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Relation between ^{201}Tl to ^{67}Ga Uptake Ratio and Histological Type in Primary Lung Cancer

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Abstract—*Quantitative ^{201}Tl and ^{67}Ga scans were performed on 44 patients with primary lung cancer to ascertain the differences in ^{201}Tl and ^{67}Ga uptake by tumors; especially the crude uptake ratio (CUR) of ^{201}Tl to ^{67}Ga was evaluated in relation to histological type. Adenocarcinomas showed a CUR of 2.00 ± 1.55, the greatest value among all histological types. Epidermoid carcinomas and oat cell carcinomas had CURs of 0.47 ± 0.30 and 0.37 ± 0.05, respectively, both showing significantly lower values than adenocarcinomas ($P < 0.01$). On the other hand, adenosquamous carcinomas indicated a CUR of 0.91 ± 0.15, an intermediate value between adenocarcinomas and epidermoid carcinomas ($P < 0.05$). These results indicated that ^{201}Tl and ^{67}Ga uptake by lung cancer was closely correlated with histological type, and also suggested that ^{201}Tl and ^{67}Ga scans enabled various histogeneses of lung cancer to be visualized.*

INTRODUCTION

THE DIFFERENCE in histological types of lung cancer is one of the most important factors affecting its prognosis [1]. However, the heterogeneity of lung cancer is not always clarified by the histological types alone; therefore its biochemical and biological properties have been discussed in relation to histological structures [2-4].

^{201}Tl-chloride and ^{67}Ga-citrate have been widely used for diagnosing lung cancer, but nucleomedical imaging using these nucleids is now being considered as a supplementary procedure for determining tumor extent or for evaluating hilar and mediastinal involvements [5]. In a previous publication we preliminarily reported that ^{201}Tl and ^{67}Ga accumulations in lung cancer differed among patients having the same histological type [6]. In this study we further attempted to measure quantitatively ^{201}Tl and ^{67}Ga uptake by tumors in order to ascertain more distinctly the differences between ^{201}Tl and ^{67}Ga accumulations in lung cancer and then evaluated whether lung cancer could be classified or not from a nucleomedical viewpoint using this measurement.

MATERIALS AND METHODS

Among the 95 patients with pulmonary tumors examined using quantitative ^{201}Tl and ^{67}Ga scans at the Departments of Nuclear Medicine and Radiology, Fukushima Medical College Hospital from October 1981 to October 1984, 44 patients who were histologically confirmed as having primary lung cancer but received no therapy before both scans were the group in this study (Table 1). Histological types were determined according to the WHO classification.

All the patients were scanned with a scintillation camera (GCA 401-5) 30 min after the intravenous injection of 2 mCi (74 MBq) of ^{201}Tl-chloride, and the images were simultaneously listed into the computer (GMS 80A) in a 128 × 128 matrix for quantitative analysis. Two millicuries (74 MBq) of ^{67}Ga-citrate were intravenously injected into the patients 7 days after the ^{201}Tl scan and the images were collected, as mentioned above, 48 hr after the injection. The energy peak

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Table 1. List of 44 patients in this study

Sex	
Male	32
Female	12
Age (yr)	32-83 (mean 63 ± 12)
Histological type (WHO)	
Adenocarcinoma	17
Epidermoid carcinoma	15
Small cell carcinoma:	
oat cell type	3
intermediate cell type	6
Adenosquamous carcinoma	3
Clinical stage (UICC, 1978)	
I	10
II	3
III	12
IV	19
Method of definitive diagnosis	
TBLB	25
Surgery	13
Autopsy	6

TBLB: transbronchial lung biopsy.

and window level for ^{201}Tl and ^{67}Ga scans were set at 80 KeV ± 20%, and at 93 and 184 KeV ± 20%, respectively.

Figure 1 shows the method of estimating ^{201}Tl and ^{67}Ga uptake by the tumor. Regions of interest (ROIs) of similar size were symmetrically set at the tumor and the normal lung field on the same patient in order to measure the mean counts of each ROI. When the mean counts of ROIs at the opposite lung were regarded as the normal background counts (N) to the tumor counts (T), ^{201}Tl or ^{67}Ga uptake by the tumor could be obtained by calculating (T - N)/N. Further, in order to clarify which uptake was greater, ^{201}Tl or ^{67}Ga uptake by the tumor, the crude uptake ratio (CUR) of ^{201}Tl to ^{67}Ga uptake was evaluated on the same patient. Results were analyzed using the Cochran-Cox test.

