Gallium-67 Citrate Imaging in Hodgkin's Disease: Final Report of Cooperative Group

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A large cooperative study of Ga-67 uptake in Hodgkin's disease showed that 88% of untreated patients had a positive uptake in one or more lesions. The percent of individual lesions seen on scan, however, was significantly lower; this indicates that negative findings at any one site do not argue strongly against the possibility of a lesion there. After treatment, the number of visualized lesions decreased sharply, but the exact role of Ga-67 in evaluating therapy is still not clear. Of the various histologic types of Hodgkin's disease, there was a high incidence of localization in all except the lymphocyte-predominance type, which showed a slightly lower uptake. No lesions less than 1 cm in diameter were successfully imaged and the size most easily detected was 4 cm in diameter. As expected, the imaging technique was much less successful for abdominal lesions than for those at other sites because of interfering concentration in bowel and liver. Both radiotherapy and chemotherapy tend to reverse the abnormalities seen on scan. The finding of a significant number of unsuspected positive lesions in asymptomatic patients returning for routine followup suggests that this is a distinctly valuable use for Ga-67, allowing early therapy for recurrences.

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This is the final report of the interinstitutional study of the localization of Ga-67 in Hodgkin's disease. An early publication (*1*) summarized partial results of the untreated patients only. We are now bringing together the data for all treated and untreated patients, including the previously reported 151 untreated cases.

These studies were done on 248 untreated and 420 treated patients. The only selection requirement was histologic proof of diagnosis. We have not included every patient with this diagnosis seen at each of the participating institutions; some were omitted because of a shortage of the radiopharmaceutical or for other reasons, but we know of no selection factors that would make this a nonrepresentative group of patients with Hodgkin's disease. In these 668 patients, 3,234 separate sites were examined for disease.

METHODS

The earlier paper (*1*) gives details on methods and procedures. Briefly, for each study, carrier-free Ga-67 citrate was given intravenously in a dose of 45–50 μCi per kg of body weight. At 48 or 72 hr, after efforts had been made to empty the colon with laxatives and/or enema, each patient was scanned with a rectilinear scanner, with a single window set for 160–320 keV. No contrast enhancement or background erase was used. The methods of encoding the results for the computer were described earlier (*1*).

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RESULTS

General for whole group. Table 1 gives a condensed summary of the total data bank on which this report is based. Each area of known or suspected lesion was considered as a "site"; some of the sites were listed solely on the basis of a positive scan. No sites were encoded, however, without some clinical, radiologic, or radiotracer reason for believing involvement likely.

Histologic types and treatment. Tables 2 and 3* give the findings for all 668 patients, divided into untreated and treated categories; they also show the relationships with histologic classification. A patient had a positive scan if any lesion was seen; the result was "negative" in the absence of any positive or equivocal lesion. Questionable scan results in the absence of any positive site were classified as equivocal. These tables emphasize the number of *patients* with *any* positive or equivocal finding, and not the percentages of positives in the total number of individual *sites*. There were 69% positive scans for the total group of patients, 88% for the untreated, and 56% for the treated.

The higher incidence of positive scans in untreated patients is consistent for all histologic types. There was little difference in scan results related to histology except that the lymphocyte-predominance category gave fewer positive scans before, and especially after, treatment than did any of the other groups.

Table 4 deals with individual *sites*, as related to histologic types and treatment. The percentages read horizontally and apply to the treatment categories; that is, all untreated sites for any one histologic type add up to 100%, etc. The sites having received both radiation and chemotherapy are listed twice, once for each type of therapy. The reason why the total number of sites is smaller than in Table 1 is that those lacking clear information about treatment status are omitted. Table 4 shows, in general, lower percentages of positives for individual sites than were seen for overall scans in Tables 2 and 3, indicating that not all the involved sites were positive when some of the lesions in a given patient showed uptake. The relatively low percentage of uptake in the lymphocyte-predominance category is again noted. An additional observation, when individual sites are considered, is concentration in an unusually high percentage of lesions of the lymphocyte-depletion type. Table 4 also suggests that radiotherapy is more effective than chemotherapy in converting sites from positive to negative.

