# $^{67}$Ga-CITRATE IMAGING IN UNTREATED MALIGNANT LYMPHOMA: PRELIMINARY REPORT OF COOPERATIVE GROUP

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***An interinstitutional cooperative study has been undertaken to evalute $^{67}$Ga as a tumor-localizing agent. A uniform protocol and computer handling of data have been used. In 167 cases of previously untreated lymphoma (other than Hodgkin's disease) scanned with $^{67}$Ga, approximately 78% had one or more positive sites demonstrated on scan. Of histologically proven sites, 51% had a positive scan and with those sites apparent or suspected but not biopsied, 54% were positive. Thus a negative scan does not exclude the presence of disease. A low "false-positive" rate was encountered; if a lesion is demonstrated by scan, it is highly likely that disease is present. Disease, unsuspected or believed absent, was first known at the time of scan in 28 sites. An additional 42 positive scan sites as yet unconfirmed by other evidence may also represent lesions discovered de novo by $^{67}$Ga. The percent of positive scans is highest in the thorax. Histiocytic types, including mixed cell types, of lymphoma have higher rates of positive scans than lymphocytic types. Overall, the rate of positive scans is lower in lymphoma than in Hodgkin's disease.***

This publication is a companion to the preceding one in this journal which deals with gallium citrate scanning of Hodgkin's disease. That paper gives information on the background of $^{67}$Ga as a scanning agent (*1–7*) and also describes the formation of the Cooperative Group to Study Localization of Radiopharmaceuticals (*8,9*).

We have systematically evaluated 168 cases of untreated non-Hodgkin's lymphoma using $^{67}$Ga-citrate. Standardized data-encoding forms were used for recording clinically significant factors. Scan interpretations for sites of pertinence were recorded as follows:

0. Negative—no abnormal focus of activity;
1. Positive—definite abnormal focus of activity at site;
2. Uncertain—uncertain whether degree of concentration is significant;
3. Uncertain—definite increased activity which may be physiologic organ uptake;
4. Uncertain—uncertainty nonspecific.

Details concerning the radiopharmaceutical, instrumentation, and physicians' interpretation were identified in the preceding paper on Hodgkin's disease and were the same for this study.

## RESULTS

**General.** Of the 168 previously untreated patients with lymphoma forming the basis for this report, 133 (78%) yielded one or more positive sites on scan and about 5% had one or more equivocal sites recorded (Table 1). As expected, one finds a lower percent of positive scans on examining individual sites.

Of the 270 histologically proven sites, 51% gave a positive image reading (Table 2). Of 444 additional sites not proven histologically but apparent or suspected, we found 53% on scan. Of 276 positive scan sites which were subsequently examined at surgery, three "false-positive" sites appeared on scan and, in addition, three other sites in which tumor had been excluded at surgery had been seen on scan as equivocal. A total of 68 sites were interpreted

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**TABLE 1. RESULTS OF $^{67}$Ga SCAN IN CASES OF UNTREATED MALIGNANT LYMPHOMA (TO APRIL 10, 1973)**

| Evidence of disease at sites | Pos | Neg | Eqv |
|---|---|---|---|
| Lymphocytic, well-differentiated | 10 | 2 | 1 |
| Lymphocytic, poorly differentiated | 33 | 11 | 6 |
| Mixed cell | 17 | 3 | 1 |
| Histiocytic | 55 | 3 | 0 |
| Not otherwise specified | 14 | 6 | 0 |
| Undifferentiated, pleomorphic type | 2 | 1 | 1 |
| Undifferentiated, Burkitt's type | 2 | 0 | 0 |
| Totals | 133 | 26 | 9 |

**TABLE 2. SCANS OF $^{67}$Ga IN UNTREATED MALIGNANT LYMPHOMA SITES (TO APRIL 10, 1973)**

| Evidence of disease at sites | Scan interpretation | | |
|---|---|---|---|
| | Pos | Neg | Eqv |
| Proven at surgery | 139 | 115 | 16 |
| Apparent | 199 | 158 | 17 |
| Suspected | 35 | 19 | 16 |
| Totals | 373 | 292 | 49 |
| Tumor excluded at surgery | 3 | | 3 |
| Nonmalignant lesion at site | 2 | | |
| No evidence of tumor | 42 | | 16 |
| Extirpated at excisional biopsy | 1 | | |
| Totals | 48 | | 19 |

as equivocal on scan; 16 were confirmed at surgery and an additional 33 presented clinical evidence apparent or suspected. The other equivocal sites noted on scans with little or no evidence indicating a lesion remain truly equivocal for the present.

