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Gallium-67 citrate imaging for the assessment of radiation pneumonitis

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In order to evaluate its usefulness in the assessment of radiation pneumonitis, gallium-67 citrate (^{67}Ga) imaging was performed before and after radiation therapy (RT) on 103 patients with lung cancer. In 23 patients with radiation pneumonitis detected radiographically, abnormal ^{67}Ga uptake in sites other than tumors was found in all post-RT ^{67}Ga lung images. Three patterns of uptake were found: (A), focal uptake corresponding to the RT field (n=10); (B), diffuse uptake including the RT field (n=4), and (C), diffuse uptake outside the RT field (n=9). The area of ^{67}Ga uptake was consistent with that of interstitial pneumonitis as revealed histopathologically in 7 cases. ^{67}Ga uptake in pattern (C) was an indicator of poor prognosis for the patients with radiation pneumonitis. ^{67}Ga uptake in the patients with reversible pneumonitis disappeared with steroid therapy. Sixteen (20%) of 80 asymptomatic patients, in whose chest radiographs there was no finding of radiation pneumonitis, showed transient ^{67}Ga uptake. These were considered to occur in the subclinical radiation pneumonitis. These data suggest that ^{67}Ga imaging is more sensitive than chest radiography in the detection of radiation pneumonitis and is useful in the assessment of the extent and clinical course of radiation pneumonitis.

Key words: Radiation pneumonitis, Gallium imaging, Radiation injury to the lung.

INTRODUCTION

SINCE ITS INTRODUCTION by Edwards and Hayes,[1] gallium-67 citrate (^{67}Ga) imaging has been widely used in imaging a variety of neoplasms and inflammatory lesions.[2–4] In inflammatory lesions of the lung, including sarcoidosis,[5,6] Pneumocystis carinii infection,[7] drug-induced pneumonitis,[8] and idiopathic interstitial pneumonitis,[9,10] ^{67}Ga imaging has been reported to be helpful in determining the degree of activity of the disease process and its spatial extent.

In patients who received radiation therapy (RT) for lung cancer, radiation injury to the lung is one of the most common complications, and is characterized by an acute and chronic reaction.[11] An acute reaction called radiation pneumonitis usually begins 1 to 3 months after RT, and may subside leaving no clinical or radiologic residua or may progress to an irreversible chronic pulmonary fibrosis.[12–14] Radiation pneumonitis occurs in only a small proportion of treated patients, but sometimes causes severe respiratory distress and even death.[15–19] It is, therefore, really important to establish its extent and to estimate the clinical course. In this paper, we have assessed the usefulness of ^{67}Ga imaging in determining the extent and clinical course of radiation pneumonitis by comparing it with clinical symptoms, chest radiographs, and histopathologic findings in the lung.

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MATERIALS AND METHODS

Between November 1976 and December 1985, 189 patients with non-resected lung cancer were treated with RT at the Department of Radiology, Ehime University Hospital. One hundred and three patients were included in this study according to the following criteria for patient selection: (a) ^{67}Ga imagings were performed before and after RT; (b) the tumor dose was over 50 Gy in patients with non-small cell

lung cancer (NSCLC), and over 20 Gy in patients with small cell lung cancer (SCLC); (c) the clinical course of each patient was known; (d) no previous RT was received. Of these criteria, (b) was the most important in patient selection, as about 40% of the 189 patients had reached a stage of cancer too advanced to treat with the intention of curing it. Eighty-eight (85.4%) were males and 15 (15.6%) females. Their ages ranged from 33 to 86 years (mean age, 67 years).

Each patient was irradiated with X-ray from a 10 MV linear accelerator, using parallel opposing anterior and posterior portals. The target volume included the lung tumor defined by chest radiography or computed tomography, plus 1 to 2 cm margin, plus adjacent hilar and mediastinal structures, even if the tumor did not extend to these structures. The tumor dose was 50 Gy to 90 Gy (mean, 67 Gy) in NSCLC patients, and 20 Gy to 70 Gy (mean, 43 Gy) in SCLC patients in a conventional fractionation schedule (1.8–2.0 Gy/fraction/day). Chemotherapy was combined with RT in about a half of the NSCLC patients, and in all of the patients with SCLC. Regimens of chemotherapy,[20–23] which varied from patient to patient, are summarized in Table 1. According to their clinical symptoms of radiation pneumonitis, the findings of chest radiograph, and their response to steroid therapy, patients were graded into 3 classes as follows: (1) asymptomatic: patients who had no evidence of radiation pneumonitis on the chest radiograph and no symptoms of radiation pneumonitis; (2) reversible: symptomatic patients who had radiation pneumonitis in the chest radiograph, but whose symptoms disappeared with steroid therapy; (3) fatal: patients who died of radiation pneumonitis. The diagnosis of radiation pneumonitis was established collectively, from the clinical symptoms, chest radiography, positive C reactive protein, increased erythrocyte sedimentation rate, the refractoriness to antibiotics therapy, and/or, in the cases of 7 patients, from the histopathology of the lung.

