Ga-67 Citrate Imaging in Malignant Lymphoma: Final Report of Cooperative Group

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In a large cooperative study of Ga-67 uptake in non-Hodgkin's malignant lymphoma, 76% of untreated patients showed positive uptake in one or more lesions. The percentage of known individual lesions seen on scan was significantly lower; thus, negative findings at any one site may have much less significance than positive findings. After treatment, the number of lesions seen decreases sharply, but the role of Ga-67 in evaluating response to therapy is uncertain, especially in view of the fairly large number of lesions undetectable before therapy. Histologic type plays a role in Ga-67 uptake. Large lesions are much more effectively detected than small ones. In spite of numerous false-negative results, Ga-67 scanning is a useful method in evaluating the extent of untreated disease and the presence of lesions posttherapy.

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This is the final report of a cooperative study on the localization of Ga-67 in malignant lymphoma undertaken by several investigators in different institutions. Work done in Hodgkin's disease is not included here, having been reported previously (*1,2*). A preliminary publication on malignant lymphoma included results on 168 untreated patients (*3*). We are now bringing together data for all treated and untreated cases, including the previously reported group.

The total series includes 296 studies on untreated and 394 studies on treated patients. The only selection requirement was histologic proof of diagnosis. In these 690 studies, 2,994 sites of special interest were examined for disease. A few patients were studied more than once—i.e., before and after therapy—but no special interpretation has been made of these, and they have been included as separate individual studies.

METHODS

The earlier paper on Hodgkin's disease (*1*) gives details on procedures, which were the same as for the malignant-lymphoma series. For each study, carrier-free Ga-67 citrate was given intravenously in a dose of 0.045–0.05 mCi per kilogram body weight. At 48 or 72 hr, after efforts had been made to empty the colon with laxatives and enemas, each patient was scanned with a rectilinear scanner set to accept gamma energies from 160 to 320 keV. Contrast enhancement and background erase were not used. The results were encoded for computer handling, according to the methods described earlier (*4*).

RESULTS

Table 1 summarizes the total data on which this report is based, including the numbers of studies on treated and untreated patients of the various histologic types. A "study" is a whole-body evaluation with Ga-67 for the presence of disease. A "site" is an area of the body harboring known or suspected disease; inclusion as a site is based upon clinical, radiologic, or radiotracer findings suggesting lymphoma in that specific local area. These findings had to be fairly definite; for example, a location would not be considered as a "site" simply because it contained the lymphatic drainage from a known lesion. Since one patient could have multiple areas of in-

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TABLE 1. CASE STUDIES OF MALIGNANT LYMPHOMA

Cell type	Studies			Sites		
	Untreated	Treated	Total studies	Untreated	Treated	Total sites
Lymphocytic, well differentiated	32	39	71	118	188	306
Lymphocytic, poorly differentiated	79	103	182	473	439	912
Histiocytic	102	154	256	406	580	986
Mixed cell	41	36	77	215	183	398
Undifferentiated	4	10	14	9	28	37
Burkitt's	4	1	5	13	4	17
Giant follicular	0	4	4	0	19	19
Type not specified	34	47	81	71	248	319
Total	296	394	690	1,305	1,689	2,994

volvement, the number of sites is, of course, much greater than the number of patient studies. Obviously, the number of scanned areas bearing lymph nodes was much larger than the number of singled-out "sites" of probable or likely involvement. The method of coding sites has been previously reported (*4*).

Histologic types and treatment. Tables 2 and 3 show the numbers of positive results in untreated and treated patients, classified by histologic type. Studies were recorded as positive if any definite lesion was seen, equivocal if the most suggestive area was doubtful, and negative in the absence of any definite or equivocal lesion. These tables tend, of course, to emphasize the positive and do not bring out the presence of sites negative to scan that may also be present in patients with positive or equivocal studies. There were 65% positive studies for the whole group, 76% for the untreated, and 57% for the treated.

The histiocytic type, represented by substantial numbers, consistently showed a high percentage of positive gallium studies, as much as 89% positive in the untreated cases. Next in avidity for the nuclide were the mixed-cell and poorly differentiated lymphocytic types, ranging from 58 to 70% of the studies. The undifferentiated and Burkitt's lesions were represented by too few cases to draw definite conclusions, but all of the small group of Burkitt's were positive.

