Discrimination of Postradiotherapy Lung Fibrosis from Recurrence by Gallium-67 Scan in Lung Cancer

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The differentiation between post-radiotherapy lung fibrosis and tumor recurrence is often a dilemma to physicians. Twenty two patients with lung cancer who had received 45~60 Gy to the chest were chosen to study the possible role of gallium-67 scan. Seventeen squamous cell carcinomas were treated with only radiotherapy, 3 small cell carcinomas with combination chemotherapy, 2 adenocarcinomas with lobectomy. A total of 8 patients with pneumonitis with or without fibrosis and recurrence showed uptake of gallium at the site of inflammation. Of the 12 recurrences and residual diseases after radiotherapy, positive gallium uptake was present in 11 cases (92%). Of the 10 recurrence-free cases, all the 5 patients with pneumonitis revealed gallium accumulation. However, 4 of the 5 patients (80%) with recurrence-free fibrosis have not accumulated gallium in the fibrotic areas. Fibroses in 6 patients were developed after 8 months of completion of radiotherapy. These facts suggest that gallium-67 scan after 1 year post-treatment may aid for the discrimination of fibrosis from tumor recurrence unless pneumonitis is present.

Key Words: postradiotheraphy, Ga-67 scan.

INTRODUCTION

It is known to be very difficult to differentiate, by conventional imaging technique including computed tomography, between the lung fibrosis induced by radiation therapy of lung cancer and the recurrence at primary site. Though recent progression of magnetic resonance imaging technology may have some potential, it is still posing the clinicians in treating patients with lung cancer. However, investigators have found that there was a significant decrease in uptake of gallium when tumors showed partial or complete fibrosis after therapy[1]. It has been shown in a number of studies that Ga-67 scans may convert to negative following radiotherapy or chemotherapy, though the mechanism of which has not been established[2,3]. Radiation-induced lung fibrosis is usually precedented for months to years by pneumonitis, which is an inflammatory process by radiation effect and gallium uptake is present at this time.

The present study was undertaken in order to 1) evaluate the ability of gallium scan for differentiation of fibrosis and recurrence, and 2) observe the time of gallium uptake after radiotherapy, from pneumonitis to fibrosis and thereafter.

MATERIALS AND METHODS

Of the patients with lung cancer treated at the Department of Radiation Oncology, Kyungpook National University Hospital from January 1989 to June 1990, twenty two patients who were prone to develop fibrosis and/or recurrence were selected and followed up every month with physical examination, chest X-ray film, gallium scan, chest CT scan, and bronchoscopy with biopsy and MRI if necessary. Gallium-67 scans were performed 48 and 72 hour after intravenous injection of 3 to 5 mCi of Ga-67. Scintigraphy was performed using a gamma camera (Scintiview, Siemens) with a medium-energy collimator and 90 and 184 KeV energy photopeaking. Anterior, posterior and, when necessary, lateral views with each 500,000 counts were obtained. There were 17 squamous cell carcinomas, 3 small cell carcinomas, and 2 adenocarcinomas. The response at the completion of radiotherapy, time of progression of pneumonitis to fibrosis, time of recurrence after radiation therapy, and gallium uptake were scrutinized.

All the patients had received radiation therapy to the mediastimum and tumor-bearing lobes with 45~60 Gy in 5~6 weeks according to the histology and the prior treatment. No chemotherapy was done on squamous cell carcinomas. Alternating

chemotherapy with CAV (Cyclophosphamide, Adriamycin, Vinblastine) and Vp-16 and cis-platin was administered to the patients with small cell lung cancers. Lobectomy was done in the two patients with adenocarcinoma.

"Recurrence (12 cases)" in the current study included 4 true recurrences after complete response, 3 partial responders, and 5 persistent diseases.

RESULTS

In the 22 study population, 14 patients have shown complete local control of their diseases at the end of radiotherapy. There were 3 partial responders and 5 persistent diseases, as shown in Table 1. The time of true recurrence after complete remission according to the post-treatment time is revealed in Table 2. There were 4 recurrences in the complete responder group. All the recurrence developed after a year from completion of treatment. Lung fibrosis had developed in 6 patients, which was evident after 8 months from the completion of radiotherapy. There were 6 patients in whom no fibrosis were developed even after a year post-treatment. Pneumonitis was developed after radiotherapy in virtually all patients, but the severity was not dose-related. All the pneumonitis and the fibrosis were developed only within the radiotherapy port. Most of the pneumonitis subsided in several months without any particular treatment. The status of gallium uptake is illustrated in Table 4. A total of 8 patients with pneumonitis showed uptake of gallium at the site of inflammatory change, regardless of the tumor status and the histology. Therefore the distinction between the pneumonitis and the active tumor could not be made. Overall, of the 12 recurrences and residual diseases, positive gallium scan was found in 11 cases (92%). Of the 10 recurrence-free patients, positive gallium scan was found also in all the 5 patients with pneumonitis. On the other hand, of the 5 recurrence-free fibrotic cases, 4 (80%) revealed negative finding on the gallium scan. Figure 1 illustrates the findings of a patient with fibrosis and negative gallium uptake (a), and a patient with recurrence and positive gallium scan (b).

