Quantitative Gallium-67 Scanning for Predictive Value in Primary Lung Carcinoma

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Gallium-67 scintigraphy was performed on 87 patients with a variety of histological types of untreated primary lung carcinoma. Gallium-67 uptake was determined, allowing for differences in tumor size. Differential uptakes were found for the various tumor types, with anaplastic small-cell carcinoma having the greatest average uptake, and adenocarcinoma and anaplastic large-cell carcinoma the smallest.

Gallium-67 uptake was compared with response to radiation therapy, incidence of metastasis, and host survival in 58 of the patients. From these results it is suggested that the greater the Ga-67 accumulation in the tumor, the more effective is radiation therapy in reducing tumor size.

Gallium-67 scintigraphy appears to be a valuable tool in estimating the sensitivity of the tumor before radiation therapy and in indicating the prognosis following radiation therapy in patients with primary lung carcinoma.

J Nucl Med 21: 628–632, 1980

In 1969 Edwards and Hayes noted the accumulation of Ga-67 in the neck lymph nodes on a skeletal scintiscan of a patient with Hodgkin's disease (*1*). Subsequently, Ga-67 has been shown to accumulate sufficiently in a variety of tumors to allow for their visualization (*2–10*).

Since the Ga-67 accumulation is not specific for neoplasia, however, the diagnosis of malignancy cannot be made from the result of a positive scan. Nevertheless, once a histologic diagnosis of malignancy has been made, Ga-67 scanning may be used not only to determine the extent of disease but to monitor the effectiveness of treatment. We have previously reported the significance of Ga-67 scanning in the estimation of radiosensitivity of malignant tumors of head and neck (*11*). To further explore the clinical usefulness of Ga-67 scintigraphy, we studied Ga-67 scans of malignant pulmonary neoplasms in an attempt (a) to estimate the radiosensitivity of the tumors before treatment, (b) to predict the incidence of metastasis, and (c) to predict survival of the host patients.

MATERIALS AND METHODS

The population studied consisted of 87 patients with various types of untreated primary pulmonary carcinoma, with the exclusion of mediastinal tumors. In histologic type these lung cancers provided 23 adenocarcinomas, 44 squamous-cell carcinomas, and 20 undifferentiated carcinomas. Of these patients, 58 received more than 5000 rads of Co-60 irradiation therapy. This group included 14 adenocarcinomas, 31 squamous-cell carcinomas, and 13 undifferentiated carcinomas.

Responses to radiation therapy were evaluated for the 58 cases, its effectiveness being determined by comparing the size of the tumor on chest radiographs before and after therapy. This resulted in three groups: Group I—ineffective or slightly effective; tumor size underwent no change or was slightly decreased during irradiation but increased afterward. Group II—effective; tumor size significantly decreased during radiation therapy, and

Received April 16, 1979; revision accepted Jan. 9, 1980

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afterward disappeared. Group III—markedly effective; tumor disappeared during radiation therapy and there was no local recurrence.

All scans were performed with dual-headed rectilinear scanners (5-in. crystals, 60-hole honeycomb collimators, focal length 10 cm), at 48 hr after injection of 2.0-2.5 mCi of Ga-67 citrate. The output of two separate 20% windows, covering the 93- and 184-keV peaks, were summed. Gallium-67 scans were made in all patients before treatment, and within 1-2 wk after its completion.

Tumor uptake of Ga-67 was estimated objectively as follows:

1. Photodensity in the Ga-67 scintigram of the tumor (T) and in a corresponding normal region in the opposite lung (N) were measured at 20 points in the scintigram with a densitometer. The T/N ratio could then be calculated.

The x-ray film used for the scintigrams was Kodak type RP. A linear relationship was observed between photodensity of this film and the radioactivity of Ga-67 within the range suitable for clinical scintigrams.

2. Tumor size was estimated from its area on the chest radiograph and the Ga-67 scintigram. We assume that the tumor is spherical, and derive the radius, R, from the area as measured by planimeter. It is considered that the tumor's photodensity in the scintigram is affected by the size of the tumor even though a honeycomb collimator with a focal distance of 10 cm was used.

3. The T/N value was divided by R to correct for effect of tumor size. The T/NR value thus may provide a relative estimate of the Ga-67 uptake by the tumor.

