

⁶⁷Ga-CITRATE IMAGING IN UNTREATED HODGKIN'S DISEASE: PRELIMINARY REPORT OF COOPERATIVE GROUP

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An interinstitutional cooperative study has been undertaken to evaluate ⁶⁷Ga as a tumor-localizing agent. A uniform protocol and computer handling of data have been used. In 151 untreated patients with Hodgkin's disease, approximately 90% had one or more positive sites demonstrated on scan. Of histologically proven or clinically evident sites of tumor known by means other than scanning, 73% were positive. A "false-positive" rate of less than 5% was discovered. Of 249 lesions proven histologically or obviously apparent by other means, 21% were first detected by ⁶⁷Ga, although the sequence of procedures in the patient's workup may have some influence on this number. The percentage of positive scans is highest in the neck and chest. Gallium-67 imaging appears to have a place in staging Hodgkin's disease but a negative scan does not exclude the presence of disease. In comparison with lymphangiography it appears to be slightly more sensitive but each of these procedures found lesions missed by the other.

In 1968 Edwards and Hayes (1) discovered that ⁶⁷Ga-citrate sufficiently concentrates in human non-osseous neoplasms to permit imaging. Since then a number of confirmatory reports have appeared from the United States and abroad (2-6). A recent review paper analyzes the published data from numerous sources (7).

With the impetus of this finding, members of a number of institutions mostly in the southeastern region formed a Cooperative Group to Study Localization of Radiopharmaceuticals. As an initial project we chose to evaluate ⁶⁷Ga as a tumor-localizing agent using a generally accepted protocol. The Group

undertook the task of developing a framework for orderly and systematic data collection of clinical scan studies which would allow a substantial number of cases to be analyzed in a reasonably brief period of time. A variety of organizational and logistical problems have been overcome and the details are available in a separate report (8).

MATERIALS AND METHODS

As of April 12, 1973, more than 1,300 case studies have been accessioned including 151 instances of untreated Hodgkin's disease. This series does not comprise all of the patients seen at these institutions with this diagnosis but does represent as many as could be reasonably included in the project. In some instances patients were referred to the nuclear medicine department because of the investigator's known interest in this study, in others because of the desire by the referring physician for the information that would be obtained. We know of no significant bias in the data that resulted from any possible selectivity in the referral process.

Carrier-free ⁶⁷Ga-citrate was administered intravenously as a single dose in the amount of 0.045 mCi/kg of body weight. Total-body scanning was done between 48 and 72 hr postinjection after the patients had been given laxatives supplemented at times by enemas to remove gallium excreted into the large bowel.

By common agreement, the primary data were collected by rectilinear scanning with no contrast

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TABLE 1. RESULTS OF ^{67}Ga SCANS IN CASES OF UNTREATED HODGKIN'S DISEASE (TO APRIL 10, 1973)

Histologic type	Scan reading		
	Pos	Neg	Eqv
Nodular sclerosis	68	1	2
Lymphocyte depletion	3	1	0
Mixed cellularity	39	3	2
Lymphocyte predominating	13	2	2
Not otherwise specified	14	1	0
Total	137	8	6

TABLE 2. SCANS OF ^{67}Ga IN 624 UNTREATED HODGKIN'S DISEASE SITES (TO APRIL 10, 1973)

Evidence of disease at sites	Scan reading		
	Pos	Neg	Eqv
Proven at surgery	161	70	18
Apparent	204	59	16
Suspected	51	15	2
Total	416	144	36
Tumor excluded at surgery	8		20
Nonmalignant lesion at site	2		3

enhancement and no background erase. Supplementary views were at times taken by gamma scintillation cameras. A standard exercise was developed to calibrate scanners and scanning techniques by means of a specially designed phantom which tested both resolution and sensitivity of each participant's instruments. Because of differences in instruments, absolute uniformity could not be achieved but the interlaboratory comparison yielded considerable progress in this direction and helped improve general scanning techniques at some institutions. Window settings were generally 160–320 keV to cover the second and third gamma-ray peaks (184 and 296 keV).