Table 4 deals with individual sites as related to histologic types and treatment. The percentages should be read horizontally and apply separately to each treatment category; that is, all untreated sites for any one histologic type add up to 100%, etc. With treatment there was a distinct increase in negative sites in general. The reason that the total number of sites is smaller than in Table 1 is that some sites in radiation-treated patients had not been included in the beam.

Results in individual scan sites as related to diagnostic data and clinical expectations. Table 5 is made up entirely of sites found positive. The vertical

TABLE 2. GENERAL RESULTS OF Ga-67 SCANS IN 296 STUDIES ON PATIENTS WITH UNTREATED MALIGNANT LYMPHOMA

Histologic Type	Positive		Negative		Equivocal	
	No.	%	No.	%	No.	%
Lymphocytic, well differentiated	19	59	11	35	2	6
Lymphocytic, poorly differentiated	58	73	16	21	5	6
Histiocytic	90	89	12	11	0	0
Mixed cell	28	70	12	28	1	2
Undifferentiated	2	50	1	25	1	25
Burkitt's	4	100	0	0	0	0
Type not specified	24	69	10	31	0	0
Total	225	76	62	21	9	3

(No patients with untreated "giant follicular" disease were reported.)

TABLE 3. GENERAL RESULTS OF Ga-67 SCANS IN 394 STUDIES ON PATIENTS WITH TREATED MALIGNANT LYMPHOMA

Histologic type	Positive		Negative		Equivocal	
	No.	%	No.	%	No.	%
Lymphocytic, well differentiated	18	46	17	44	4	10
Lymphocytic, poorly differentiated	59	57	38	37	6	6
Histiocytic	95	62	52	33	7	5
Mixed cell	23	64	13	36	0	0
Undifferentiated	4	40	6	60	0	0
Burkitt's	1	100	0	0	0	0
Giant follicular	4	100	0	0	0	0
Type not specified	22	48	21	46	4	6
Total	226	57	147	37	21	6

TABLE 4. RESULTS OF Ga-67 SCANS BY HISTOLOGIC TYPE IN 2,780 UNTREATED AND TREATED LYMPHOMA DISEASE SITES

	Untreated (296 studies)						Chemo-treated (121 studies)						Radiation-treated (126 studies)						Chemo and radiation treated (86 studies)					
	Pos	%	Neg	%	Eqv	%	Pos	%	Neg	%	Eqv	%	Pos	%	Neg	%	Eqv	%	Pos	%	Neg	%	Eqv	%
Lymphocytic, well differentiated	58	49	56	48	4	3	35	38	53	57	5	5	19	28	45	68	3	4	9	38	15	62	0	0
Lymphocytic, poorly differentiated	192	41	246	52	35	7	59	37	92	59	7	4	52	37	76	55	11	8	23	37	37	60	2	3
Histiocytic	270	67	104	26	32	7	54	42	73	56	3	2	86	46	91	48	12	6	69	38	113	61	1	1
Mixed cell	118	54	85	40	12	6	11	28	27	69	1	3	31	39	44	56	4	5	8	31	18	69	0	0
Undifferentiated	6	67	2	22	1	11	3	19	13	81	0	0	2	40	3	60	0	0	2	29	5	71	0	0
Burkitt's	12	92	1	8	0	0	8	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Giant follicular	0	0	0	0	0	0	0	0	0	0	0	0	8	62	4	30	1	8	6	100	0	0	0	0
Type not specified	42	60	24	34	5	6	6	17	29	80	1	3	29	40	31	43	12	17	23	38	36	59	2	3
Total	708	53	533	40	93	7	176	34	320	63	17	3	227	40	294	52	43	8	140	38	224	61	5	1

columns classify them according to degree of substantiation of the lesion by other means, either shortly before or shortly after the scan study. The data in the horizontal lines indicate the pre-scan clinical opinion about the presence of disease at the site. The percentage figures read horizontally. (See Discussion for comments.)