RESULTS

Table 2 summarizes the CUR of each histological type. Adenocarcinomas had a CUR of 2.00 ± 1.55, the greatest value among all histological types. On the contrary, epidermoid carcinomas and oat cell carcinomas showed CURs of 0.47 ± 0.30 and 0.37 ± 0.05 respectively, both indicating significantly lower values than adenocarcinomas ($P < 0.01$). On the other hand, adenosquamous carcinomas represented a CUR of 0.91 ± 0.15, significantly intermediate between adenocarcinomas and epidermoid carcinomas ($P < 0.05$). In other words, epidermoid carcinomas, adenosquamous carcinomas and adenocarcinomas were indicated as a tumor series with low, intermediate and high CURs, respectively. Further, the 44 patients were revealed, as shown in Fig. 2, to range continuously from low-CUR epidermoid carcinoma to high-CUR adenocarcinoma. We could generally classify lung cancer into two groups from the differences between ^{201}Tl and ^{67}Ga uptake. Thirty (68.2%) of the 44 patients were classified into the first group, which took up much more ^{67}Ga than ^{201}Tl, whereas the other 14 (31.8%) patients were included in the second group, which took up much more ^{201}Tl than ^{67}Ga. Eleven (78.6%) of the 14 patients in the second group were diagnosed as having adenocarcinomas, while 22 (73.3%) of the 30 patients in the first group were diagnosed as having either epidermoid carcinomas or small cell carcinomas. Accordingly, most adenocarcinomas showed an uptake contrary to that of epidermoid and small cell carcinomas. However, ^{67}Ga uptake was greater than ^{201}Tl uptake in six (35.3%) of the 17 adenocarcinomas; hence both uptakes varied between patients with the same histological type. Similarly, one case of small cell carcinoma had a high CUR of 4.31, showing a pattern of uptake contrary to other small cell carcinomas.

Table 2. Crude uptake ratio (CUR) of ^{201}Tl to ^{67}Ga in lung cancer

Histological type	No. of cases	CUR
Adenocarcinoma	17	2.00 ± 1.55
Epidermoid carcinoma	15	0.47 ± 0.30*
Adenosquamous carcinoma	3	0.91 ± 0.15†
Small cell carcinoma		
Oat cell type	3	0.37 ± 0.05*
Intermediate cell type	6	1.19 ± 1.54

*Statistically significant from adenocarcinoma ($P < 0.01$).
†Statistically significant from adenocarcinoma ($P < 0.05$) and epidermoid carcinoma ($P < 0.05$) by Cochran-Cox's test.

DISCUSSION

The role of ^{201}Tl and ^{67}Ga scans in diagnosing lung cancer is now limited to determining the tumor extent or to evaluating hilar and mediastinal involvements [5]. According to our preliminary report [6], however, we have noticed that ^{201}Tl and ^{67}Ga accumulations in lung cancer have occasionally shown contrary patterns. Namely, it has been presumed that lung cancer could be classified into two large groups: a tumor series which takes up much more ^{67}Ga than ^{201}Tl and one that takes up much more ^{201}Tl than ^{67}Ga. Further study was undertaken to ascertain the differences in ^{201}Tl and ^{67}Ga accumulations by quantitatively measuring ^{201}Tl and ^{67}Ga uptake by the tumor and also to evaluate whether the uptake of both nucleids had a close relation with histological type. The results indicate that lung cancer could be classified into two major groups using quantitative ^{201}Tl and ^{67}Ga scans and that