A standard encoding form for computer storage and analysis was developed and field-tested. A series of modifications were made based on initial trials. In addition to data identifying the patient, institution, and isotope batch, the form includes descriptive information for each study: the patient's age, sex, his clinical status at the time of the scan (untreated, early followup after initial therapy, later followup with symptoms of recurrence or without symptoms, etc.), the morphologic type of tumor, and how many previous gallium studies have been done. A computer-compatible coding system for recording sites of lesions was designed and details are available on request (9). Each lesion or site of special interest

known by any means, whether seen on the scan or not, was recorded and coded. A scan interpretation for each site was recorded according to the following convention:

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

In this report we have consolidated under the term equivocal those three categories of scan interpretation recorded as uncertain.

Similarly, the evidence, other than the scan itself, for tumor at each site is recorded according to the following convention:

1. Proven by histology—(surgery, biopsy, autopsy);
2. Apparent—radiographic (definite lesion described) or directly visualized at surgery or endoscopy, or by palpation of superficial lesion;
3. Suspected—palpation of deep tissues (abdomen, etc.) or suspected lesion on x-rays;
4. Local pain;
5. No evidence of tumor;
6. Tumor excluded by surgical exploration;
7. Nonmalignant lesion demonstrated at site;
8. Scans followed presumably complete extirpation;
9. Unknown.

In the following text and tables, the terms "proven", "apparent", and "suspected" represent a classification according to the above-listed convention rather than a description.

The following are also recorded for each site where applicable: results of the lymphangiograms; a statement on whether the lesion was known, suspected, unsuspected, or believed to have been absent at the time of scan; the size of the lesion; the dates and dose of radiation therapy. Data on chemotherapy including type of drugs and dates are also recorded for each study.

RESULTS

General. Of the 151 untreated patients that form the basis for this report, 137 (90%) yielded one or more positive sites on scan and an additional 4% had one or more equivocal sites recorded (Table 1). Not unexpectedly, when individual sites or lesions are examined, this extremely high percentage of positive results is not found. Of the 249 sites with histologically proven tumor, 65% gave a positive image

TABLE 3. RESULTS OF ⁶⁷Ga SCANS BY ANATOMIC REGIONS IN UNTREATED HODGKIN'S DISEASE 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	75	13	2	15	1	0	5	3	2	57	44	14	6	6	0
Apparent	58	14	3	93	9	7	20	8	4	22	16	2	7	11	0
Suspected	9	1	0	17	1	2	3	1	0	17	6	0	3	4	0
Total	142	28	5	125	11	9	28	12	6	96	66	16	16	21	0
Tumor excluded at surgery	1									7	17				1
Nonmalignant lesion at site										2	1				2

reading (Table 2). In 279 additional sites not histologically proven but apparent as defined above, we encountered positive scan readings in 73%. Of the 169 positive scan sites subsequently examined at surgery, there were only 8 instances where tumor was not found, thus indicating a "false-positive" site rate of 5%. In addition, two nonmalignant lesions showing as a positive scan were verified. A total of 93 sites* had been interpreted on scans as "equivocal"; among these, 18 tumors were proven to be present at surgery, 16 sites had apparent tumor, and 2 sites had suspected tumor. Of the remaining 57 sites, surgical exploration failed to show tumor in 20 although nonmalignant lesions were found in 3.

Anatomic regions. Five major anatomic lymph node-bearing regions in untreated patients were analyzed for diagnostic reliability of the ⁶⁷Ga-citrate scan (Table 3).

In the neck, positive scans were obtained in 83% of surgically verified tumor sites. Clinically apparent or suspected, but not biopsied, sites gave positive scans in 79%. In the thorax, 15 positive scans were noted at 16 biopsied sites and approximately 85% of the apparent or suspected sites gave positive scans. In the axilla, only five of ten tumors had positive scans while 64% of apparent or suspected sites were positive.

In the abdomen, positive scans were obtained in only 50% of proven sites and 62% of sites of apparent or suspected tumor. The inguinal-femoral region had 6 positive scans of 12 histologically proven sites but only 10 positive scan sites of 25 apparent or suspected lesions.

