Gallium-67 Scintigraphy in Untreated and Treated Non-Hodgkin Lymphomas

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One hundred and seventy-four gallium scans of patients with biopsy-proved non-Hodgkin lymphoma were reviewed. When the lymphomas were subdivided into histologic groups, there was a significant difference in detection rates, with 62% of the histiocytic lymphomas being identified, while only 39% of the poorly differentiated lymphocytic lymphomas were detected. There was a high detection rate for lesions in the mediastinum and in extranodal locations. When analyzed with regard to therapy, the detection rate was higher in all histologic subgroups after therapy than before.

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The utility of gallium scanning in patients with Hodgkin's disease has been well established (*1–3*), but patients with non-Hodgkin lymphomas have not been studied as thoroughly. The initial reports stressed a case-by-case evaluation, whereas a site-by-site analysis is necessary to define adequately the utility of gallium scanning in the patient with non-Hodgkin lymphoma.

The literature on non-Hodgkin lymphoma shows somewhat contradictory results in detection rates when site-by-site analysis is made on the basis of histologic subtypes. Reports by McCaffrey et al. (*4*) and Adler et al. (*5*) showed no significant difference among the various histologic types of non-Hodgkin lymphoma, whereas the preliminary report of the Cooperative Group to Study Localization of Radiopharmaceuticals (CGSLR) (*6*), and reports by Levi et al. (*7*) and Horn et al. (*8*), demonstrated significantly greater detection rates for histiocytic lymphoma than for poorly differentiated lymphocytic lymphoma.

This study reports the detection results in a series of treated and untreated patients with non-Hodgkin lymphoma. Analysis is made by histologic type, anatomic site, degree of uptake, and the effect of previous therapy.

MATERIALS AND METHODS

One hundred and seventy-four consecutive Ga-67 scans of patients with histologically proved non-Hodgkin lymphoma were reviewed. Patients were seen at our hospital between 1972 and 1977 and were studied for staging, routine followup, or resolution of clinical problems. All studies were done 48 and 72 hr after the i.v. administration of 3 mCi of carrier-free Ga-67 citrate. Simultaneous anterior and posterior views were obtained on a dual-probe rectilinear scanner with high-energy collimation. Total-body scans were performed with a window spanning 80–440 keV.

All scans were reviewed by two of us (JHT, MLB) without knowledge of the patient's diagnosis or previous therapy. The major nodal sites were recorded—cervical, supraclavicular, axillary, medias-

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tinal, hilar, periaortic, iliac, and inguinal. Extranodal sites of gallium accumulation, or disease sites without gallium localization, also were recorded. Sites were recorded as being positive or negative, and if positive, the degree of uptake was noted in comparison with liver activity as follows: 1+-abnormal with activity less than liver (often felt to be an equivocal lesion); 2+-abnormal with activity equal to liver; and 3+-abnormal with activity greater than liver.

After histologic confirmation of the lymphoma, most patients do not undergo laparotomy or multiple biopsies; therefore, the extent of disease was estimated by the lymphoma board, an interdepartmental group composed of hematologists, pathologists, surgeons, diagnostic radiologists, diagnostic nuclear medicine physicians, and the radiotherapists. Their opinion was based on pathologic, surgical, radiographic, and clinical criteria. Radiographic criteria included plain films, chest radiography, upper g.i. exams, barium enemas, i.v. pyelograms, lymphangiograms, and—when the chest x-ray was normal or equivocal—by hilar tomography. The scan findings were analyzed by major histologic subclassification, prior therapy, and anatomic site. An indeterminate site was one in which proof was unavailable because of technical failure (as in a failed lymphangiogram) or in which the confirming study was not performed (lymphangiography, hilar tomography).

The findings were evaluated and reported as the percentage of correctly classified sites: $\frac{TP + TN}{TS} \times 100$, where TP = true-positive sites, TN = true-negative sites, and TS = total sites. Sensitivity (detection rate) was defined as the percentage of positive sites detected: $\frac{TP}{TP + FN} \times 100$, where FN = false-negative sites. Indeterminate sites were listed as neither true positive nor false negative, but were included in the total sites for determination of correctly classified sites.

Evaluation of two groups of patients for statistically significant differences requires that the groups be independent. Thus, when the relative sensitivity of gallium scanning was evaluated in regard to therapy, data on patients who had a pretreatment and a posttreatment scan (15 cases) were excluded. (The data from the excluded pairs is discussed in the results.)

Chi-squared tests were used in the statistical analysis of all data groups.

RESULTS

The 174 scans of histologically proved non-Hodgkin lymphoma form the basis of this report. The ages of the 162 patients (85 men and 77 women) ranged from 18 to 83 yr, with a median of 58. Ninety-six patients had poorly differentiated lymphocytic lymphoma, 42 had histiocytic lymphoma, 10 had well-differentiated lymphocytic lymphoma, 13 had undifferentiated or unclassified lymphoma, and one had Burkitt's lymphoma. The mode of therapy (chemotherapy or radiation) and the length of time after therapy were not used in the evaluation of the posttreatment group.