Among 419 untreated sites explored surgically—excluding nonlymphomatous lesions and equivocal scan results—we found 52% true-positive scans, 42% false-negative scan results, only 2% false-positive scan results, and 4% true-negative scan results. Only 23 of the 419 biopsied lesions did not contain lymphoma; thus the ability of the scan to give true-negative results is not adequately tested. In treated patients subjected to a repeat biopsy, the results relating scan findings to histologic proof were about the same.

Relationship of scan findings to stage of disease, therapy, and symptoms. Table 6 gives results for scans and individual sites, classified vertically as positive, negative, or equivocal, and horizontally according to clinical status and stage of treatment. The percentages, with studies separated from sites, add up vertically. This table gives evidence for the general effectiveness of therapy in converting lesions from positive to negative. The fewest positive studies and sites were in treated patients without symptoms.

Anatomic regions. Table 7 shows the results of analyzing five major lymph-node areas for effectiveness of Ga-67 in detecting lesions there, with and without prior treatment. This is based on "sites" as previously defined. The results, which include 2,780 sites, are expressed as the percentage (read horizontally) in each category; the categories are defined by lymph-node area and treatment status.

Size of lesion. All proved or apparent lesions, treated and untreated, that could be measured by palpation or by radiographic images comprise Table 8. No lesion less than 1 cm in diameter was seen. Above this diameter, detectability by scan increased progressively with increasing size.

Lymphangiography, scans, and surgical findings. Table 9 gives results for 232 abdominal and pelvic sites that were examined by both lymphangiography and scanning. If we make the reckless assumption that all of these sites contained malignant tissue, then the lymphangiograms yielded 149, whereas scans yielded only 91. In 28 cases included but not separately designated in Table 9, surgical exploration yielded proof of lymphoma and in this group

TABLE 5. POSITIVE FINDINGS AT INDIVIDUAL SITES AS RELATED TO DIAGNOSTIC DATA AND CLINICAL EXPECTATIONS IN BOTH UNTREATED AND TREATED GROUPS

Nonradiotracer evidence of tumor before or shortly after scan	Clinician's expectation (before scan) of lesion at site							
	Known		Suspected		Unsuspected		Believed absent	
	No.	%	No.	%	No.	%	No.	%
Proven	250	71	58	17	42	12	0	0
Apparent	247	44	273	49	36	6	4	1
Equivocal	16	10	83	50	65	38	3	2
Local pain	0	0	11	79	2	14	1	7
No evidence	0	0	17	9	128	66	50	25
Surgical exclusion	0	0	3	33	1	11	5	56
Nonmalignant	8	35	7	30	5	22	3	13
After extirpation	1	9	2	18	3	27	5	46
Unknown	0	0	3	9	29	85	2	6
Totals	522	38	457	34	311	23	73	5

the lymphangiogram was superior, yielding 15 positives, 12 negatives, and one equivocal, whereas the gallium scans yielded only 11 positives, 14 negatives, and three equivocals.

DISCUSSION

In spite of the uncertainties and changing practices in classifying malignant lymphomas, there appeared to be considerable uniformity among institutions at the time of this study, and enough differences in gallium uptake among the groups to justify listing the separate histologic types, although we recognize that there was undoubtedly some lack of consistency in histologic classification. Approximately 60% of the cases consisted of only two types, the poorly differentiated lymphocytic and the histiocytic. The overall percentage of positive scans in 296 studies on untreated patients was 76%, with only 3% equivocals. Of those that were negative, we believe that very few, if any, could be explained by total removal of the disease by diagnostic surgery before the scan; thus there were about 20% in which the scan study completely failed to show the disease. Of those categories with adequate numbers of cases, the poorly differentiated lymphocytic and the histiocytic groups had the highest incidence of positive studies. The patients with Burkitt's tumors, although very small in number, were all positive; furthermore, the amount of uptake in tumor was high, yielding scans in which lesions showed extreme contrast with normal tissue; and with no equivocal results. Thus one might be justified in predicting that Ga-67 will be very useful in detecting and evaluating this disease.