Positive scan readings were obtained at one site in the neck and at seven sites in the abdomen in which subsequent surgery revealed no evidence of

tumor. Negative surgical findings were also noted in 17 abdominal sites and one inguinal-femoral site where the scan results were equivocal.

Splenectomy. We have data from 59 patients with splenectomy after the scan study. Thirty-eight of these spleens contained Hodgkin's disease. In 14 of these patients the scans indicated splenic involvement and in 18 they did not. Six were interpreted as uncertain. Twenty-one excised spleens contained no Hodgkin's disease, and none of these had positive scans, but two were equivocal.

Histologic types. Sites of untreated cases of Hodgkin's disease were examined according to histologic type (Table 4). For nodular sclerosis we found 71% positive scans in histologically verified areas and 76% positive scans in apparent or suspected lesions. There were seven so-called false-positive sites where tumor was excluded by surgical exploration although the scan was read as positive.

For mixed cellularity type, we found positive sites in 54% of proven lesions and 75% of apparent or suspected lesions with only one proven false-positive site.

In 27 verified lesions of lymphocytic predominance type we found 18 positive, 6 negative, and 3 equivocal scans; 13 of 21 apparent or suspected lesions gave positive scans.

Detectability according to size of lesions. For those lesions where objective radiologic or pathologic measurements were recorded, we examined the rate of positive scans. Scan detectability was not clearly related to the size of the lesion.

Systemic symptoms. In staging, cases are grouped as either A, free of symptoms, or B, having symptoms. The data in untreated cases at this point show no higher incidence of positive scans in patients with systemic symptoms.

Unsuspected sites found first by scan. A number of unsuspected sites, or sites believed to be free of disease, were first found to contain Hodgkin's dis-

* These 93 sites include 59 sites listed in Table 2, 31 sites defined as "no evidence", and 3 sites listed as "evidence unknown".

TABLE 4. SCAN RESULTS BY HISTOLOGIC TYPE VERSUS OTHER EVIDENCE OF DISEASE IN SITES OF UNTREATED HODGKIN'S DISEASE (TO APRIL 10, 1973)

Evidence of disease at sites	Nodular sclerosis			Mixed cellularity			Lymphocyte depletion			Lymphocyte predominance			Not otherwise specified		
	Pos	Neg	Eqv	Pos	Neg	Eqv	Pos	Neg	Eqv	Pos	Neg	Eqv	Pos	Neg	Eqv
Proven at surgery	94	31	7	35	24	6	4	6	0	18	6	3	10	3	2
Apparent	116	24	11	59	25	5	12	2	0	8	5	0	9	3	0
Suspected	26	8	2	17	2	0	1	0	0	5	3	0	2	2	0
Totals	236	63	20	111	51	11	17	8	0	31	14	3	21	8	2
Tumor excluded at surgery	7		16	1		2						2			
Nonmalignant lesion at site			1			2									

TABLE 5. RESULTS OF ⁶⁷Ga SCAN AND LYMPHANGIOGRAPHY IN SURGICALLY EXPLORED LYMPH NODAL SITES OF UNTREATED HODGKIN'S DISEASE (TO APRIL 10, 1973)

Scan Lymphangiogram	Sites with tumor								
	Neg Pos	Neg Eqv	Neg Neg	Pos Pos	Pos Eqv	Pos Neg	Eqv Pos	Eqv Eqv	Eqv Neg
Abdominal	4	2	13	16	0	16	3	0	3
Inguinal-femoral	3	1	1	1	1	0	0	0	0
Totals	7	3	14	17	1	16	3	0	3
Sites without tumor									
Abdominal	6	5	—	0	1	3	0	4	4

ease on the basis of ⁶⁷Ga imaging. Among the 528 sites with proven or apparent tumor at the time of the scan, 106 were thought to be free of tumor or the tumor was unsuspected. Of these, 53 were initially detected on gallium scans and subsequently confirmed by other procedures.