^{67}Ga imaging was performed 72 hours after intravenous injection of 111 MBq (3 mCi) of ^{67}Ga, with a large-field-of-view gamma camera with three energy window settings and a medium-energy parallel hole collimator. The first post-RT imaging was performed at a time ranging from 0 to 8 weeks (mostly within one month) after the completion of RT. The second post-RT imaging was performed within 5 months after the completion of RT, if clinically indicated. All ^{67}Ga images, including those obtained before RT, were retrospectively compared and analyzed for abnormal ^{67}Ga uptake in sites other than the original or recurrent tumors. ^{67}Ga images after RT were classified as positive when the pulmonary uptake in sites other than tumors exceeded the body background, and were classified as negative in the other cases. Routine chest radiography was performed once a week for the first month after the end of RT, at 2-week intervals during the second month, and at 1-month intervals thereafter. Additional radiography was carried out when radiation pneumonitis was suspected, or ^{67}Ga images were positive. We compared the findings in ^{67}Ga images with clinical symptoms and with the chest radiograph findings, and in 7 patients with the histopathology of the lung.

Table 1 Regimen of chemotherapy

Contents	Timing; Pre-RT	Intra-RT	Post-RT
Non-small cell lung cancer (n=42)			
Poly-chemotherapy	6	7	13
"FAMT" (*20*) *	0	1	6
"METT" (*21*) †	3	4	1
"MFC" (*21*) ‡	1	1	2 (1)**
others	2	1	4
Mono-chemotherapy	1	12	3
5-FU	0	10 (1)**	0
Bleomycin	1	2	3 (1)**
Small cell lung cancer (n=19)			
Poly-chemotherapy	6	8	2
Endoxan+Vincristine	2	5 (1)**	0
"COMP" (*22*) §	1	1	1 (1)**
"MOCA" (*23*) ¶	1	0	1
others	2	2	0
Mono-chemotherapy	1	2	0

* 5-FU, cyclophosphamide, mitomycin C, chromomycin
† mitomycin C, cyclophosphamide, thio-TEPA, chromomycin
‡ mitomycin C, 5-FU, cytocin-arabinoside
§ cyclophosphamide, vincristine, methotrexate, procarbazine
¶ methotrexate, vincristine, cyclophosphamide, adriamycin
** parentheses show number of cases who died of radiation- and/or drug-induced pneumonitis

RESULTS

(1) The relationship between the patterns of ^{67}Ga uptake and the extent and clinical course of radiation pneumonitis

In 39 out of 103 cases, ^{67}Ga images after RT showed abnormal pulmonary uptake in sites other than the original or recurrent tumors. These cases bore no evidence of bacterial pneumonia, viral infection or of pneumocystis carinii infection from radiographic

examination and/or histopathological examination at biopsy or autopsy. Four patterns of ^{67}Ga uptake were found in these cases as shown in Figure 1: types O, A, B, and C. The relationship between these patterns of ^{67}Ga uptake and the previously described clinical gradings of pneumonitis are summarized in Table 2. When type O changed to type A, O to B, O to C, A to B, A to C, or B to C in follow-up ^{67}Ga images, each patient was classified into the latter type. Sixteen (20%) of the asymptomatic cases revealed positive ^{67}Ga images. All of the 23 symptomatic (reversible and fatal) cases showed positive ^{67}Ga images, which were distributed in type A, B, or C. In the non-chemotherapy group, ^{67}Ga uptake outside the RT field (i.e., types B and C) was noted in 6 cases. Seven (78%) out of those who had ^{67}Ga uptake in type C had been treated with chemotherapy combined with RT, and 5 (56%) had fatal pneumonitis. Six (26%) of the 23 symptomatic cases were asymptomatic when their ^{67}Ga images showed positive findings but became symptomatic later.

Changes in the pattern of ^{67}Ga uptake in 21 patients on whom ^{67}Ga imagings were performed twice or more within 5 months after RT are shown in Figure 2. In 7 asymptomatic cases, type A or B changed to type O in 1 to 5 months without any therapy. In 6 out of 10 reversible cases, type A, B, or C changed to type O with steroid therapy, and in 4 cases, a third post-RT imaging was not performed. In 4 fatal cases, type O or A changed to type C, and 3 out of 4 cases died of radiation pneumonitis within a month after the ^{67}Ga image showed type C. A fatal case is shown in Figure 3.