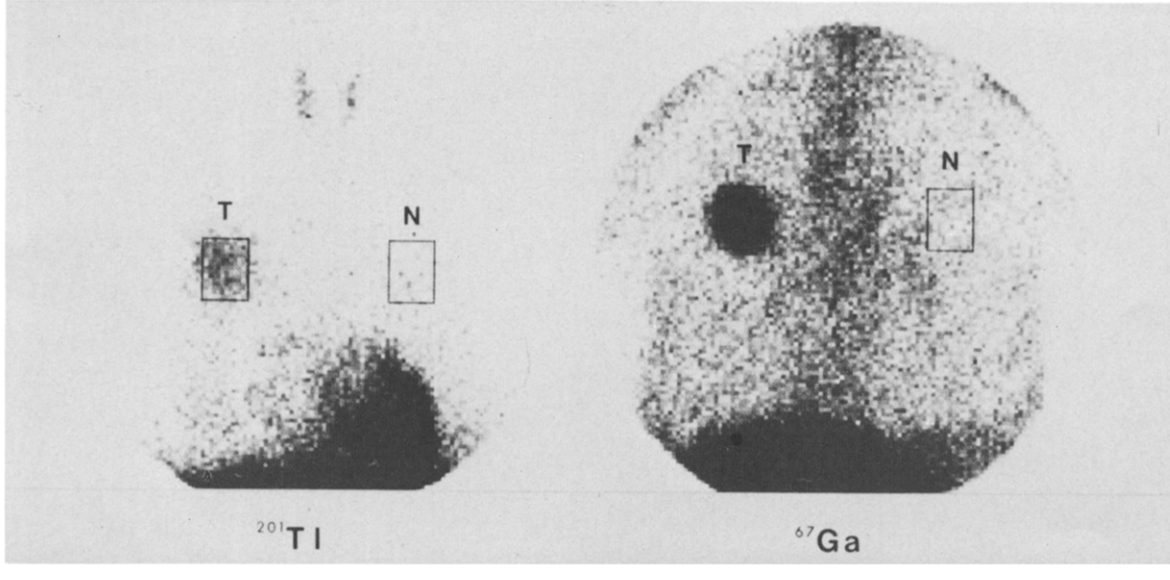

Fig. 1. The measurement of ^{201}Tl *and* ^{67}Ga *uptake by the tumor. Regions of interest (ROIs) of similar size were symmetrically set at the tumor and the normal lung. When T and N on both scans were regarded as the tumor count and normal background count, respectively,* ^{201}Tl *or* ^{67}Ga *uptake by the tumor was measured by* $(T - N)/N$.

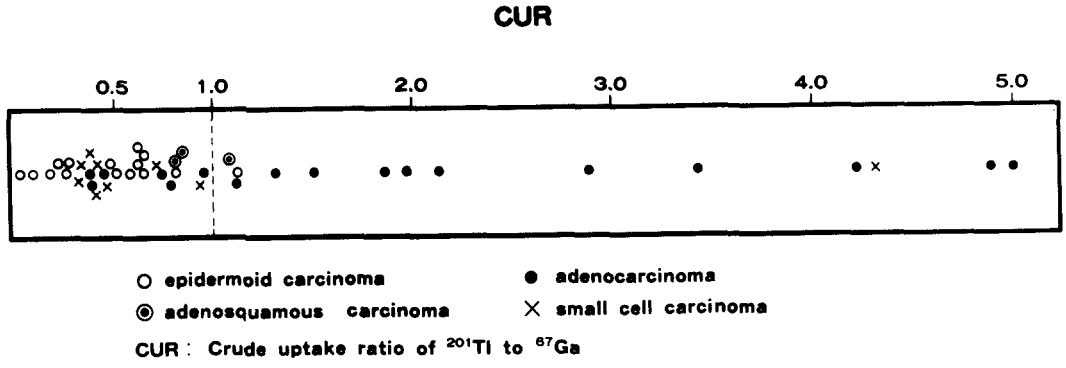

Fig. 2. The CUR and histological type in 44 patients with lung cancer. The 44 patients were divided into two groups according to the CUR. Many epidermoid and small cell carcinomas were classified into the group which took up much more ^{67}Ga than ^{201}Tl, whereas many adenocarcinomas belonged to the other group, which took up much more ^{201}Tl than ^{67}Ga.

many epidermoid carcinomas and small cell carcinomas belong to a tumor series which takes up much more ^{67}Ga than ^{201}Tl, whereas many adenocarcinomas are included in the tumor series which takes up much more ^{201}Tl than ^{67}Ga.

The differences in tumor affinities between ^{201}Tl and ^{67}Ga are thought to be based on the biochemical properties involving mineral metabolism in the tumor cells. It is well known that tumor accumulation of ^{201}Tl is associated with the potassium metabolism [7], while Muranaka has suggested that ^{201}Tl accumulation correlates to the active transport involving Na^+-K^+ ATPase as well as K^+ [8]. Also, concerning tumor accumulation of ^{67}Ga, Anghileri *et al.* [9, 10] have indicated a competitive binding of $^{67}Ga^{3+}$ to Ca^{2+}- and Mg^{2+}- binding sites. Therefore ^{201}Tl and ^{67}Ga uptake by lung cancer is assumed to be closely associated with potassium, calcium and magnesium metabolism, which play an important role in the control of cell transformation and growth [11, 12].

On the other hand, the fact that adenosquamous carcinomas revealed an intermediate uptake between epidermoid carcinomas and adenocarcinomas indicated a close correlation between the uptake of both nucleids and the histogenesis of lung cancer. Also, the results that ^{201}Tl and ^{67}Ga uptake occasionally showed contrary patterns even in patients classified into the same category at the light microscopic level suggested that ^{201}Tl and ^{67}Ga scans possess the possibility of estimating the heterogeneity of lung cancer. Therefore it can be concluded that quantitative ^{201}Tl and ^{67}Ga scans provide an additional, simple and useful diagnostic tool in evaluating the heterogeneity and histogenesis of lung cancer.

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