In the 174 scans performed, there were 14 nodal sites per patient for a total of 2,436 nodal sites, and based on the findings of the lymphoma board, there were 66 extranodal sites, for a potential 2,502 sites. A total of 1,935 sites were true negative, 301 were false negative, 245 were true positive, and two were false positive. Nineteen sites were indeterminate: three in the periaortic chains in which lymphangiograms had failed technically, nine in the mediastinal area, and seven in the hilar regions in which chest roentgenograms were negative and tomography had not been performed. Two of the patients with mediastinal sites that were positive by gallium scanning and negative by chest roentgenogram developed radiographically positive chest roentgenograms within 1 mo, but for purposes of this study these have been left in the indeterminate grouping.

The overall detection rate was 45%, and the rate of correctly classified sites was 87%. The two false-positive sites were both in a supraclavicular fossa: one in a pretreatment unclassified lymphoma and the other in a posttreatment histiocytic lymphoma.

Patients were histologically classified by a modified Rappaport system (*9,10*), in which the division of poorly differentiated lymphocytic lymphomas into nodular and diffuse disease was not uniformly recorded. There were no statistical differences in detection rates between the group with nodular lesions (52 patients) and the group with diffuse lesions (19 patients). Accordingly, these two groups with poorly differentiated lymphocytic lymphomas were combined.

When the detection rates according to histologic types were analyzed, histiocytic lymphomas had higher positive detection rates than did the other groups (Table 1). The difference in the pretreatment group was significant ($p < 0.01$), while the difference in the posttreatment group was significant but slightly less so ($0.01 < p < 0.05$). When all the patients were considered, the rate of detection of lesions was 62% for histiocytic lymphoma, 39% for poorly differentiated lymphocytic lymphoma, and 40% for all other categories ($p < 0.01$).

When the detection rate was analyzed with regard to therapy, the rate of detection was greater for each category in the posttreatment group; the significance

TABLE 1. SITE-BY-SITE ANALYSIS IN NON-HODGKIN LYMPHOMA

Lesion	Percentage	
	Sensitivity*	Sites correctly classified†
Pretreatment group‡		
Poorly differentiated lymphocytic lymphoma	34	78
Histiocytic lymphoma	59	88
Other	29	87
Total	40	82
Posttreatment group‖		
Poorly differentiated lymphocytic lymphoma	49	91
Histiocytic lymphoma	82	98
Other	52	96
Total	53	93

* Percentage of positive sites detected $= \frac{\text{true positives}}{\text{true positives} + \text{false negatives}} \times 100.$

† $\frac{\text{true positives} + \text{true negatives}}{\text{total sites}} \times 100$; true negatives were only for nodal sites.

‡ Fifty-four poorly differentiated lymphocytic lymphomas, 25 histiocytic lymphomas, six unclassified or undifferentiated lymphomas, and one Burkitt's lymphoma.

‖ Forty-two poorly differentiated lymphocytic lymphomas, 17 histiocytic lymphomas, eight well-differentiated lymphocytic lymphomas, and seven unclassified or undifferentiated lymphomas.

was $p < 0.01$ for the "other" lymphoma category and $0.01 < p < 0.05$ for the poorly differentiated lymphocytic lymphoma, histiocytic lymphoma, and summed pretreatment and summed posttreatment groups.

In the group of 15 patients who had both pretreatment and posttreatment scans, the following results occurred. In the PDLL group, seven patients with positive disease sites pretherapy had no evidence of disease clinically or scintigraphically posttreatment. In two patients with PDLL with pretherapy disease seen scintigraphically, one had a positive scan in the same sites 4 mo later, the other reverted to a normal scan 1 yr posttherapy without evidence of recurrent disease, and then developed disease with positive scan findings the next year. In the histiocytic lymphoma group, five patients went from positive scan results pretherapy to normal scans and no evidence of disease posttherapy. One patient had two false-negative disease sites pretherapy and was felt to have the same two false-negative sites posttherapy.

Table 2 gives the results of detection sensitivity in a site-by-site analysis. Only disease sites (either true positive or false negative) are included in these data. The detection sensitivity in the total pretreatment group was 45% for nodal disease above the diaphragm and 32% below the diaphragm. For the total posttreatment group, the sensitivity was 42% for above the diaphragm and 47% below. When nodal groups were analyzed by histologic subtype, the highest detection rate was in the pretreatment histiocytic lymphoma group, with 68% sensitivity above the diaphragm; the lowest rate was in the poorly differentiated lymphocytic lymphomas, with a detection rate of only 27%. Extranodal disease sites—an important category in the non-Hodgkin lymphomas