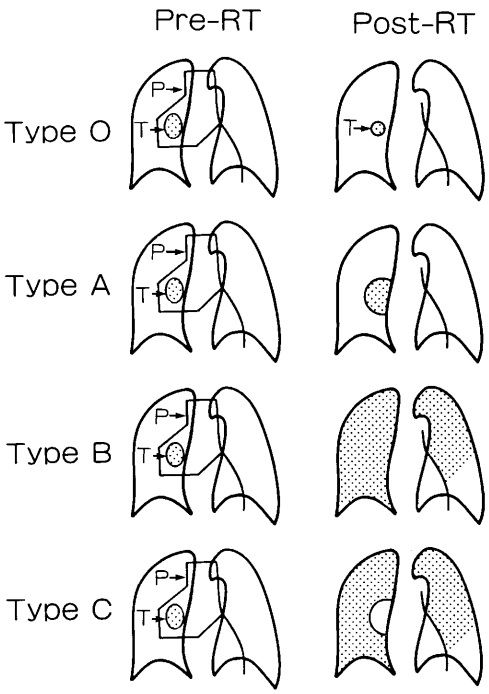


Fig. 1 Schema of pattern of ^{67}Ga uptake. Type O: no abnormal ^{67}Ga uptake in sites other than tumors; type A: abnormal ^{67}Ga uptake corresponding to the RT field, i.e., definitely larger uptake area than the original tumor; type B: diffuse ^{67}Ga uptake including the RT field, i.e., definitely larger uptake area than the RT field; and type C: diffuse ^{67}Ga uptake outside the RT field, i.e., large uptake area without uptake in the RT field. Stippled area shows the area of ^{67}Ga uptake. P: RT portal, T: primary tumor.

(2) Comparison of ^{67}Ga uptake with pulmonary histopathology

In 7 cases, histopathological examination of the lung

Table 2 Patterns of ^{67}Ga uptake and clinical gradings of radiation pneumonitis

Gradings of pneumonitis		Patterns of ^{67}Ga uptake			
		O	A	B	C
non-chemotherapy group (n=42)					
asymptomatic	(n=33)	27	5	1	0
reversible	(n=7)	0	3	2	2
fatal	(n=2)	0	1*	1	0
chemotherapy group (n=61)					
asymptomatic	(n=47)	37	6	4	0
reversible	(n=9)	0	6	1	2
fatal	(n=5)	0	0	0	5
Total	(n=103)	64	21	9	9

* This case was treated with very large treatment portals.

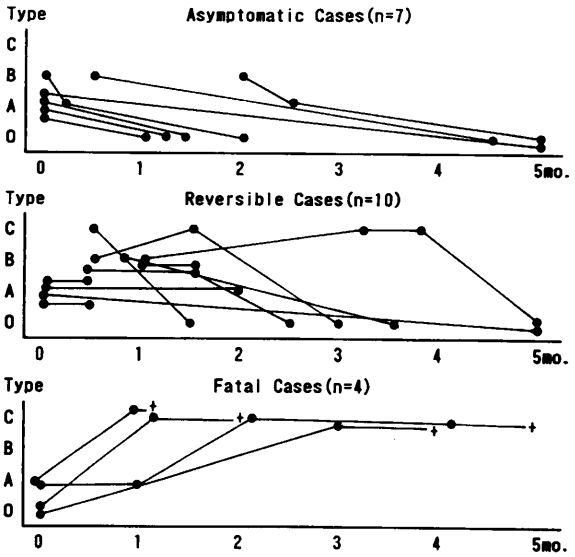
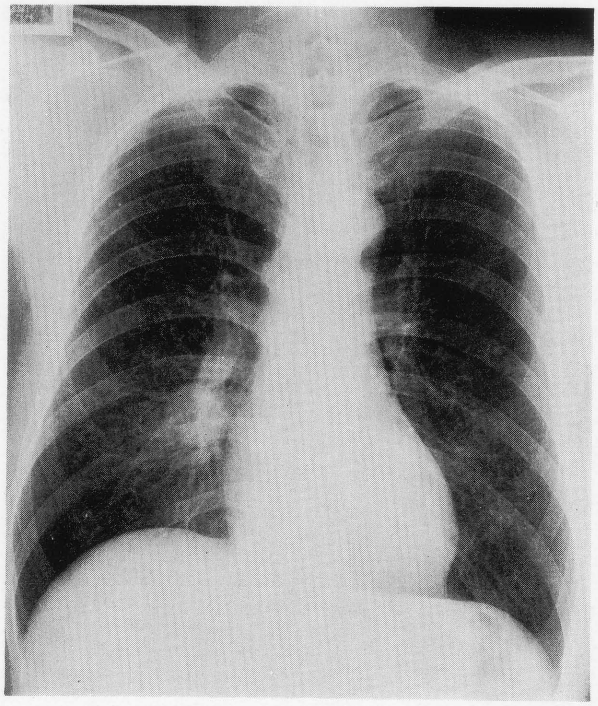
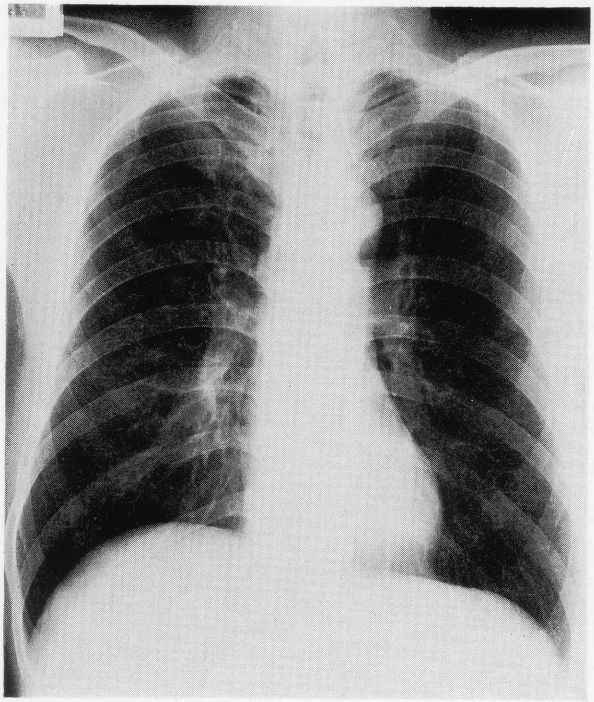