From the data on individual *sites*, a somewhat different picture emerges. In these untreated cases, where histologic confirmation is available for specific areas, we find a low percentage of false-positive* scan readings (2%) but a disappointingly large number of false negatives, i.e., confirmed lesions that were not shown by the scan (42%). Thus positive findings are highly significant but negative ones much

TABLE 6. PHASE OF DISEASE, THERAPY, AND SYMPTOMS

Studies	Untreated		Patients undergoing treatment		Early followup		Late followup, with evidence of recurrence		Late followup, without symptoms	
	No.	%	No.	%	No.	%	No.	%	No.	%
Positive	225	76	59	53	34	58	114	72	13	21
Negative	62	21	45	41	23	39	36	23	43	71
Equivocal	9	3	7	6	2	3	8	5	5	8
Total	296		111		59		158		61	
Sites										
Positive	708	53	160	36	75	32	385	49	20	10
Negative	533	40	265	60	145	62	353	45	160	86
Equivocal	93	7	23	4	14	6	37	6	8	4
Total	1,334		448		234		775		188	

TABLE 7. RESULTS BY ANATOMIC REGION IN 2,780 UNTREATED AND TREATED LYMPHOMATOUS DISEASE SITES

	Untreated (296 studies)					Chemo-treated (121 studies)					Radiation-treated (126 studies)					Chemo- and radiation-treated (86 studies)				
	Pos	%	Neg	%	Eqv	%	Pos	%	Neg	%	Eqv	%	Pos	%	Neg	%	Eqv	%	Pos	%	Neg	%	Eqv	%
Neck	160	56	115	40	10	4	27	24	86	75	1	1	42	39	62	56	5	5	15	25	44	73	1	2
Axilla	65	48	64	47	7	5	14	24	44	73	2	3	18	32	37	66	1	2	7	23	23	77	0	0
Thorax	125	71	34	19	18	10	54	51	48	46	3	3	71	63	31	28	10	9	44	56	35	44	0	0
Abdomen and pelvis	226	48	207	44	39	8	55	36	92	59	7	5	58	34	96	56	18	10	46	41	63	56	4	3
Inguinal-femoral	82	46	78	45	15	9	17	27	42	68	3	5	16	27	40	66	4	7	10	28	26	72	0	0
Other	50	56	35	40	4	4	9	50	8	48	1	2	22	40	28	50	5	10	18	35	33	65	0	0
Total	708	53	533	40	93	7	176	34	320	63	17	3	227	40	294	52	43	8	140	38	224	61	5	1

less so. When we compare the results in malignant lymphoma with those in Hodgkin's, we find that the overall detection rate is significantly poorer in the former than in the latter, and that in Hodgkin's there was less variability with histologic type, except for a somewhat reduced uptake in the lymphocyte-predominant category of Hodgkin's.

From the studies on patients with malignant lymphoma who have been treated, we can draw information about the effects of therapy, even though the pretreatment and posttreatment groups are not comprised of the same patients. The previous existence of a lesion in a local area was generally accepted as a justification for considering that area a "site" in a posttreatment evaluation. The average percentage of positive studies falls to 57% (Table 3), showing that in a considerable number of patients all lesions disappeared, or lost their ability to concentrate Ga-67, as a result of therapy. When we analyze these data (Table 4) by dealing with a large number of individual sites, we see again that treatment reduces the number that are positive. However, in the small group of giant-follicular lymphomas, both forms of treatment appear to have been ineffective in reducing uptake. In general, it appears that chemotherapy may be slightly more effective than radiotherapy in converting positives to negatives; this is different from the results with Hodgkin's disease. It might be suggested that some poor results with radiotherapy in either group could be explained by the presence of lesions outside the radiation portal, or, more likely, development of new lesions after therapy. It is puzzling to find in lymphoma that the results of radiation and chemotherapy combined are not as good as those with chemotherapy alone in decreasing the incidence of positive scans. The responses to chemotherapy, as denoted by the lowering of the percentage of positive sites, were especially pronounced in the histiocytic type, and apparently also in the nonspecified and the small group of Burkitt's tumors.

