^{67}Ga-CITRATE IMAGING IN UNTREATED PRIMARY LUNG CANCER: PRELIMINARY REPORT OF COOPERATIVE GROUP

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An interinstitutional cooperative study has been undertaken to evaluate ^{67}Ga as a tumor-localizing agent. A uniform protocol and computer handling of data have been used. In 172 untreated patients with primary lung cancer, approximately 84% had one or more sites demonstrated on scanning with ^{67}Ga; 80% of individual lesions histologically verified had positive scans. It is occasionally possible to detect rather small lesions and, conversely, on occasion to miss some large lesions (5 cm or larger). Negative scans were obtained in 16% of lesions histologically proven. In the present analyses, rates of detection differ somewhat according to histologic type but not strikingly. With further developments in tumor-localizing agents and instruments, the agent may eventually be useful in the initial diagnostic workup of suspected lung carcinoma in certain clinical situations. As a single screening scan procedure, it should prove helpful in assessing the extent of disease before surgery or other type of therapy.

This is a companion paper to the two preceding ones in this journal. The background of the diagnostic use of ^{67}Ga for imaging neoplasms is presented in the first paper and in references (*1–7*) as is information about the formation of the Cooperative Group to Study Localization of Radiopharmaceuticals (*8,9*).

MATERIALS AND METHODS

The Cooperative Group has systematically evaluated 172 cases of untreated pulmonary carcinoma with ^{67}Ga-citrate. Standard recording forms were developed upon which were recorded clinically significant variables. Scan interpretations of the sites of gallium uptake were recorded according to the following convention:

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.

In this report we have consolidated under the term "equivocal" those three categories of scan interpretation recorded as uncertain. Standardization of the radiopharmaceutical, instrumentation, and physician interpretation was accomplished by methods defined in the preceding paper on Hodgkin's lymphoma.

RESULTS

General. Of 172 untreated cases of the various types of primary lung cancers, 84% yielded one or more positive sites on scan and an additional 6% had equivocal scans (Table 1). The rates of detection by ^{67}Ga for 214 individual sites which include

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TABLE 1. RESULTS OF ^{67}Ga SCANS IN CASES OF UNTREATED PRIMARY LUNG CANCER (TO APRIL 10, 1973)

	Pos	Neg	Eqv
Squamous, mod. or well-differentiated	43	5	2
Squamous, large cell undifferentiated	47	6	1
Adenocarcinoma, bronchoalveolar	20	1	6
Small cell, oat cell	14	3	0
Not otherwise specified	22	1	1
Totals	146	16	10

TABLE 2. SCANS OF ^{67}Ga IN UNTREATED PRIMARY AND METASTATIC SITES OF PRIMARY LUNG CANCER (TO APRIL 10, 1973)

Evidence of disease at sites	Scan reading		
	Pos	Neg	Eqv
Proven at surgery	171	34	9
Apparent	116	25	12
Suspected	17	11	11
Totals	304	70	32
Nonmalignant lesion at site	1	1	
No evidence of tumor	17		20
Totals	18	1	20

both the primary lesion and metastases, proven histologically, ran 80% (Table 2). An additional 192 sites apparent or suspected but not proven by biopsy averaged 69% positive. We had no false-positive sites proven by surgery, but at 21 sites interpreted as positive on scan we still have no verification of the presence of a lesion. Some of these positive sites may later turn out to be tumor now occult; others may have a different explanation.

Anatomic regions. In our data tabulated according to anatomic region, in 130 lung lesions histologically verified, we achieved a positive scan rate of 85% but a lower yield of positive scans in apparent or suspected sites (Table 3). The 139 recorded lymph node sites of the chest, axilla, and neck encoded as proven, apparent, or suspected, gave a rate of 80% positive scans; those verified histologically had a somewhat lower rate (72%). Remote sites including bone and brain grouped together gave a lower percent of positive scans (49%).

Histology. The results of ^{67}Ga scans in primary and metastatic sites according to histologic type are shown in Table 4. In proven sites, the percentage of positive scans was noted as follows: squamous cell, well-differentiated, 85%; squamous cell, undifferentiated large cell, 81%; adenocarcinoma, 73%; small cell, 70%. Although differing slightly, similar types of percentages were recorded when apparent or suspected sites were examined.

Detectability according to size. For those lesions with objective radiologic or pathologic measurements of size, we tabulated the scan results (Table 5). Not surprisingly, larger lesions have a higher percentage of positive scans. Nevertheless of 158 lesions larger than 5 cm, 15% failed to be visualized on scan and 10% were negative when 3–5 cm in diam. The ability to visualize lesions 2 cm or less in diam with our current protocols averaged 43% positive.

Sites first detected by ^{67}Ga. Our first lung cancer protocol was not designed to answer the question concerning the use of ^{67}Ga for screening to gain a diagnosis or for diagnoses when other evidence was absent. Nevertheless, 17 positive and 20 equivocal sites that were recorded currently have no confirming evidence; a number of these may represent the first detection of a primary lesion or a recurrence or a metastasis. In addition, four lesions detected on scan but not otherwise suspected were subsequently proven histologically. An additional 20 lesions were first found by scan and subsequently were found to be apparent or suspected by other methods.