Fig. 2 Changes in the patterns of ^{67}Ga uptake in follow-up image

with abnormal ^{67}Ga uptake was performed by transbronchial biopsy or autopsy. Biopsies were performed on 2 patients immediately after the ^{67}Ga images had shown positive findings, and autopsies were performed on 4 patients with fatal pneumonitis, and on one patient who had active pneumonitis but died of another cause. Patient characteristics and the histopathological classification[24,25] of the lung in these cases are shown in Table 3. In 4 patients, who were treated with RT alone, the lung outside the RT field with abnormal ^{67}Ga uptake proved to have mild to severe interstitial pneumonitis due to irradiation. In



(A)



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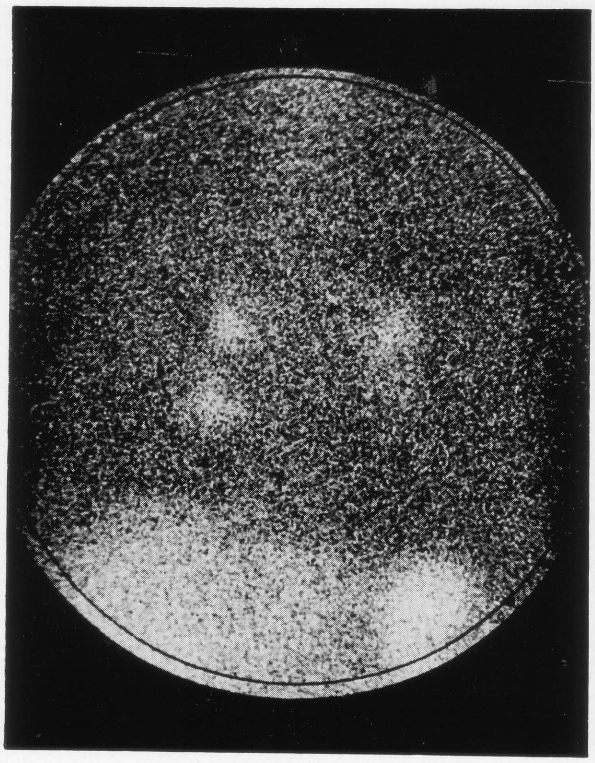

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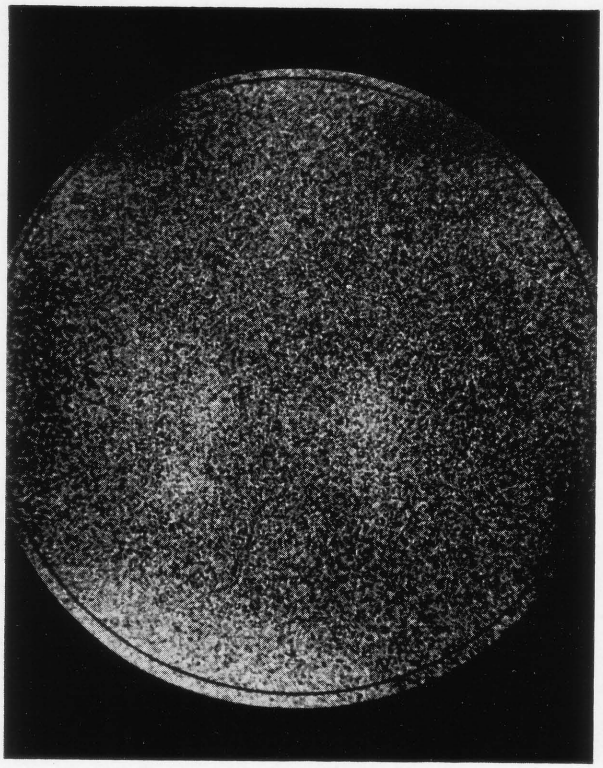
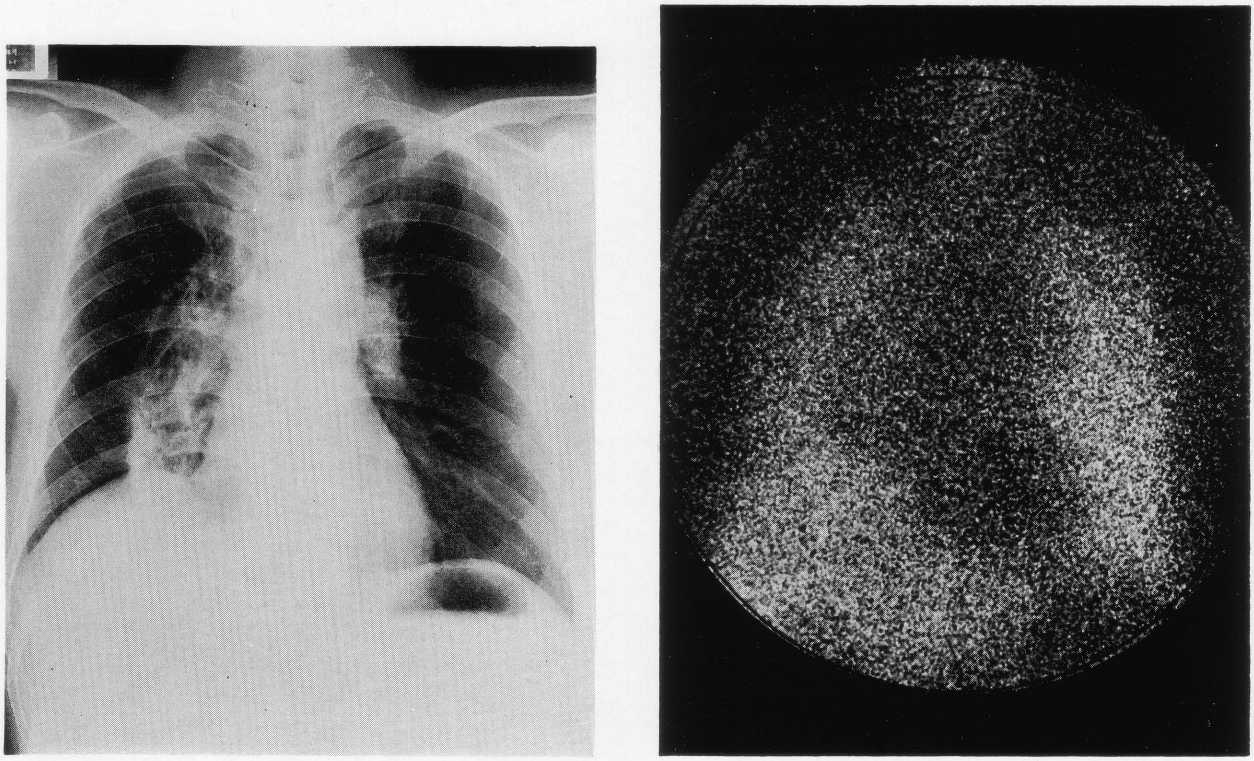