TABLE 2. SENSITIVITY IN NON-HODGKIN LYMPHOMA ACCORDING TO LESION SITE

Sites	Poorly differentiated lymphocytic lymphoma		Histiocytic lymphoma		Other		Total	
	pre-treatment	post-treatment	pre-treatment	post-treatment	pre-treatment	post-treatment	pre-treatment	post-treatment
Nodal sites above the diaphragm (cervical, supraclavical, axillary, mediastinal, hilar)	43/126 (34%)	30/74 (41%)	36/53 (68%)	3/6	4/6	5/10	83/185 (45%)	38/90 (42%)
Nodal sites below the diaphragm (periaortic, iliac, inguinal)	30/111 (27%)	22/43 (51%)	16/35 (46%)	1/1	3/8	1/7	49/154 (32%)	24/51 (47%)
Extranodal								
Bone	1/1	1/1	3/5	3/3	0/0	1/1	4/6	5/5
Lung	3/4	5/5	0/0	0/0	0/0	0/0	3/4	5/5
Abdomen†	9/11	5/7	2/5	4/4	0/0	3/3	11/16	12/14
Other‡	1/2	3/5	3/4	3/3	1/2	0/3	5/8	6/8

* Sensitivity $= \frac{\text{true positives}}{\text{true positives} + \text{false negatives}}$.

† Abdominal other than periaortic or inguinal nodal groups; includes mesenteric and gastrointestinal involvement.

‡ Includes orbit, kidney, thyroid, and breast.

TABLE 3. DISTRIBUTION OF NON-HODGKIN LYMPHOMAS ACCORDING TO INTENSITY, HISTOLOGY, AND TREATMENT

Lesion	Degree of uptake* 1+	2+	3+	Total
Pretreatment group				
Poorly differentiated lymphocytic lymphoma	35	29	23	87
Histiocytic lymphoma	10	17	31	58
Total	45	46	54	145
Posttreatment group				
Poorly differentiated lymphocytic lymphoma	15	15	36	66
Histiocytic lymphoma	2	0	12	14
Total	17	15	48	80

* 1+ = abnormal with activity less than liver; 2+ = abnormal with activity equal to liver; and 3+ = abnormal with activity greater than liver.

—showed a high detection rate (77%) overall, and the detection rate also was high for the mediastinum (94%) and hilar nodal areas (95%).

In both the pretreatment and posttreatment groups, there was a higher percentage of 3+ lesions in the histiocytic lymphoma group (Table 3).

DISCUSSION

Some controversy exists regarding the importance of the histologic subclass in non-Hodgkin lymphoma and the effect of previous therapy on the detection sensitivity of gallium scanning. In 1974, the Cooperative Group (CGSLR) (*6*), in a preliminary report on untreated malignant lymphomas, reported that gallium scanning detected more histiocytic lymphomas (70%) than poorly differentiated lymphocytic lymphomas (35%). Levi et al. (*7*) in 1975 and Horn et al. (*8*) in 1976 also reported definite differences in detection rates when histologic subgroups were analyzed. In 1975, Adler et al. (*5*) and in 1976 McCaffrey et al. (*4*), disagreed with those findings and reported no significant difference in detection rate between histiocytic lymphoma and poorly differentiated lymphocytic lymphoma in untreated patients. Our series, the largest from a single institution, supports the conclusion of the preliminary report of the Cooperative Group. The sensitivity of gallium scintigraphy is significantly greater for the histiocytic lymphoma than for both other types of non-Hodgkin lymphoma in both the pretreatment and posttreatment groups.

As proposed by the Cooperative Group (CGSLR) (*6*), one explanation for this histologically dependent sensitivity is that gallium localizes in the lysosomes of macrophages, as described by Swartzendruber et al. (*11*), and therefore should localize better in histiocytic lymphoma. This hypothesis is supported somewhat by the finding of a higher percentage of 3+ lesions in both the pretreatment and the posttreatment histiocytic lymphoma groups. No attempt, however, was made to correlate the degree of uptake with lesion size.

McCaffrey et al. (*4*) reported no difference in detection rate between the pretreatment and posttreatment groups. Cabanillas et al. (*12*) found a good correlation in detection rates between gallium scans and lymphangiograms in non-Hodgkin lymphoma before therapy, but the rate decreased after therapy. In this regard, our series differs with the previously reported series. In all categories, the sensitivity of correctly classified sites was greater after therapy than before, although the statistical significance was borderline. The reasons for this finding are not readily apparent and may be related to the timing of the scans after therapy or to the type of therapy used.

In body areas that are difficult to define by routine studies, such as the mediastinum and the extranodal regions, detection with gallium studies is good. This is true even in poorly differentiated lymphocytic lymphoma—a group in which the overall detection rate is low. Our results suggest that gallium scanning be used routinely for the staging of all histiocytic lymphomas and when poorly differentiated lymphocytic lymphoma is diagnosed with suspected or confirmed extranodal disease. Gallium scans are also worthwhile in suspected or proved recurrent disease.

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