Table 5, rather puzzling but interesting, is comprised entirely of positive sites, and shows how these relate to the physician's opinions and to objective data of other types. Some of the apparent discrepancies may be explained by delays of a few days between the scanning and the other diagnostic procedures. We note that in 28% of the positive sites, disease was clinically unsuspected or believed absent, yet demonstrable on scan. This number, involving a total of 384 sites of which about half had no supporting evidence from other diagnostic tests, may be erroneously high because of false-positive scan results, but in view of the low number of false posi-

TABLE 8. SIZE OF TUMOR DETECTED

Scan results	Largest diameter in cm						
	<1	1	2	3	4	5	>5
Neg. and eqv.	0	69	87	58	38	19	29
Pos.	0	39	83	92	58	43	130
Percentage pos.	0	46	49	61	60	69	81

TABLE 9. RESULTS OF SCAN FINDINGS AND LYMPHANGIOGRAMS IN 232 UNTREATED ABDOMINAL AND PELVIC LYMPH-NODE SITES

Lymphangiograms	Scan findings			Total lymphangiograms per category
	Pos.	Neg.	Eqv.	
Positive	60	79	10	149
Negative	30	35	7	72
Equivocal	1	10	0	11
Total scan findings per category	91	124	17	

tives in the surgically explored group, it appears that the great majority were actual lesions. Thus, the scan calls attention to significant numbers of lesions not otherwise discovered. The results in Table 5 are very similar to those found for Hodgkin's disease; however, local pain appeared a more frequent indication of a lesion in lymphoma than in Hodgkin's.

The results in Table 6 confirm the effectiveness of therapy in generally reducing the number of positive scans. The value of χ^2 for the studies in Table 6 is 78.2. With four degrees of freedom, this shows a very strong association between treatment status and scan findings. Again, as in Hodgkin's disease, the scan is most likely to be negative in the late-followup asymptomatic group but does reveal a significant number of unsuspected disease sites. In the late followup with symptoms, the percentage of positive studies returns almost to the pretreatment level.

In general, this study does not show fully the degree of success achieved with therapy. Many of the scan studies done after treatment had been started were not timed so as to show the maximal degree of improvement. Furthermore, the reduction in size that was shown in many lesions is not reflected in the recorded results.

In considering Table 7, it is important to recall that the listing of a site had to be based on some clinical, historical, radiographic, or radiotracer reason for considering that local area. In general, if we assume that the criteria for determining sites were the same as for Hodgkin's disease, the overall incidence of positive results in untreated cases is lower for lymphoma. In both treated and untreated groups, detection appeared best for the thoracic region and somewhat poorer for axillary, abdomino-pelvic, and inguinal regions.

Table 8 shows that the incidence of positive scan findings increases with the size of the lesion; this is like the situation in Hodgkin's disease, except that in lymphoma detectability continued to increase above the 5-cm diameter.

Table 9 shows a higher incidence of positives by lymphangiography than by scan for abdominal and pelvic disease, and if we assume that there were not many false positives, lymphangiography will be the more sensitive detector of disease in this region. Surgical and histological results, available for only a small number of patients, tend to confirm this impression to some degree.

In malignant lymphoma the histologic type influences Ga-67 uptake to a greater extent than in Hodgkin's disease, the highest incidence of positive results being seen in histiocytic and, probably, Burkitt's forms of lymphoma, the lowest in the small-cell lymphocytic type.

Whereas the Ga-67 scan shows less detection sensitivity in malignant lymphoma than in Hodgkin's disease, it nevertheless provides a valuable, noninvasive method of discovering unknown lesions in both treated and untreated lymphoma patients. Positive findings are highly significant, but negative scan studies are not strong evidence for the absence of disease. Presumably the failure of treatment to make a previously seen lesion become undetectable by gallium scanning is a sign of unsuccessful therapy, although this has not been clearly proven. Many of the general comments about the cooperative study have already been published in the Hodgkin's disease paper (*1*) and will not be repeated here.

FOOTNOTE

* For the purposes of this report we have defined as false positive any site coded as positive and later proved to have no lesion of any kind. There is, of course, another small group of patients (approximately 2% in the untreated group) that have other significant lesions giving positive scan findings.

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3rd ANNUAL WESTERN REGIONAL MEETING THE SOCIETY OF NUCLEAR MEDICINE

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