**Anatomic regions.** The five major lymph node-bearing regions were analyzed for the diagnostic reliability of the $^{67}$Ga scan as follows: neck, thorax, axilla, abdomen, pelvis, and inguinal-femoral areas (Table 3). In the neck 53% of the lesions proved histologically gave positive scans; an additional 104 apparent or suspected lesions, not surgically verified, yielded 55% positive scans. In the thorax seven of nine proved lesions yielded positive scans; 66% of apparent or suspected lesions were positive. In the axilla, only 6 of 18 proved lesions appeared on scan but 65% of apparent or suspected lesions gave positive results. The abdomen yielded 48% proven positive sites and with apparent or suspected lesions 49% were shown on scan. The inguinal-femoral area had 15 of 27 proven lesions shown on scan but only 38% of apparent or suspected lesions, not surgically confirmed, gave positive results.

**Histology.** In examining untreated cases of lymphoma according to histologic types (Table 4) in well-differentiated lymphocytic lymphoma, we found six of seven positive scans in sites histologically proven; 18 of 22 apparent or suspected sites were positive. Sites of poorly differentiated lymphocytic lymphoma histologically proven gave only 31% positive results; 36% of apparent or suspected sites were positive on scan.

In contrast, sites of mixed cell (histiocytic-lymphocytic) lymphoma, histologically verified, were 53% positive; those apparent or suspected gave 60% positive results. Even higher percentages were seen in verified histiocytic type lymphoma (reticulum cell sarcoma) with a 71% incidence of proven positive scans and similarly a 70% incidence of positive scans at apparent or suspected sites.

The data on cases of not otherwise specified (NOS) type and undifferentiated types is too sparse for firm conclusions but average over 50% positive scans.

**Unsuspected sites found first by scan.** Of 634 sites either proven at surgery or apparent, 65 were either unsuspected or believed absent at the time of the scan and 28 of these gave positive scan results. In

**TABLE 3. RESULTS OF $^{67}$Ga SCANS BY ANATOMIC REGION IN UNTREATED MALIGNANT LYMPHOMA SITES (TO APRIL 10, 1973)**

| Evidence of disease at sites | Neck | | | Thorax | | | Axilla | | | Abdomen-pelvis | | | Inguinal-femoral | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pos | Neg | Eqv | Pos | Neg | Eqv | Pos | Neg | Eqv | Pos | Neg | Eqv | Pos | Neg | Eqv |
| Proven at surgery | 34 | 28 | 2 | 7 | 2 | 0 | 6 | 12 | 0 | 60 | 54 | 12 | 15 | 11 | 1 |
| Apparent | 49 | 41 | 4 | 43 | 11 | 3 | 24 | 28 | 2 | 46 | 49 | 4 | 20 | 26 | 4 |
| Suspected | 8 | 1 | 1 | 5 | 4 | 7 | 1 | 3 | 2 | 18 | 6 | 5 | 3 | 3 | 4 |
| Totals | 91 | 70 | 7 | 55 | 17 | 10 | 31 | 43 | 4 | 124 | 109 | 21 | 38 | 40 | 9 |
| Tumor excluded at surgery | | | | | | | | | | 2 | | 3 | | | |
| Nonmalignant lesion at site | | | | 1 | | | | | | 1 | | | | | |

**TABLE 4. RESULTS OF $^{67}$Ga SCAN BY HISTOLOGIC TYPE VERSUS OTHER EVIDENCE OF DISEASE IN SITES OF UNTREATED MALIGNANT LYMPHOMA (TO APRIL 10, 1973)**

| Evidence of disease at sites | Lymphocytic well-differentiated | | | Lymphocytic poorly-differentiated | | | Mixed cell | | | Histiocytic | | | Not otherwise specified (NOS) | | | Undifferentiated (pleomorphic) | | | Undifferentiated Burkitt's type | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pos | Neg | Eqv | Pos | Neg | Eqv | Pos | Neg | Eqv | Pos | Neg | Eqv | Pos | Neg | Eqv | Pos | Neg | Eqv | Pos | Neg | Eqv |
| Proven at surgery | 6 | 7 | 0 | 31 | 61 | 9 | 28 | 23 | 2 | 54 | 17 | 5 | 13 | 6 | 0 | 2 | 1 | 0 | 5 | 0 | 0 |
| Apparent | 15 | 3 | 0 | 60 | 100 | 7 | 39 | 18 | 5 | 70 | 19 | 5 | 13 | 18 | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| Suspected | 3 | 1 | 0 | 14 | 5 | 7 | 6 | 2 | 0 | 7 | 6 | 3 | 3 | 5 | 6 | 0 | 0 | 0 | 2 | 0 | 0 |
| Totals | 24 | 11 | 0 | 105 | 166 | 23 | 73 | 43 | 7 | 131 | 42 | 13 | 29 | 29 | 6 | 2 | 1 | 0 | 9 | 0 | 0 |
| Tumor excluded at surgery | | | | 2 | | | | | 1 | 1 | | 2 | | | | | | | | | |
| Nonmalignant lesions at site | | | | 1 | | | | | | 1 | | | | | | | | | | | |

42 sites recorded as positive on scan, no other evidence of neoplasm was found by the various means of assessment. Such sites may well represent additional new found lesions, still cryptic to conventional methods. Passage of time, repeat scans, and careful followup may clarify this finding. Tabulations failed to show that any particular anatomic region or histologic type of neoplasm gave a higher yield of these unexplained positive scans.

