10^6 counts were acquired per study. A 64 $\times$ 64 matrix and a Hanning filter were used. Data were reconstructed using a 32-bit processor (SP-1, Elscint, Haifa, Israel) and tomographic images were obtained in the transaxial, coronal and sagittal planes.

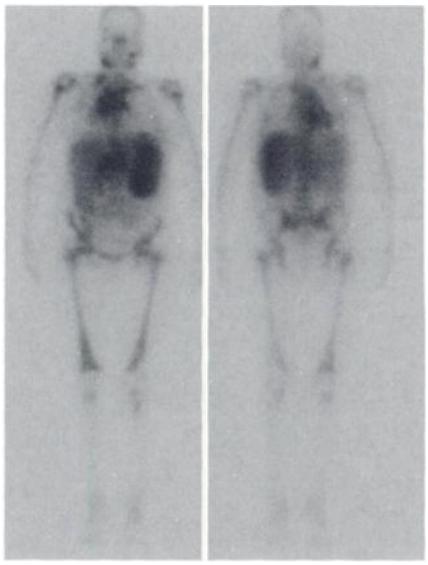

FIGURE 1. A 53-yr-old female with a nonHodgkin's diffuse lymphocytic lymphoma had a relapse after 1 yr of continuous clinical remission. A whole-body scintigraph, obtained in a single pass with a dual-headed camera, shows abnormal uptake in the cervical region bilaterally, right supra- and infraclavicular region, mediastinum on both sides, abdomen, porta hepatis region and mesenteric lymph nodes. There is also diffuse uptake in an enlarged spleen and in both femora.

RESULTS

Thirty-two patients with 41 documented events of recurrence served in the calculation of true-positives and false-negatives. This group had a mean continuous clinical remission period of 23.2 mo (range 2–120 mo). Relapses were in the original site of disease in 12 events (29%), in new sites in 11 events (27%) and were located in both the original and new sites in 18 events (44%). The new sites of disease were diagnosed from clinical and imaging results during routine follow-up. There were 39 true-positive and two false-negative ^{67}Ga studies, yielding a sensitivity of 95%. Gallium-67 scintigraphy did not detect bone marrow involvement in one patient with HD, which was detected by bone marrow aspiration and small intestine involvement in a patient with NHL which was found at surgery. Specificity was determined 53 times in 47 patients in continuous clinical remission by the determination of true-negative and false-positive results. This group had a mean continuous clinical remission period of 24.7 mo (range 3–58 mo). In the patients with complete remission, there were 47 true-negative and six false-positive ^{67}Ga scintigraphic studies, yielding a specificity of 89%. The patients with false-positive ^{67}Ga scans included three with mediastinal uptake, two patients with abdominal uptake and one with axillary uptake.

In 12 events of recurrence occurring in 10 patients (Table 1, Fig. 2), ^{67}Ga scintigraphy was abnormal in the site of disease on an average of 6.8 mo before the appearance of clinical symptoms and abnormalities in other studies. Physical examination, chest x-ray (2 patients) and CT (8 patients) were normal or noncontributory in these patients. In two of the 12 recurrences, the early scintigraphic abnormalities, while unequivocal, were noted only later when the patient was diagnosed as having a recurrence. The

TABLE 1
Clinical Findings and Test Results in Lymphoma Patients When ^{67}Ga Scintigraphy Was Positive Before Other Tests

	Age (yr)	Histology (no. of patients)†	Time to positive Ga (mo)*	Time to diagnosis (mo)‡	Findings when Ga first positive (no. of events)
Ten patients	Mean: 40.7	HD–5 MC–2 NS–3	Mean: 9.8 Range: 2–37	Mean: 16.6 Range: 6–33	Normal physical examination: 12
Twelve events	Range: 20–67	NHL–5 High–1 Intermed.–3 Low–1			Chest x-rays: 2 No. positive: 0 CT: 8 No. positive: 0

*Time of clinical remission to first positive ^{67}Ga scintigraphy.
†Histology: MC = mixed cellularity; NS = nodular sclerosis; high grade = large-cell immunoblastic; intermediate grade, diffuse mixed (one patient), diffuse large (two patients); low grade = follicular mixed.
‡Time of remission after treatment to diagnosis of recurrence.

abnormal sites of disease, diagnosed early by ^{67}Ga scintigraphy, were confirmed later in all patients by physical examination, chest x-ray, CT or a combination of these.