Statistical analysis was performed by a nonparametric Mann-Whitney test for paired data.

RESULTS

The relationships between the tumor area, the histologic type, and the Ga-67 uptake as defined by the T/NR concept are shown in Fig. 1. The plot indicates that the T/NR value is independent of tumor size. The relationship between histologic type and Ga-67 uptake (T/NR) in 87 cases of untreated primary lung cancer are shown in Table 1. In spite of the low T/NR value for the large-cell carcinoma, the only significant difference ($P < 0.01$) is between adenocarcinoma and anaplastic small-cell carcinoma.

The relationship between the Ga-67 T/NR uptake, the histologic type, and the value of radiation therapy is shown in Table 2. These 58 patients received complete radiation therapy (more than 5000 rads) with CO-60. The averages show that, irrespective of histological type, the highest T/NR value occurs in the group responding best to radiation; its value (1.87) differs significantly ($P < 0.05$ or better) from those of the other two groups. This suggests a tendency for good gallium uptake to accompany a favorable response to radiation therapy.

Figure 2 illustrates the results of Table 2. There were many patients with anaplastic or squamous-cell carcinomas in the "effective" and "markedly effective" therapy groups, and there were few patients with adenocarcinoma among them. The plot shows that all 25 cases in which T/NR > 1.27 belong to the "effective" and "markedly effective" groups, and 17 of 25 cases (about 70%) fall in the "markedly effective" group.

The average T/NR value for the patients with metastasis within 3 mo following radiation therapy is 1.57 ± 0.94, that of the patients without metastasis is 1.32 ± 0.81, irrespective of histologic type. These values are not significantly different. Similarly no significant difference

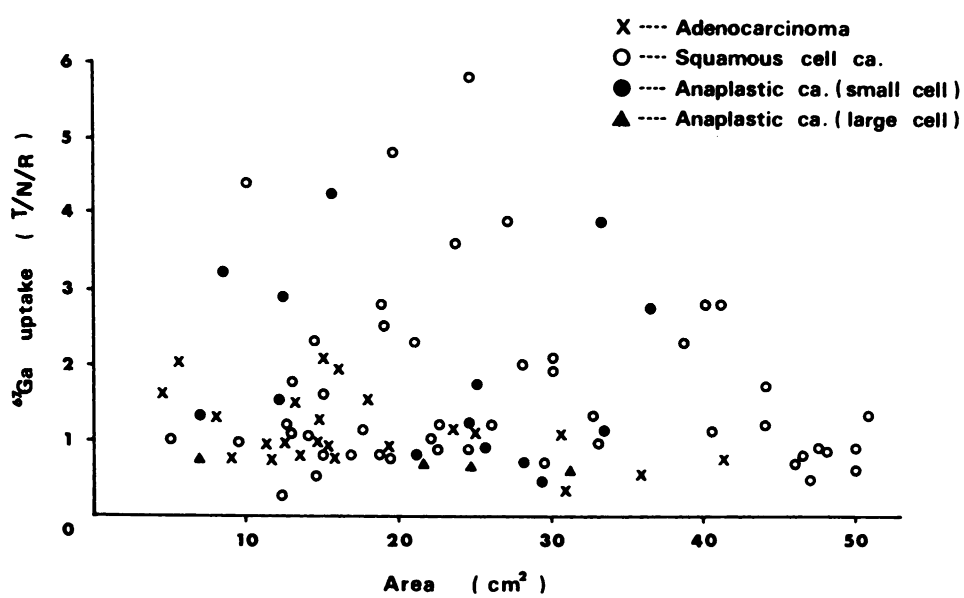

FIG. 1. Ga-67 uptake (T/NR) as function of scintigraphic area in various histologic types of primary lung carcinoma. Plot indicates that T/NR is independent of tumor size.