Lymphangiography. Data in 48 patients were available to compare ⁶⁷Ga scans with lymphangiograms in surgically verified sites (Table 5). In 64 lesions, lymphangiograms detected the site in 27 and scans in 32. In seven instances, lymphangiograms found the lesion when ⁶⁷Ga failed; in 16 sites the scan was positive where lymphangiograms were negative. On the other hand, the lymphangiogram gave six false-positives compared with four false-positive scans in sites subsequently found to have no tumor.

In ten patients the scan revealed tumor in the abdomen not found by lymphangiogram; conversely, in five patients the lymphangiogram was interpreted as positive in sites not detected on scan.

DISCUSSION

Clearly a remarkable phenomenon is at work in the localization of ⁶⁷Ga in Hodgkin's disease. The mechanism, not yet well understood, is under investigation with animal tumor models and human tissue. From this first look at the data bank estab-

lished by the Cooperative Group, we learn that a high percentage of untreated patients with Hodgkin's disease will have one or more tumor sites displayed on scan by the present dosage schedule and instrumentation but when we examine the yield of positive scans from individual lesions, verified or clinically evident by other means, the rate drops to about 70%. This is still an impressive value but does not answer the question of whether ⁶⁷Ga is of use in staging.

Staging has been shown to be a vital part of the proper management of Hodgkin's disease but extensive radiography, surgical exploration, and other scanning procedures still fail to locate all lesions in some patients. Even at this point of development, our results support the published observation (10) that this agent is a useful supplement in staging Hodgkin's disease and at times is the only noninvasive study that will signal sites of tumor. The fact that 53 out of 249 proven lesions were first detected by scan is noteworthy. This incidence of de novo detection with ⁶⁷Ga, however, should be tentative and requires further analysis. The sequence of procedures in the staging workup could affect the numbers. If the gallium scan is the initial diagnostic procedure, obviously more lesions will be initially detected by scanning than if it is done after the laparotomy. We are optimistic that improvements in instrumentation or ma-

nipulations in the radiopharmaceutical can improve the percentage of positive scans and increase the detection rate of otherwise cryptic lesions.

The question of false-positive rates is also of importance. We found a relatively insignificant incidence of sites believed to have tumor where surgery failed to disclose a lesion (less than 5%). Some of these may subsequently turn out to be true positives which escaped the surgeon's eye.

Not surprisingly the detection rate of lesions varies according to anatomic site. The scans appeared to be most reliable in the neck and chest with an overall positive rate of 81% and 86% respectively. The overall yield in the axilla was 60%, in the abdomen 54%, and in the inguinal-femoral region 43%. Although normal ⁶⁷Ga content in the gut, liver, and spleen can account for some confusion relating to the abdomen, the lower rate of positive scans in the inguinal-femoral region remains unexplained at present. The favorable percentages in the chest may be explained in part by the lower rate of surgical exploration which if done would disclose lesions not giving a positive scan. On the other hand, in the neck, axilla, and groin, palpable nodes can be overcalled on palpation and hence explain higher rate of false-negative scans at sites of apparent but unverified tumor. In other words, diverse factors undoubtedly contribute to the resulting differences in the incidence of positive scans in different regions that should not be attributed to instrument limitations or differences in tumor uptake.

Of the histologic types, Hodgkin's with nodular sclerosis appears to have the highest percentage of positive scans with an overall positive incidence of 74% in known, apparent, and suspected lesions compared with 64% for mixed cellularity and lymphocytic predominance. The numbers of sites in the lymphocytic depletion type are too few for percentages to be significant. Because of the special problem in classifying these tumors, the group has been persuaded that a systematic review is necessary to insure comparable populations of histologic types of lymphoma and Hodgkin's disease. Therefore those particular data of the subclasses of Hodgkin's disease will remain tentative until a pathology panel review has been completed.

Another important question is the relative value of lymphangiography and scanning. Since lymphangiography is a difficult technical procedure, not free of morbidity or of false results, an alternative procedure is attractive. Our limited data on this point do not permit firm generalization though our results sug-

gest ⁶⁷Ga is slightly more sensitive. Each procedure found lesions missed by the other.

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