Table 1. Response after Radiotherapy

Complete response	14
Partial response	3
Persistence	5
Total	22

Table 2. Time of True Recurrence after CR*

Recurrence	
below 12 months	0
over 12 months	4
No recurrence	10
Total	14

* Complete Response

DISCUSSION

Gallium-67 is concentrated in a variety of neoplastic and inflammatory lesions. Since its accumulation is not specific for neoplasm, the diagnosis of malignancy cannot be made from a postitive scan. However, once a histologic diagnosis of the malignancy has been made, Ga-67 scanning may be useful not only for the determination of the extent of disease, but also for the monitoring of the effectiveness of treatment[1~6].

The mechanism of Ga-67 accumulation in tumors is complex. Multiple factors contribute to the local-

Table 3. Time of Development of Fibrosis

Fibrosis (+), time after radiotherapy		
below 8 months	0	
8 – 12 months	3	
over 12 months	3	
total		6
Fibrosis (–), after 12 months		6
Pneumonitis in virtually all patients		

Table 4. Result of Gallium Scan

Chest Status	Ga uptake (+)	Ga uptake (–)	Total
Recurrence (+)			12
pneumonitis (+)	3		
fibrosis (+)	3		
none	5	1	
Recurrence (–)			10
pneumonitis (+)	5		
fibrosis (+)	1	2	
none		2	

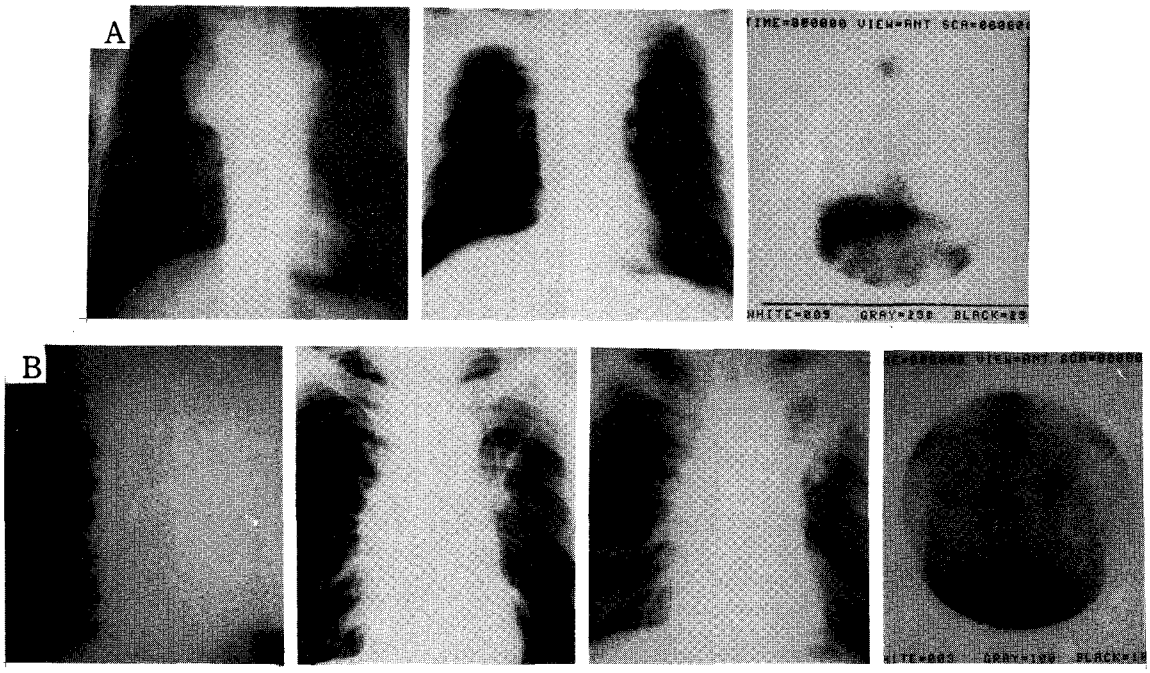

Fig. 1. (A) A patient with small cell carcinoma treated with 45 Gy to the right upper lobe and mediastinum combined with CAV and Vp-16, cis-platin. A year later there was fibrosis with no evidence of disease. Gallium scan shows no abnormal uptake.
(B) A patient with squamous cell carcinoma in the left upper lobe treated with 60 Gy to the chest. After a year, firosis and recurrence at the primary site were evident with positive gallium uptake.

ization of Ga-67 in tumors. a) Adequate blood supply is essential. At areas without any blood supply such as the necrotic center of a large tumor and areas of fibrosis, there is no accumulation of Ga-67[8]. b) Increased capillary permeability and expanded extracellular space of tumors may play an important role[9]. c) Gallium-67 enters tumor cells by a variety of ways[10~12]; by simple diffusion as a result of the hyperpermeability of the tumor cell membrane, by competition of binding Ga-67 to calcium- and magnesium-binding sites, by binding to lactoferrin present in some tumors, and by transferrin-mediated uptake by the tumor cells mainly in the form of transferrin-Ga-67 complex. d) Some Ga-67 may also be taken up by the inflammatory cells when they are present in the tumors[13]. e) The acidic pH of the interstitial fluid of tumors promotes dissociation of Ga-67 from transferrin-Ga-67 complex, that may contribute to the more effective entrance of Ga-67 into tumors[14].