Individual sites. A total of 3,234 sites were evaluated in this study. Table 5 shows the efficiency of

TABLE 1. HODGKIN'S DISEASE CASE STUDIES

Morphology	Clinical Status: Untreated	Treated	Total no. cases	Total sites
Nodular sclerosis	116	196	312	1,602
Mixed cellularity	73	101	174	888
Lymphocyte depletion	10	14	24	117
Lymphocyte predominance	34	23	57	246
Not otherwise specified	15	86	101	381
Total	248	420	668	3,234

TABLE 2. GENERAL RESULTS OF Ga-67 SCANS IN 248 PATIENTS WITH UNTREATED HODGKIN'S DISEASE

Histologic type	Untreated: Positive No.	%	Negative No.	%	Equivocal No.	%
Nodular sclerosis	103	89	7	6	6	5
Mixed cellularity	66	90	6	8	1	1
Lymphocyte depletion	9	90	1	10	0	0
Lymphocyte predominance	27	79	3	9	4	12
Not otherwise specified	15	100	0	0	0	0
Total	220	88	17	7	11	5

TABLE 3. GENERAL RESULTS Ga-67 SCANS IN 420 PATIENTS WITH TREATED HODGKIN'S DISEASE

Histologic type	Treated: Positive No.	%	Negative No.	%	Equivocal No.	%
Nodular sclerosis	111	57	72	37	13	7
Mixed cellularity	53	55	34	30	14	14
Lymphocyte depletion	7	50	4	29	3	21
Lymphocyte predominance	9	39	11	48	3	13
Not otherwise specified	58	67	25	29	3	4
Total	238	58	146	34	36	8

* In Tables 2, 3, and 5 the percentages refer to the categories at the left-hand column of each portion of the chart and should total 100% along any horizontal line. Viewed vertically, of course, the percentages do not add up to 100%, but they are useful for comparison of uptake trends in various groups of cases.

TABLE 4. RESULTS OF Ga-67 SCANS BY HISTOLOGIC TYPE IN UNTREATED AND TREATED HODGKIN'S DISEASE SITES (2,587)

	Positive scans						Negative scans						Equivocal Scans					
	Untreated		Chemo-treated		Radiation treated		Untreated		Chemo-treated		Radiation treated		Untreated		Chemo-treated		Radiation treated	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Nodular sclerosis	401	(60)	47	(32)	88	(18)	210	(30)	100	(66)	403	(80)	69	(10)	3	(2)	8	(2)
Mixed cellularity	202	(55)	25	(21)	36	(20)	138	(37)	64	(33)	127	(70)	31	(8)	31	(26)	13	(10)
Lymphocyte depletion	30	(70)	9	(45)	9	(33)	11	(25)	11	(55)	18	(67)	2	(2)	0	(0)	0	(0)
Lymphocyte predominance	68	(42)	3	(30)	7	(13)	75	(48)	7	(70)	44	(80)	16	(10)	0	(0)	5	(7)
Not otherwise specified	32	(59)	36	(44)	43	(30)	17	(31)	45	(56)	88	(64)	6	(10)	0	(0)	8	(6)
Total	733		120		183		451		227		680		124		34		34	

TABLE 5. RESULTS AT LOCAL SITES SHOWING RELATION TO TREATMENT AND PROOF OR DISPROOF OF DISEASE

Evidence of disease at sites	Untreated						Chemotreated						Radiation-Treated					
	Pos.	%	Neg.	%	Eqv.	%	Pos.	%	Neg.	%	Eqv.	%	Pos.	%	Neg.	%	Eqv.	%
Proven at surgery	224	63	106	30	24	7	88	38	127	55	17	7	28	31	52	58	9	10
Apparent	266	75	70	20	17	5	247	57	176	40	13	3	77	59	51	39	2	2
Suspected	68	69	28	28	3	3	83	50	67	41	15	9	12	—	29	—	2	—
Total	558	69	204	25	44	5	418	50	370	44	45	5	117	45	132	50	13	5
Tumor excluded at surgery	15	9	128	74	29	17	5	9	46	84	4	7	3		2			
Nonmalignant lesion at site	3		2		4		15		4				5					

gallium scanning if we consider the total number of lesions as proven by surgery, apparent by other criteria, or suspected.