(D)



(E) (F)

Fig. 3 A 58-year-old male. He received RT in a dosage of 60 Gy for adenocarcinoma of the lung. Following the completion of RT, mitomycin C, 5-FU, and cytosine-arabinoside were administered intravenously for the residue of the original tumor. He died of radiation pneumonitis 5 months after the completion of RT. (A), (B); Chest radiograph and ^{67}Ga image before RT showed an abnormal mass in the right lower lobe, and abnormal ^{67}Ga uptakes in the bilateral hila as well as in the primary tumor. (C), (D); Chest radiograph and ^{67}Ga image 1 week after the completion of RT showed the mass decreased in size, and widened ^{67}Ga uptake corresponding to the RT field (type A). (E), (F); Chest radiograph and ^{67}Ga image 9 weeks after the completion of RT showed pulmonary fibrosis of the irradiated lung, and diffuse ^{67}Ga uptake outside the RT field (type C).

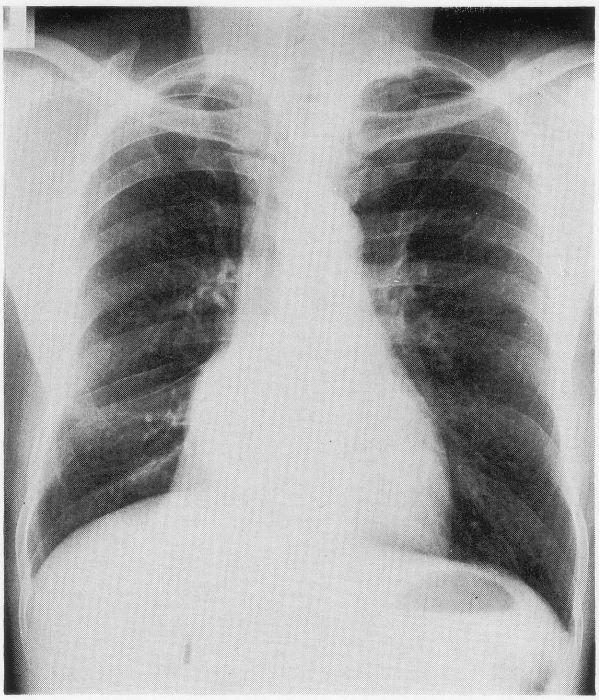
3 patients who were treated with chemotherapy combined with RT, the lung outside the RT field with abnormal ^{67}Ga uptake proved to have mild to severe interstitial pneumonitis, or pulmonary fibrosis due to chemotherapy and/or irradiation. An asymptomatic case is shown in Figure 4.