DISCUSSION

The overall scan results (84% positive) with ^{67}Ga in primary lung cancer agree well with the various

TABLE 3. RESULTS OF ^{67}Ga SCANS BY ANATOMIC REGIONS IN UNTREATED LUNG CANCER SITES (TO APRIL 10, 1973)

Evidence of disease at sites	Lung			Regional lymph nodes Thorax, neck, and axilla			Remote sites					
							Bone			Brain, other sites		
	Pos	Neg	Eqv	Pos	Neg	Eqv	Pos	Neg	Eqv	Pos	Neg	Eqv
Proven at surgery	111	12	7	44	16	1	5	2	1	4	3	0
Apparent	36	10	5	57	4	1	10	9	4	12	3	2
Suspected	4	1	3	10	3	3	2	2	4	1	5	0
Totals	151	23	15	111	23	5	17	13	9	17	11	2

TABLE 4. SCAN RESULTS BY HISTOLOGIC TYPE VERSUS OTHER EVIDENCE OF DISEASE IN PRIMARY AND METASTATIC SITES OF UNTREATED PRIMARY LUNG CANCER (TO APRIL 10, 1973)

Evidence of disease at sites	Squamous, moderately or well-differentiated			Squamous, large cell, undifferentiated			Adenocarcinoma, bronchoalveolar			Small cell, oat cell			Not otherwise specified		
	Pos	Neg	Eqv	Pos	Neg	Eqv	Pos	Neg	Eqv	Pos	Neg	Eqv	Pos	Neg	Eqv
Proven at surgery	51	9	0	65	14	1	25	2	7	17	6	1	13	3	0
Apparent	27	1	6	36	11	2	18	4	4	21	4	0	14	5	0
Suspected	10	1	3	2	4	4	2	2	2	1	4	0	2	0	2
Totals	88	11	9	103	29	7	45	8	13	39	14	1	29	8	2

TABLE 5. SIZE OF SITES OF LUNG CANCER AND DETECTABILITY BY ^{67}Ga (TO APRIL 10, 1973)

Scan interpretation	Size of lesion in cm					Greater than 5	Total
	1	2	3	4	5		
Negative	3	10	8	4	3	23	51
Positive	4	16	56	36	31	119	262
Equivocal	2	12	6	4	3	16	43
Totals	9	38	70	44	37	158	356

published reports. We must ask, however, whether the procedure is of value in finding lesions not known by other means. This particular protocol was not specifically designed to evaluate lung cancer suspects. It is noteworthy that small lesions indeed are detectable, though in low percentages. From these data, one might be encouraged to use ^{67}Ga, for example, as an adjunct in a diagnostic workup of heavy smokers with suspicious symptoms who have no definite radiographic evidence of pulmonary disease. Those disappointing equivocal scans or scan failures, rather than causing abandonment of the procedures, illuminate the urgent need for continued research. It is of interest that we detected 17 positive and 20 equivocal sites which until now have not been verified by other methods. Some may be sites of physiologic uptake but followup studies may indicate that these were lesions found de novo by ^{67}Ga. When followup surgical findings have become available, positive sites have rarely been shown to be false positive. Only one nonmalignant lesion was recorded as positive in this series of lung cancer, representing the bias in the selection process since the patients studied were proven to have carcinoma. It is known that some granulomas and Boeck's sarcoid can also concentrate ^{67}Ga.

A second field of usefulness for the gallium scan in lung cancer may be in the staging of disease before possible surgical intervention. Patients were selected for this study without regard to the probability of metastatic lesions. The high percentage of positive uptake within the nodes of the thorax suggests that the gallium scan may be used as an important screening procedure in assessing metastatic spread to mediastinal or subclavicular nodes. Furthermore, the percentage of positive scans for remote metastases averages 50% (Table 3). This additional yield on a single scan screening procedure would also be an aid in deciding the extent of disease prior to surgery and/or other therapy.

It is of interest that all histologic types of lung cancer are associated with a relatively high affinity for ^{67}Ga. Although there appears to be a slightly higher preponderance of positive scans in the squamous cell varieties, the numbers of cases examined in the adeno and small cell carcinomas are relatively small compared with the squamous group and thus these differences may be more apparent than real. These findings in lung carcinoma are in contrast with those of malignant lymphoma in which much more striking differences in the uptake of ^{67}Ga are noted in the different cell types.

Further analysis of the data may reveal additional clues concerning the nature of this remarkable phenomenon of ^{67}Ga uptake. The fact that some quite small lesions have avid uptakes and that a few huge ones fail to adequately concentrate the agent indicates differences in tumor biology that are obscure at this time, e.g., changes in tumor avidity for ^{67}Ga after initiation of therapy.

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