TABLE 1. RELATIONSHIP BETWEEN Ga-67 UPTAKE (T/NR) AND HISTOLOGIC TYPE

Histologic type	Ga-67 T/NR (mean ± s.d.)	
Adenocarcinoma	1.12 ± 0.47 (23 cases)	NSD*
Squamous-cell carcinoma	1.61 ± 1.17 (44 cases)	
Anaplastic carcinoma		
small-cell	2.01 ± 1.20 (14 cases)	NSD*
large-cell	0.81 ± 0.34 (6 cases)	

* NSD = no significant difference. The differences were significant ($P < 0.05$ by nonparametric Mann-Whitney test) between adenocarcinoma and anaplastic small-cell carcinoma.

was found between the Ga-67 uptake (T/NR) and the incidence of metastasis, or the Ga-67 uptake (T/NR), histologic type, and host survival after radiation therapy.

DISCUSSION AND CONCLUSION

The exact mechanism of the uptake of Ga-67 by malignant cells is still obscure. The factors proposed to influence the uptake include increased vascularity, altered tissue permeability, cellular proliferation, and changes in metabolic activity.

In pulmonary cancer, it is noteworthy that small lesions are indeed detectable, though in low percentages. It has been reported, however, that Ga-67 uptake by lung cancers differs somewhat according to the histologic type. Higashi et al. (*6*) reported that the Ga-67 uptake of undifferentiated carcinoma of the lung was greater than that of squamous-cell carcinoma and adenocarcinoma. DeLand et al. (*10*) reported that there appears to be a slightly higher preponderance of positive scans in the squamous-cell varieties compared with the adeno- and small-cell carcinomas in 172 untreated cases of primary lung cancer. Thesingh et al. (*12*), using autoradiographic techniques, studied the relationship between the accumulation of Ga-67 in the tumor and the histologic type of lung cancer. They found that the highest grain counts for tumor cells in autoradiograms and the highest gamma counts for tissue samples occur in the group of undifferentiated and squamous-cell carcinomas. Adenocarcinomas have lower grain counts in autoradiograms and lower gamma counts in tissue samples.

On the other hand, Langhammer et al. (*7*) reported that there was no dependence of Ga-67 accumulation on the histologic type of tumor, either for bronchial carcinoma or for other tumors. Kempken et al. (*13*) also reported that the degree of differentiation of the lung tumor will not influence the Ga-67 incorporation.

Thus, the relationship between Ga-67 uptake and histologic type of lung carcinoma differs according to various investigators. It may be that the discrepancy in these results is due to subjective interpretation of Ga-67 scintigrams without regard to tumor size. However, Thesingh's autoradiographic techniques (*12*) found differential Ga-67 uptake depending on histological type.

TABLE 2. RELATIONSHIP BETWEEN Ga-67 UPTAKE (T/NR), HISTOLOGIC TYPE, AND EFFICACY OF RADIATION THERAPY (58 CASES)

Histologic type	Ineffective or slightly effective (T/NR)*	Effective (T/NR)*	Markedly effective (T/NR)*
Adenocarcinoma (14 cases)	0.79 (4 cases)	0.79 (5 cases)	1.29 (5 cases)
Squamous-cell ca. (31 cases)	0.84 (6)	1.38 (9)	1.91 (16)
Anaplastic ca.			
small-cell (10 cases)	—	2.27 (2)	2.31 (8)
large cell (3 cases)	0.77 (1)	0.63 (1)	0.59 (1)
Average (T/NR) value (58 cases)	0.82 ± 0.21 (11 cases)	1.27 ± 0.90 (17 cases)	1.87 ± 1.07 (30 cases)
	NSD†	P‡ < 0.05	

* Mean ± s.d.

† NSD = no significant difference.

‡ Application of a nonparametric Mann-Whitney test for differences between means establishes a statistically significant difference ($P < 0.01$) between the ineffective or slightly effective group and the markedly effective group.

Relationships between the ^{67}Ga uptake (T/N/R), the histologic findings and the efficacy of irradiation therapy.