The percentages of true-positive and false-negative identification by scan were obtained by considering only the relatively small number of surgically explored sites. Among the untreated patients, of 239 sites examined subsequently at surgery, there were 15 not confirming the lesion, giving a false-positive† rate of 6%; there were three nonmalignant lesions that were positive on scan. Among the chemo-treated patients the false-positive rate was 5%; and in addition, 15 nonmalignant lesions showing a positive scan were identified. Among the smaller group of radiation-treated patients the false-positive rate was just below 3%, and five nonmalignant lesions giving positive scans were found.

Positive findings at individual sites as related to diagnostic data and clinical expectations. Table 6 gives sites with positive scans, classified in the vertical column 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 whether or not there was any clinical knowledge of the lesion before the scan. (See comments under Discussion.)

Relationship to stage of disease, therapy, and symptoms. Table 7 gives additional evidence that therapy, both radiation and chemical, tends to convert positive findings to negative, sometimes even during the course of treatment. At the point of early followup, the lower percentage of positive *sites* than of positive *scans* is probably explained by the fact that radiotherapy is directed to specific known sites, whereas a new, untreated focus of activity can account for a positive scan. The lowest incidence of

† For the purposes of this report we have defined as a false positive any area coded as positive and later proved to have no significant lesion of any kind. We have listed separately the instances in which a nonmalignant tumor, abscess, or some other lesion accounted for the positive scan.

TABLE 6. POSITIVE FINDINGS AT INDIVIDUAL SITES AS RELATED TO DIAGNOSTIC DATA AND CLINICAL EXPECTATIONS

Nonradiotracer evidence for lesion (before or shortly after scan)	Clinician's Expectation of Lesion at Site Before Scan							
	Known		Suspected		Unsuspected		Believed absent	
	No.	%	No.	%	No.	%	No.	%
Proven	224	67	55	16	45	13	11	3
Apparent	234	42	286	51	39	7	1	0
Suspected	18	11	83	53	52	33	4	3
Local pain	0	0	7	47	7	47	1	7
No evidence	1	0	17	8	160	77	29	14
Surgical exclusion	2	10	2	10	12	60	4	20
Nonmalignant lesion	8	44	5	28	4	22	1	6
After extirpation	2	15	0	0	2	15	9	69
Unknown	0	0	3	8	30	81	4	11
Totals	489	36	458	34	351	26	64	5

TABLE 7. PHASE OF DISEASE, THERAPY, AND SYMPTOMS

Scans	Untreated		Patient under treatment		Early followup		Late followup with evidence of recurrence		Late followup without symptoms	
Positive	221	(89%)	32	(50%)	25	(51%)	142	(74%)	26	(26%)
Negative	16	(7%)	29	(46%)	16	(32%)	36	(19%)	63	(63%)
Equivocal	11	(4%)	3	(4%)	8	(17%)	15	(7%)	11	(11%)
Total	248		64		49		193		100	
Sites										
Positive	733	(56%)	88	(29%)	50	(20%)	424	(44%)	57	(16%)
Negative	451	(35%)	202	(64%)	179	(71%)	491	(51%)	181	(79%)
Equivocal	124	(9%)	22	(7%)	19	(9%)	58	(5%)	24	(5%)
Total	1,308		312		248		973		363	

TABLE 8. RESULTS BY ANATOMIC REGION, IN UNTREATED AND TREATED LESIONS*

	% Positive Scans			% Negative Scans		
	Untreated	Chemo-treated	Radiation-treated	Untreated	Chemo-treated	Radiation-treated
Neck	80	40	44	17	55	54
Axilla	36	48	55	29	43	35
Thorax	90	64	47	6	33	51
Abdomen	48	47	33	43	66	67
Inguinal–femoral	47	36	25	51	55	50

* Based on a total of 3,234 sites studied in 668 cases.

positive Ga-67 scans was seen in the late followup of treated patients who had no symptoms. The false-positive rates were lower in the chemotreated (8%) than in the radiation-treated (13%) sites, and the difference was more pronounced (4% compared with 14%) in the thoracic region.