Residual mass and tumor recurrence after treatment of lung cancer constitute a common and difficult diagnostic problem. A variety of radiologic imaging do not contribute to the understanding of its nature. Biopsy, which can hardly be used routinely, is invasive and may be misleading because the tumor mass cannot usually be totally resected and it is often difficult to obtain adequate samples from the tumor[15]. Gallium-67 studies in animals, where it is possible to examine the entire tumor, suggest that Ga-67 is an indicator of tumor viability[16]. Recently, several papers[15~17] underscored the important role of gallium-67-citrate scintigraphy in the evaluation of the treated patients with malignant lymphoma, Hodgkin's disease, and lung cancer, to assess tracer avidity within a residual mass as an indicator of response to therapy and tumor recurrence after completion of therapy. It is possible to assume that Ga-67 negative post-therapy residual mass indicates a positive therapeutic response and absence of remnant or recurred tumor. If such importance is associated with the negative Ga-67 image in terms of major therapeutic decision, caution is needed in depicting scintigraphic data. Few false positive Ga-67 scans due to benign pulmonary uptake are reported in patients with lung cancer[16]. Documentation of true negative image is more

difficult because of the tumor heterogeneity, count density, patient positioning, some normal uptake in mediastinal nodes, and prior chemo- or radiotherapy[15,18,19].

In this current study, strong gallium uptake was demonstrated in patients with recurrence (active tumor) and simultaneous fibrosis, whereas no gallium uptake in patients with only fibrosis, as in Fig. 1. In the 10 patients without recurrence, all the 5 patients with pneumonitis showed moderate gallium uptake. However, no gallium accumulation was present in 4 of 5 recurrence-free patients with or without fibrosis as shown in table 4. Since fibrosis is generally evident about one year after radiotherapy and recurrence in this period is also possible, gallium-67 scan might be of help when used after one year of radiotherapy to discriminate recurrence from lung fibrosis if pneumonitis is not present.

Newly developed imaging techniques to increase sensitivity and thereby eliminate false negative image will improve usefulness of Ga-67 scan in patients with lung cancer. Sensitivity would be increased by SPECT imaging with larger doses (8-10 mCi) of gallium instead of small dose (3~5 mCi) administration and planar imaging used in our study[20]. Waxman et al[21] have used Ga-67 chloride and thallium-201 chloride to differentiate hilar uptake due to tumor from that secondary to post-therapy inflammatory change. They reported that Ga-67-hilar uptake due to a benign etiology showed no Tl-201 uptake, but others disagree about it[16]. We suppose that Ga-67 imaging is capable of differentiating viable or recurred tumor from radiation-induced lung fibrosis. Efforts to provide accurate data for utilization and prospective randomized clinical study would be necessary to confirm our results.

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= 국문초록 =

갈륨 스캔을 이용한 폐암의 치료 후 섬유성 변성과 재발의 감별

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폐암의 방사선 치료 후 발생하는 치료 부위의 섬유성 변성과 암종의 재발의 구별이 어려울 때가 많으나 아직 이렇다 할 감별진단 방법이 없다. 경북대학교 병원 치료방사선과에서 1989년 1월 부터 1990년 6월까지 방사선 치료를 받은 폐암 환자 중 섬유성 변성이나 재발의 가능성이 높은 22명을 대상으로 Gallium-67 스캔의 유용성을 연구하였다. 대상환자는 편평 세포암 17명, 소세포암이 3명, 선암 2명이었고, 편평 세포암은 약물치료를 하지 않았고, 소세포암은 CAV와 Vp-16 및 cis-platin 으로 병용치료 하였으며, 선암은 폐엽절제술을 시행하였다. 방사선 치료는 조직형과 병용치료의 양상에 따라 5~6주에 걸쳐 45~60 Gy를 투여하였으며, 치료 후 정기적으로 추적 검진하였다. 재발과 상관없이 방사선 폐염이 발생한 군에서는 모두 Gallium 축적을 보였고, 12명의 재발 혹은 잔여 종양이 있는 군에서는 11명이 Gallium 축적을 보였다(92%). 무병상태의 10명 중 방사선 폐염을 가진 5명에서는 Gallium 축적이 있었으나, 섬유성 변성만 있는 5명에서는 4명에서 Gallium이 축적되지 않았다(80%). 섬유성 변성은 모두 치료 종료 후 8개월 이후에 임상적으로 출현되었다. 이 시기에 재발과 섬유성 변성의 구별이 용이하지 않고 치료방침에도 결정적 영향을 미치므로, 치료 후 1년이 지난 환자에서 Gallium-67 scan이 임상적으로 유용할 것으로 사료된다.