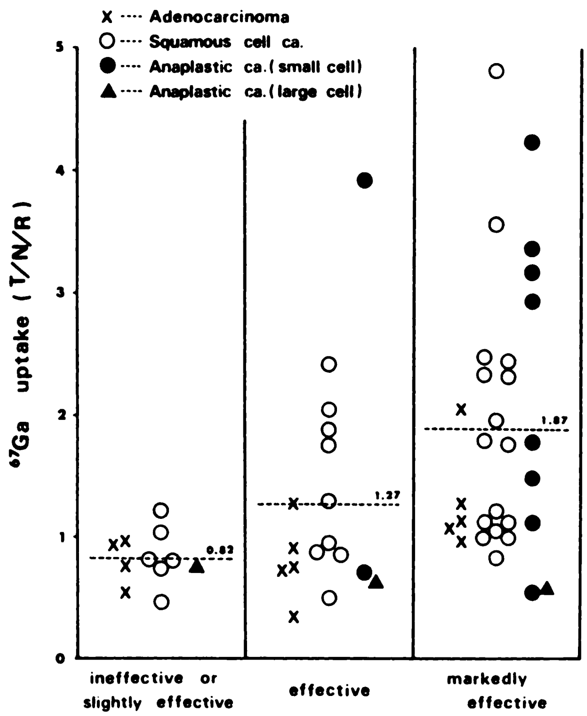

FIG. 2. Efficacy of radiation therapy as function of Ga-67 uptake in various types of lung carcinoma. Significant difference ($P < 0.05$) could be seen between effective and markedly effective groups, and significant difference ($P < 0.01$) was found between ineffective or slightly effective group and markedly effective group.

In this report, therefore, we measured the density of the Ga-67 scintigram with a photodensitometer and gave specific consideration to tumor size.

As seen in Fig. 1, Ga-67 T/NR and tumor size are independent. This plot indicates a tendency toward a characteristic specific Ga-67 T/NR, highest for anaplastic small-cell and squamous-cell carcinomas and lowest for adenocarcinoma and anaplastic large-cell carcinoma.

Furthermore, Table 2 and Fig. 2 show the relationship between Ga-67 uptake, histologic type, and efficacy of radiation therapy. In each histologic type, the Ga-67 uptake of the markedly effective group was greatest, followed by the effective group, and was the smallest in the group having little or no response to radiation therapy. This suggests that the greater the Ga-67 accumulation in the tumor, the more effective radiation therapy will be. There were many patients with anaplastic carcinoma, small-cell, or squamous-cell carcinoma in the group of effective and markedly effective responses to radiation therapy, and there were few patients with adenocarcinoma in this group. Previously, Higashi et al. (*11*) reported similarly prognostic Ga-67 uptake findings for head and neck tumors. Sugawara et al. (*14*) also recently reported that the accumulation of Ga-67 in pulmonary tumors correlates significantly with radioresponsiveness. It is noteworthy that the local radiosensitivity is not necessarily equal to radiocurability of the disease.

Although Ga-67 uptake by lung cancer may be correlated with radiotherapeutic sensitivity, it is difficult to explain these clinical observations by known mechanisms of Ga-67 concentration in tumor cells. Hayes et al. (*15*) and Ito et al. (*5*) reported that uptake of Ga-67 in transplanted animal tumors is mainly associated with viable rather than necrotic tissue. Bichel and Hansen (*16*) found that the Ga-67 concentration in malignant cells is related to the rate of cellular proliferation. Hammersley and Taylor (*17*) suggested that there is some relationship between Ga-67 uptake and the rate of DNA synthesis in the tumors studied. Okuyama et al. (*18*) also studied the difference in tumor affinity for Ga-67 in experimental tumors of various histologic types, and reported that Ga-67 uptake by cancer cells correlates well with the degree of malignancy.

Hoffer et al. (*19*) recently demonstrated that Ga-67 is locally bound to tissue lactoferrin. Lactoferrin levels are also increased in certain tumors, and very recently, increased lactoferrin content has been confirmed in two tumors associated with increased Ga-67 avidity: Hodgkin's disease and Burkitt's lymphoma (*20*). We note that such tumors have high Ga-67 uptake and high radiotherapeutic sensitivity. Gallium-67 deposition may therefore be a sensitive index of activity in tumor cells. If certain limitations are borne in mind, Ga-67 scans performed before treatment may prove valuable in estimating the radiosensitivity of the tumor before radiation therapy begins.

ACKNOWLEDGMENT

The authors express their sincere thanks to Dr. E. Kashio, Medical Equipment Division, Toshiba Co., for his advice regarding the techniques of measurement of the Ga-67 uptake. Thanks also to K. Kato, RI technician of Keiyu General Hospital, Yokohama, for technical assistance.

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