Anatomic regions. Five major anatomic regions bearing lymph nodes were analyzed for reliability of the Ga-67 scan, using only those areas that qualified as "sites" according to the previous definition. Table 8 shows the results in untreated and treated cases. The low percentage of positive scans in the

abdominal region is notable; there is also a 15% incidence of false-positive results in that anatomic location. The diagnostic value of Ga-67 imaging of untreated thoracic (mediastinal) and cervical lesions is confirmed.

Size of lesion. Information on the relationship of size of lesion to percentage of positive scans is presented in Table 9, which shows the results in 544 lesions as a function of size. This included all proved or apparent lesions that could be measured, either by x-ray image or by direct palpation. Both treated and untreated patients were included. No discrete lesion less than 1 cm in its greatest dimension was found in any of the patients by any methods, but it cannot be concluded that a smaller lesion could not possibly be seen by scanning. The tendency toward a linear relationship between size of the lesions (up to 5 cm diam.) and detectability by scanning with Ga-67 is demonstrated.

Lymphangiography. In 261 untreated sites (223 abdominal, 38 inguinal–femoral) with proved, apparent, or suspected involvement, lymphangiograms detected 95, and scans detected 89. Lymphangiograms showed the lesion in 42 instances when gallium failed. In 39, the scan located the site when the lymphangiogram failed. Of 167 chemotreated sites, defined by the same criteria (141 abdominal, 26 inguinal–femoral), the lymphangiogram detected 77 and the scan 46. In 46 instances the lymphangiogram found the site, and gallium did not; gallium gave successful localization in 15 instances when lymphangiogram did not. Of 33 radiation-treated lesions, again defined by the same criteria (30 abdominal, 3 inguinal–femoral), the lymphangiogram detected 18, and scans, 7. In 12 instances the lymphangiogram located the site and gallium did not; in two the site was found by gallium but not by the lymphangiogram.

Among the untreated abdominal sites there were 149 that were explored surgically, so that definitive information on the presence or absence of Hodgkin's lesions was available. The results are shown in Table 10.

TABLE 9. SIZE OF TUMOR DETECTED

Scan results	Less than 1	Largest dimension (cm) 1	2	3	4	5	Greater than 5
Negative	0	53	59	38	13	5	23
Positive	0	35	67	68	32	44	80
Equivocal	0	10	4	6	0	0	7
Total	0	98	130	112	45	49	110
% positive	0	36	52	61	71	90	73

TABLE 10. UNTREATED ABDOMINAL LYMPH-NODE SITES SURGICALLY EXPLORED

	Lymphangiograms		Scans	
True positive	29	(20%)	37	(25%)
False positive	12	(8%)	7	(5%)
True negative	60	(40%)	57	(38%)
False negative	35	(23%)	23	(15%)
All equivocals	13	(9%)	25	(17%)
Total	149		149	

DISCUSSION

Hodgkin's disease is the condition that led to the recognition of the usefulness of Ga-67 citrate in imaging soft-tissue tumors. Considerable experience has been gained with this disease, and in the literature there are many reports indicating a high degree of usefulness of the nuclide in this group of patients. No effort has been made to present a literature review with this present paper. The advantage of the study reported here is a relatively large number of patients, all studied by the same protocol. The disadvantage is that although the study was very carefully planned, the method of encoding the data leaves certain facets inadequately covered. Particularly lacking are data on patients who received multiple sequential studies after therapy; such information might help us evaluate the effectiveness of treatment as indicated by sequential changes in Ga-67 imaging.

Information in our study indicates the significance of histologic classification in relation to Ga-67 uptake; almost 90% of untreated patients with all histologic types except lymphocyte predominance had at least one positive lesion on scanning, while for the latter type, the value was 76% (Table 2; further data in other tables).

With treatment the positive results for most types fell to 50–57% while those for lymphocyte predominance were reduced to 39%. These figures indicate that chemotherapy and radiation therapy impair Ga-67 concentration by Hodgkin's lesions. Radiotherapy appears more effective than chemotherapy (Table 4), irrespective of histologic type.