DISCUSSION

After complete remission in lymphoma patients, it is difficult to make an early diagnosis of recurrence. Weeks et al. (*6*) did not find any diagnostic test that could reliably detect recurrence before or at the appearance of clinical symptoms. Even at the time of clinical relapse, the sensitivity of CT in their patients was only 45% for the chest and 55% for the abdomen. Gallium-67 scintigraphy could not be evaluated in Weeks' study because there were not enough patients, but they did find that nine of ten ^{67}Ga studies were positive when this diagnostic procedure was done at clinical relapse. The results of the present study indicate that ^{67}Ga scintigraphy accurately identified lymphoma recurrence in patients with gallium-avid tumors. One must realize, however, that the 85% sensitivity and 98% specificity before treatment (*10*) requires scanning all patients prior to therapy to identify gallium avidity of individual tumors (*8,10,13*). Only patients with ^{67}Ga-avid tumors should be evaluated for recurrence. The 95% sensitivity and 89% specificity of ^{67}Ga achieved in the present study suggest that scintigraphy is a valuable test for the early diagnosis of recurrence.

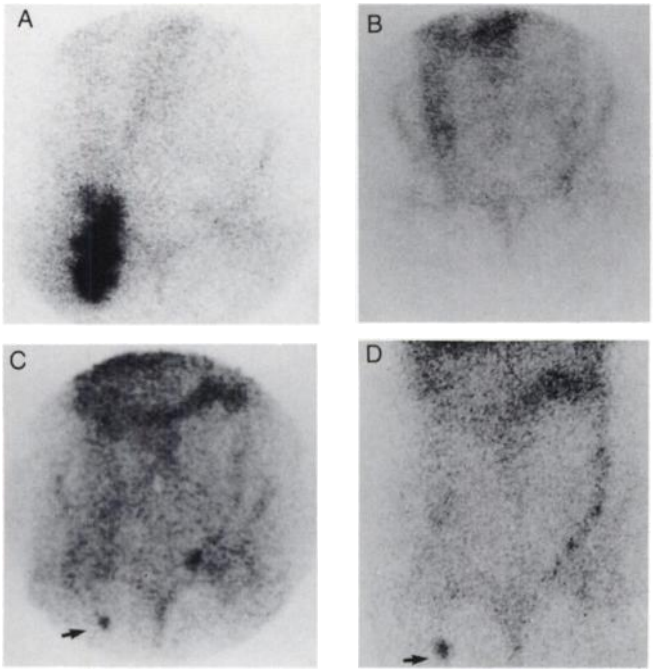

FIGURE 2. A 63-yr-old woman with inguinal nonHodgkin's lymphoma, immunoblastic type. (A) Baseline scintigraph shows markedly increased uptake in the right inguinal region. (B) Normal scintigraph obtained while the patient was in continuous clinical remission. (C) Recurrence (arrow) in the right inguinal region. Palpation and CT were normal and the patient did not have any other evidence of disease. (D) Another study performed 8 mo later shows the same lesion (arrow). The lymph node was now palpated and removed. Histology showed recurrence of the disease.

Since ^{67}Ga is a viability agent (*16*), it is taken up by cancer tissue and not by fibrotic and necrotic masses which may remain at the tumor site when a patient is in continuous clinical remission. On the other hand, CT or chest x-rays may demonstrate a residual mass of nonviable tumor long after the patient has achieved complete remission (*17*). Gallium is taken up in sites where disease recurs and sometimes in nontumoral tissue, hence the 89% specificity.

Whole-body ^{67}Ga scintigraphy should be performed to detect new disease regions (Fig. 1). This is important since 27% of our patients and 25% of the patients in the Weeks et al. study (*6*) relapsed in only new disease regions as compared to primary site involvement. The patients described by Weeks et al. had CT to the region of original disease only. False-negative determinations were made when recurrence occurred at another site in the 25% of patients who did not have CT performed.

Scintigraphy was particularly useful in the early diagnosis of relapse in our patients. It was abnormal in 12 events in 10 patients before the appearance of clinical symptoms,

abnormal physical examination and CT or chest x-ray findings. At that time, tumor load was probably much smaller than at the later stage when relapse was diagnosed. Scintigraphy in these patients became increasingly abnormal when repeat studies were done over time (Fig. 2). The stable, clinical state in these patients was in contrast to abnormal ^{67}Ga scintigraphy. Therapy was not started until the disease state was more advanced and was confirmed by symptoms, physical examination, CT or chest x-rays.

Presently there is no established protocol for the timing of tests for diagnosis of relapse in lymphoma (*6*). Too frequent testing for recurrence may be prohibitively expensive. Gallium-67 whole-body scintigraphy with a modern, dual-headed camera, which allows performance of the test in 20 min (Fig. 1), may yield a high rate of early diagnosis of lymphoma recurrence at an acceptable cost. In the future, early detection could lead to the institution of more effective early therapy.

In conclusion, the results of the present study indicate that ^{67}Ga scintigraphy is a useful test for diagnosing recurrence and that it may diagnose a recurrence even before clinical symptoms or other diagnostic tests. Whole-body planar ^{67}Ga and SPECT scintigraphy should be done on a routine basis in the follow-up of patients who achieve continuous clinical remission after treatment for lymphoma.

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