DISCUSSION

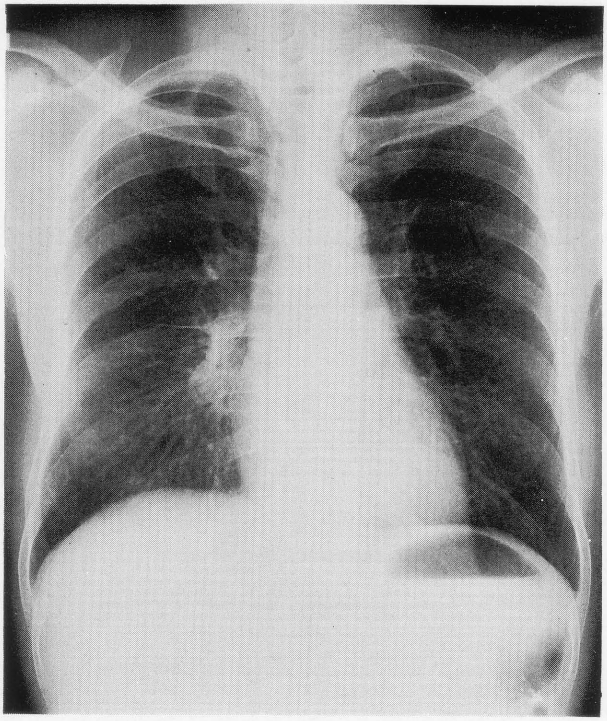
^{67}Ga uptake in the irradiated lung was first described by Schoot, et al in 1972.[26] They reported that transient ^{67}Ga uptake in the irradiated field was seen in 5 patients out of 6 who were restudied 2 months after the completion of RT. Gupta, et al[27] described diffuse ^{67}Ga uptake in radiation pneumonitis after focal irradiation of the lung. There have been few reports on the correlation between ^{67}Ga imaging findings and clinical and radiologic findings.[28]

This study demonstrates that ^{67}Ga imaging showed transient ^{67}Ga uptake in 20% (16 cases) of the asymptomatic patients, who had no clinical evidence of radiation pneumonitis. Histopathological examination of the lung at biopsy in one patient proved that the lung with such transient ^{67}Ga uptake had mild interstitial pneumonitis, which was considered to be subclinical radiation damage (Fig. 4). The ^{67}Ga imaging depicted subclinical and silent radiation pneumonitis which could not be detected on chest radiography. These findings suggest that ^{67}Ga imaging is more sensitive than chest radiography in the detection of radiation pneumonitis. Detecting an asymptomatic patient may seem to have no clinical significance, because the asymptomatic cases do not need any therapy. However, 23 (59%) of the patients with positive ^{67}Ga images already had clinical radiation pneumonitis at that time (17 cases) or later (6 cases). It is, therefore, considered important to give pause to adding more chemotherapy and irradiation in asymptomatic patients with positive ^{67}Ga images and to search for the cause of ^{67}Ga uptake or follow

those patients carefully. One of the roles of ^{67}Ga imaging in radiation pneumonitis is believed to detect patients who are susceptible to radiation pneumonitis. Pulmonary ^{67}Ga uptake after RT would be a risk factor for radiation pneumonitis. It is believed that ^{67}Ga imaging should be performed in cases wherein the occurrence of radiation pneumonitis is suspected or in cases who have risk factors for radiation pneumonitis, such as a large irradiated lung volume, a large radiation dosage, a preexisting chron-



(A)



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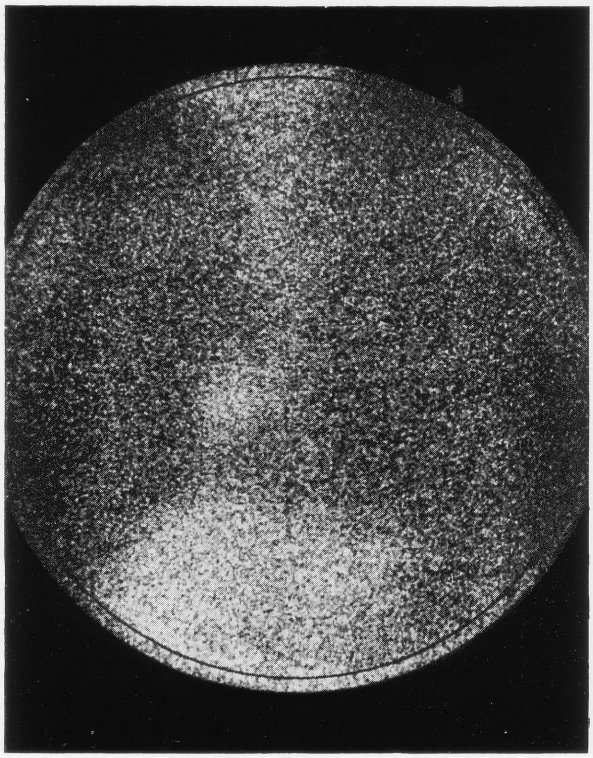