In Table 5 we have considered proven, apparent, and suspected lesions and have given results for them separately and added together. We believe that almost all of the "apparent" lesions except those in the abdominal area would have proved positive on biopsy, and this would probably be true also for a large share of the "suspected" sites.

Table 6 appears to be somewhat unsatisfactory because the clinician's expectation of the presence or absence of a local lesion at the time of scan (hori-

zontal entries) is sometimes peculiarly inconsistent with the other evidences for disease (vertical column). Much of this discrepancy is due to variations of timing and recording of the other diagnostic procedures in relation to the scans. The striking finding, however, is that the scans revealed a significant number of lesions not suspected or shown by other means. Although a majority of these were never histologically confirmed at the local site, and it is impossible to determine the incidence of false positives in the group, most were undoubtedly Hodgkin's lesions, and the scan was often the basis for their treatment with radiotherapy.

Therapy is known to convert many positive lesions to negative. Table 7 confirms this, but we have not attempted to separate types of therapy and exact timing. The value of the procedure as a followup measure is brought out. In patients with symptoms or other evidence of recurrence, about three-fourths may be expected to have positive scan findings, and in an important group of asymptomatic patients, unsuspected lesions may be discovered.

Table 8 shows that the success rate for showing Hodgkin's lesions with Ga-67 varies for different anatomic sites. As has been shown by other investigators, the reliability is particularly good for neck and thorax. It is clear that the abdominal region presents the most difficulties, with many definite lesions missed and a fair number of sites labeled positive or equivocal but proving later to be tumor free. This was also the region having the largest number of significant but non-Hodgkin's lesions seen on scan. The problem of the abdominal region involves sorting out Hodgkin's lesions, other types of disease, normal uptake in liver, spleen, feces, and sometimes sites of postoperative inflammation, i.e., after splenectomy.

It is surprising that the axilla is the region with the lowest percentage of positive scans in untreated cases. If we assume that most of the "apparent" lesions were truly Hodgkin's, then it is notable that they were not more successfully visualized, since this is a region of the body usually easily scanned without much interference from overlying tissues. We have no explanation for the recorded increase in positive scans in this region after treatment.

The relatively low percentage of positives in the inguinal–femoral region is influenced by quite a number of apparent lesions; a significant share of these sites may have been free of Hodgkin's since nonspecific adenopathy is known to be frequent in this region. Furthermore, the problems of bone lesions and bowel uptake may have confused the picture there at times.

A tumor's size has been a factor in its detectability on Ga-67 scan (Table 8). No tumors were recorded under 1 cm in diameter by any method of detection. At the 1-cm size, 36% gave a positive scan. There is almost a linear increase in detectability with increase in diameter of the lesions. In lesions over 5 cm in diameter, however, the percent of positive gallium scans decreases. We do not know why the largest lesions showed this lower percentage of positives, but it could possibly be explained by poor blood supply.

The comparisons between scans and lymphangiograms (Table 10) shows that the two methods are approximately comparable in detecting untreated disease sites. When the two techniques are combined, results do not necessarily coincide; more lesions and more false positives will be reported. The scan appears to miss fewer lesions than the lymphangiogram, but yields a slightly higher incidence of equivocal results. Radiotherapeutic reversal of positive lymph-node sites to negative is more commonly shown in scans than by lymphangiography.

The performance of the study provided a valuable experience for those participating and had some subsidiary benefits, including an increased awareness of the subjectivity of image interpretation. On the other hand, the effort proved more cumbersome and time-consuming than had been anticipated. There are particular difficulties in performing the diagnostic procedures and reporting interpretations of images according to a uniform protocol.

The data bank that is being stored at the Medical and Health Sciences Division of Oak Ridge Associated Universities contains more information than was thought practical to present in this publication. Further analyses of the information as it now exists could be made. To further explore certain additional questions, it is necessary to contact the participating institutions for clarification and augmentation in selected cases, as well as for followup information.

The data bank is available for comparison of other diagnostic radiopharmaceutical agents with Ga-67 citrate.

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