## DISCUSSION

It is interesting to compare these results in lymphoma with those obtained in Hodgkin's disease. Whereas the ability of $^{67}$Ga to localize one or more lesions in a given case is still impressively high (79%), the rate of positive scans in individual sites is less striking: overall 53% in lymphoma compared with 65% in Hodgkin's disease (*10*). Since the mechanism of localization is not yet clearly understood, no ready explanation is at hand. Clearly, though, the rate of positive scans does somehow depend in part on the histologic type, ranging from 36% in proven, apparent, or suspected lesions of poorly differentiated lymphocytic type to 70% in histiocytic type. One explanation may come from the findings of Swartzendruber, et al (*11*); the highest uptake of $^{67}$Ga at the ultrastructural level in animal tissues is within lysosomes of macrophages. Thus it is noteworthy that histiocytic type of lymphoma has the highest rate of positive scans. This point has not been verified in patients since the test dose is far lower than that needed for detection with microscopic autoradiography.

The incidence of negative scans in sites where tumor was found at surgery may be attributable to small size, failure of the tumor to concentrate the nuclide adequately because of low uptake per gram, adjacent tumor sites not resolved by the instrumentation, or complete removal of tumor by biopsy. Observers sometimes have also seen $^{67}$Ga in healing wounds where there is strong evidence that no residual tumor remains after excisional biopsy. Thus an argument might be supported for analyzing only those lesions apparent by other means since a 53% rate of positive scans is found for apparent sites compared with 46% proved at surgery.

The equivocal scans representing a variety of uncertainties about sites of increased activity constitute one group of failures, either due to inadequate concentration of nuclide, failure of the observer, or inadequacy of his instruments.

When we consider the scan data in the context of whether disease is present, we find a rather high degree of reliability. If the scan is positive, it is most likely that disease is present. In Table 2 note that of 421 sites of positive scans, only 11% failed to have proof or clinical evidence pointing to a lesion. On the other hand, disease may frequently be present when the scan is negative, thus strongly suggesting the need for further research into improved instrumentation and techniques of scanning as well as manipulations of the radiopharmaceutical. For example, we may discover ways to block normal binding sites, or enhance the specificity of uptake into neoplastic tissue, or increase excretion of unbound agent. We already know, for example, that in animals stable scandium given along with $^{67}$Ga will increase urinary excretion of $^{67}$Ga without diminishing tumor uptake (*12*). However a serious question remains about toxicity of scandium in man and probably other pharmacologic mechanisms must be developed to achieve this effect.

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## REFERENCES

*1.* EDWARDS CL, HAYES RL: Tumor scanning with $^{67}$Ga citrate. *J Nucl Med* 10: 103–105, 1969

*2.* HIGASI T, NAKAYAMA Y, IKEMOTO S: Diagnosis of malignant tumor with $^{67}$Ga citrate (1st report). *Jap J Nucl Med* 6: 217–226, 1969 (in Japanese)

*3.* LAVENDER JP, LOWE J, BARKER JR, et al: Gallium 67 citrate scanning in neoplastic and inflammatory lesions. *Br J Radiol* 44: 361–366, 1971

*4.* EDWARDS CL, HAYES RL: Scanning malignant neoplasms with gallium 67. *JAMA* 212: 1182–1190, 1970

*5.* LANGHAMMER H, GLAUBITT G, GREBE SF, et al: $^{67}$Ga for tumor scanning. *J Nucl Med* 13: 25–30, 1972

*6.* HIGASI T, NAKAYAMA Y, MURATA A, et al: Clinical evaluation of $^{67}$Ga-citrate scanning. *J Nucl Med* 13: 196–201, 1972

*7.* HAYES RL, EDWARDS CL: New applications of tumor-localizing radiopharmaceuticals. In *Medical Radioisotope Scintigraphy*, Vienna, IAEA: to be published

*8.* KNISELEY RM: *A Cooperative Group to Study Localization of Radiopharmaceuticals.* USAEC Report ORAU-118, Oak Ridge Associated Universities, 1973

*9.* KNISELEY RM: A coding index for tumor scanning. In *The Cooperative Group to Study Localization of Radiopharmaceuticals.* USAEC Report ORAU-119, Oak Ridge Associated Universities, 1973

*10.* JOHNSTON G, TEATES CD, BENUA RS, et al: $^{67}$Ga-citrate imaging in untreated Hodgkin's disease. Preliminary Report of Cooperative Group. *J Nucl Med* 15: 399–403, 1974

*11.* SWARTZENDRUBER DC, NELSON B, HAYES RL: Gallium-67 localization in lysosomal-like granules of leukemic and nonleukemic murine tissues. *J Natl Cancer Inst* 46: 941–952, 1971

*12.* HAYES RL, BYRD BL, CARLTON JE, et al: Effect of scandium on the distribution of $^{67}$Ga in tumor-bearing animals. *J Nucl Med* 12: 437–438, 1971