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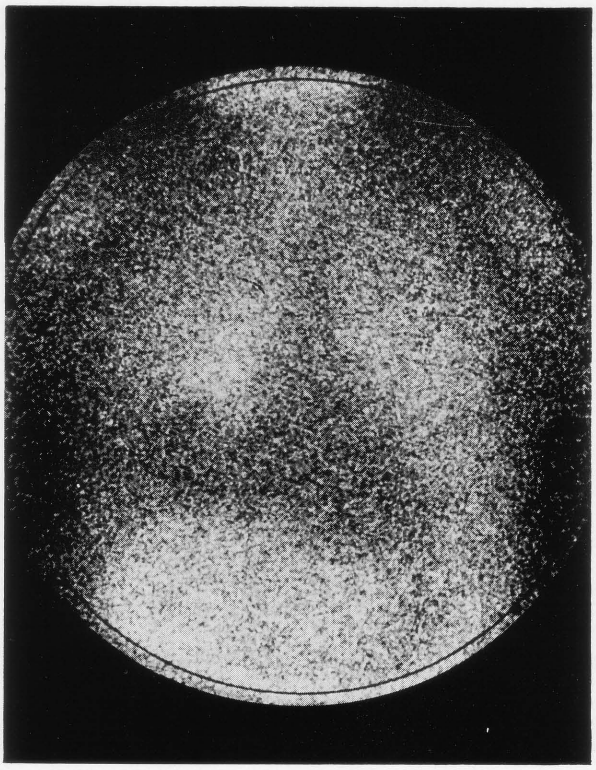

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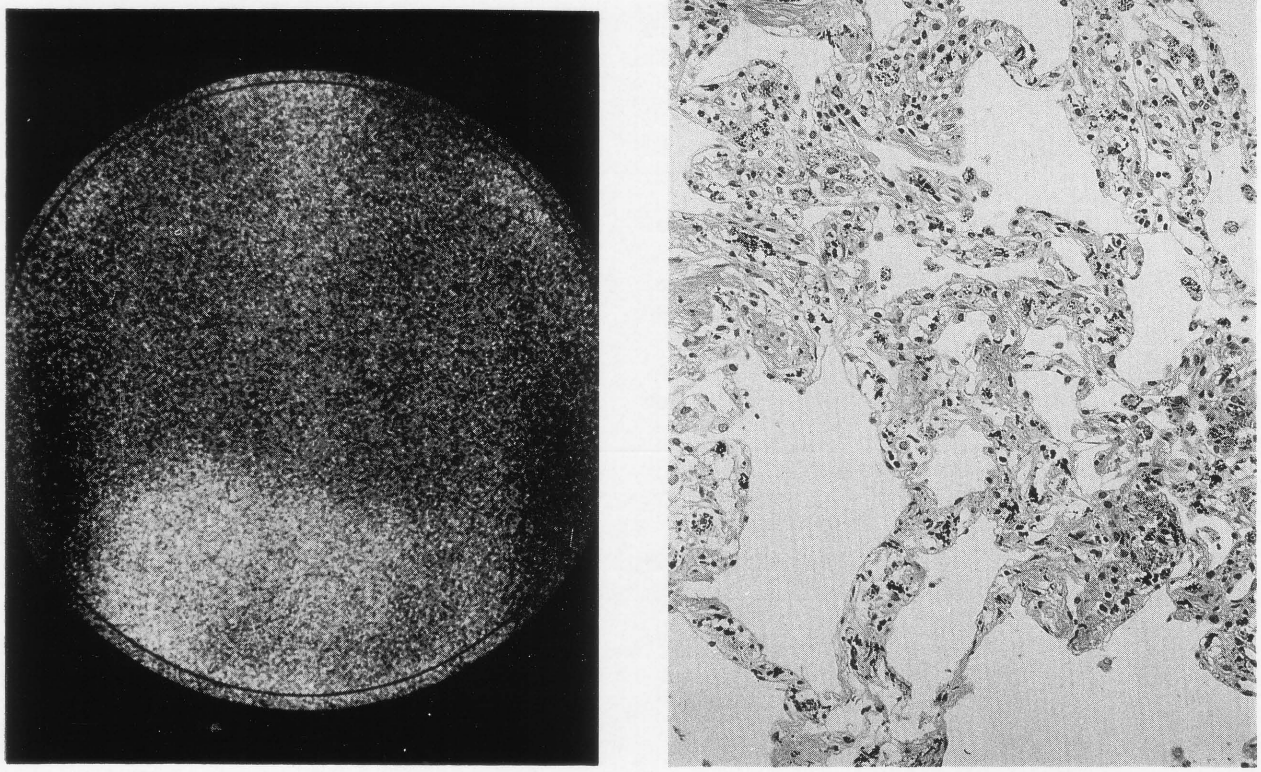

(E) (F)

Fig. 4 A 50-year-old male. He received RT in a dosage of 60 Gy for squamous cell carcinoma of the lung. (A), (B); Chest radiograph and Ga image before RT showed a collapse of the right lower lobe, and an abnormal ^{67}Ga uptake at the right hilum. (C), (D); Chest radiograph and ^{67}Ga image immediately after the completion of RT showed the lower lobe reinflated, but no evidence of radiation pneumonitis, and diffuse Ga uptake including the RT field (type B). (E); ^{67}Ga image 7 days after the completion of RT showed no abnormal uptake. (F); Histopathological specimen, which was taken from the periphery of the right upper lobe outside the RT field, showed mild interstitial pneumonitis with enlarged and degenerated septal cells of the alveoli. This was considered to be subclinical radiation damage.

ic lung disease, a chemotherapy combined with irradiation, old age, etc.

In symptomatic cases, all ^{67}Ga images were positive. These were classified into three types. Type A showed the direct effect of irradiation on the lung, which might have occurred in the rapidly proliferating connective tissue cells present after RT.[29] Type B in the non-chemotherapy group suggested that radiation pneumonitis had spread beyond the irradiated lung, as proved histopathologically in selected cases treated with RT alone. Such diffuse ^{67}Ga uptake, of course, should be carefully differentiated from bacterial pneumonia, viral infection, pneumocystis carinii infection, and tumor extension. Although it is controversial whether radiation pneumonitis extends over the irradiated lung or not, a few cases with radiation pneumonitis extending outside the RT field radiographically or histopathologically have been reported (15–19, 30). The present study supports the possibility that radiation pneumonitis sometimes extends beyond the irradiated lung. Two theories may be considered to account for this extension: (1) mediastinal lymphatic blockade[15] and (2) hypersensitivity immune reaction.[16,31]

The third pattern of ^{67}Ga uptake for radiation pneumonitis was designated type C. The clinical implications of type C in non-chemotherapy groups were still only slightly understood at the time of the present study, for want of histopathological specimens. Prato et al[32] emphasized that an early decrease in regional blood flow was significant in the irradiated lung. It is possible that decreased regional blood flow may lead to decreased ^{67}Ga uptake. It is also likely that radiation pneumonitis spreading outside the RT field in these patients occurred in the same manner as in type B.

Table 3 Summary of histopathologic findings in the lung with abnormal ^{67}Ga uptake outside RT field in 7 patients who underwent biopsy or autopsy

No.	Age	Sex	Dose/d*	Chemo-therapy†	Outcome	Cause of death	Pneumonitis	^{67}Ga scan	Histo-pathology‡
Biopsy proven cases									
1	50	M	60/36	(−)	37mo died	metastases	asymptomatic	B	mild
2	56	F	62/39	(−)	10.5mo died	local	reversible	B	moderate
Autopsy proven cases									
3	72	M	60/63	(−)	3mo died	local (hemoptysis)	reversible	B	mild∼moderate
4	69	M	70/49	(−)	3mo died	pneumonitis	fatal	B	mild∼severe
5	70	M	60/37	5-FU (intra)	2.4mo died	pneumonitis	fatal	C	moderate∼severe
6	69	M	60/44	Bleo (post)	4.7mo died	pneumonitis	fatal	C	mild∼fibrosis
7	66	M	39.6/30	COMP (intra)	4mo died	pneumonitis	fatal	C	moderate∼severe

* Dose in Gy/day

† "intra"; at the same time as RT, "post"; after RT, "Bleo"; Bleomycin, and "COMP"; Cyclophosphamide, Vincristine, Methotrexate and Procarbazine.

‡ "mild"; mild interstitial pneumonitis with degenerating alveolar epithelium.
"moderate"; moderate interstitial pneumonitis with desquamation of septal cells into alveoli and macrophage infiltration.
"severe"; severe interstitial pneumonitis with fibrous thickening of interstitial septa with infiltration of mononuclear cells.
"fibrosis"; interstitial pulmonary fibrosis.

In the chemotherapy group, the effects of both drug and irradiation on the lung contributed to the findings in ^{67}Ga images. Several chemotherapeutic agents have been reported to interact with irradiation[33-35] and cause pulmonary damage themselves.[36-38] In addition ^{67}Ga uptake in drug-induced pneumonitis is well known.[8] Type C in the chemotherapy group consisted of a ^{67}Ga negative area in the RT field and a positive area outside the RT field, and the findings in the chest radiograph and the microscopic findings in the lung suggested that the former was radiation fibrosis and the latter drug-induced and/or radiation-induced pneumonitis. The patients whose ^{67}Ga image was type C in both the non-chemotherapy and chemotherapy groups suffered from reversible (in 4 cases) or fatal (in 5 cases) radiation pneumonitis. It is likely that the ^{67}Ga uptake of type C would be an indicator of poor prognosis for the patients with radiation- and/or drug-induced pneumonitis. ^{67}Ga uptake of type B, however, would not be an indicator of poor prognosis, as most of the patients with type B had asymptomatic (55.6%) or reversible (33.3%) pneumonitis (Table 2).

The close relationship between radiation pneumonitis and ^{67}Ga uptake is evident in our study of the reversible cases (Fig. 2), where 6 cases out of 10 showed negative images after steroid therapy (follow-up imaging was not performed in 4 cases). This observation corresponds to the reported results in sarcoidosis,[2,5,6] tuberculosis,[2] and in idiopathic pulmonary fibrosis.[9,10] The follow-up ^{67}Ga imaging is a sensitive indicator of the assessment of the response to steroid therapy in patients with radiation pneumonitis.

In conclusion, ^{67}Ga imaging is a sensitive tool for the detection of radiation pneumonitis and a useful indicator both for the assessment of the extent of radiation pneumonitis and for the estimation of the prognosis of the patients suffering from radiation pneumonitis. Follow-up ^{67}Ga imaging is also fundamental for the assessment of the response to steroid therapy.

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