Annals of Nuclear Medicine Vol. 12, No. 6, 355–362, 1998

^{201}Tl SPECT as an indicator for early prediction of therapeutic effects in patients with non-small cell lung cancer

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This study retrospectively investigated the good parameters on thallium-201 chloride (^{201}Tl) SPECT for early assessment of the therapeutic effects in patients with non-small cell lung cancer.

Based on tumor response as determined by chest CT scan about 9 weeks after the end of irradiation with adjuvant chemotherapy, the subjects were divided to the responder group (tumor regression > 50%, n = 13) and non-responder group (tumor regression < 50%, n = 13). ^{201}Tl SPECT was performed before and at the halfway through the course of therapy (average tumor dose, 27.4 Gy ± 4.5) in all the patients. SPECT was conducted twice 15 min (early scan) and 120 min (delayed scan) after intravenous injection of 148 MBq (4 mCi) of ^{201}Tl. Tumor-to-contralateral normal lung tissue count ratios on both scans were calculated as early and delayed uptake ratios (EUR and DUR), and a retention index (RI) was also derived from these ratios.

In the responder group, a significant decrease in DUR and RI halfway through the therapy was observed compared to pretreatment (2.6 ± 0.6 vs. 3.5 ± 1.0 ; $p < 0.01$, and −2.3% ± 25.5 vs. 37.4% ± 17.8; $p < 0.001$, respectively), even though EUR did not change significantly (N.S.). By contrast, in the non-responder group, there were no significant changes in any of these parameters (N.S.). When comparing DUR and RI for the two groups halfway through the therapy, DUR and RI were significantly lower in the responder group (both; $p < 0.01$), but no significant difference was noted in EUR (N.S.), and the percent reduction in tumor size did not correlate with the percent decrease in DUR or RI (N.S.).

These results indicate that the extent of decrease in DUR and RI after therapy can be a useful parameter for early assessment of the therapeutic effects in patients with non-small cell lung cancer.

Key words: thallium-201 chloride, single photon emission computed tomography (SPECT), lung cancer, radiation therapy

INTRODUCTION

COMPUTED TOMOGRAPHY (CT) has been a standard method of measuring tumor size and assessing tumor response to radiation and/or chemotherapy. Nevertheless, this method is insufficient for assessing the therapeutic effects soon after starting therapy, since treated tumors may show signs of slow regression even in successful therapy.[1–7]

Thallium-201-chloride (^{201}Tl) has recently been proven useful for assessing the therapeutic response of a variety of malignant tumors,[7–15] and our previous animal study using VX-2 tumors indicated that tumor ^{201}Tl uptake was altered soon after irradiation.[16] If we could assess tumor response soon after starting therapy, it would be beneficial when considering additional therapeutic regimens in some patients, and ultimately the patient's prognosis would improve. In this study, the authors retrospectively survey the parameters measured by ^{201}Tl SPECT available for the early evaluation of therapeutic effects in treated patients with non-small cell lung cancer.

Received August 3, 1998, revision accepted October 2, 1998.

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Table 1 Summary of data in 26 patients

Case No.	Age/ Sex	Histological diagnosis	TNM	RT/Chemo dose (Gy/mg)	Tumor volume Pre (mm^2)	Tumor volume Post (mm^2)	Early ratio Pre	Early ratio Post	Delayed ratio Pre	Delayed ratio Post	Retention index Pre (%)	Retention index Post (%)	Total dose of RT/Chemo (Gy/mg)	Final tumor volume (mm^2)	Tumor response
Responder group															
1.	65 M	Squamous cell	T1N2M0	22/—	552	552	3.35	4.34	3.78	2.60	12.7	−40.0	54/—	0	CR
2.	67 M	Squamous cell	T2N2M1	18/100 (VDS 8, MMC 11)	224	195	2.80	1.87	3.97	2.21	41.6	19.7	52/220 (VDS 13, MMC 11)	100	PR
3.	69 M	Adenocarcinoma	T1N2M0	28/—	226	234	2.17	3.27	2.75	2.01	26.7	−38.5	50/—	0	CR
4.	60 M	Squamous cell	T3N2M1	34/—	1208	1031	3.75	2.72	4.02	1.74	7.30	−36.0	52/220	543	PR
5.	63 M	Squamous cell	T3N1M1	28/110	3394	3458	1.87	3.03	2.91	2.90	54.8	−4.2	50/250	1562	PR
6.	68 M	Large cell	T3N3M0	26/100 (VDS 12)	1825	1283	2.26	1.83	2.94	2.23	29.3	21.8	50/200 (VDS 18)	584	PR
7.	65 F	Adenocarcinoma	T4N3M1	30/—	4804	2084	4.96	1.50	6.51	1.82	31.2	21.3	44/230	1681	PR
8.	72 M	Adenocarcinoma	T4N3M0	30/—	4506	2928	3.40	3.16	5.30	3.56	55.8	12.6	50/220	1577	PR
9.	64 M	Squamous cell	T3N3M1	22/180 (VDS 12)	1676	1283	2.21	2.80	3.90	3.37	76.3	20.3	50/250 (VDS 18)	703	PR
10.	60 M	Adenocarcinoma	T3N2M1	34/100 (VDS 10)	2242	1405	2.15	1.61	3.17	1.80	47.8	12.5	54/240 (VDS 16)	807	PR
11.	73 M	Large cell	T2N2M0	26/110 (VDS 8, MMC 11)	1235	1022	2.89	3.10	3.91	3.36	35.3	16.5	50/220 (VDS 10, MMC 17)	284	PR
12.	64 M	Squamous cell	T3N2M1	28/—	1984	1883	2.84	2.35	3.78	2.36	32.9	0.4	50/—	753	PR
13.	62 M	Squamous cell	T2N2M0	24/100	1456	1321	2.96	3.23	3.97	2.02	34.0	−37.4	46/260	378	PR
Non-responder group															
14.	63 M	Adenocarcinoma	T3N2M1	18/—	6630	7560	3.45	2.86	3.72	2.94	7.82	2.70	54/210	7854	PD
15.	59 M	Squamous cell	T3N3M0	24/100 (VDS 10, MMC 6)	1575	1673	3.11	2.63	4.70	3.78	51.8	43.7	52/200 (VDS 12, MMC 10)	1260	NC
16.	54 F	Adenocarcinoma	T2N2M1	34/110	1620	1734	1.57	1.73	1.73	2.35	15.3	35.8	58/260	1458	NC
17.	67 F	Squamous cell	T3N2M0	28/—	2786	2560	2.75	3.66	5.15	5.67	87.2	55.4	60/240	2972	PD
18.	65 M	Adenocarcinoma	T4N3M1	34/110 (VDS 12)	1292	682	2.14	2.02	2.65	2.66	23.8	31.6	59/250 (VDS 18)	1033	NC
19.	61 M	Adenocarcinoma	T2N2M1	28/100	896	1190	2.67	2.48	3.85	3.40	44.0	37.0	67/230	1345	PD
20.	72 M	Adenocarcinoma	T3N2M0	26/—	1575	1347	3.29	3.81	5.40	5.09	68.7	31.5	78/230	1338	NC
21.	71 F	Adenocarcinoma	T3N1M1	22/120 (VDS 12)	3465	2493	3.92	4.48	5.03	5.50	28.2	22.7	67/250 (VDS 15)	3773	PD
22.	74 M	Adenocarcinoma	T3N2M1	30/110 (VDS 14)	1876	2074	1.77	4.79	2.26	4.27	28.0	−10.6	56/240 (VDS 20)	1594	NC
23.	60 M	Adenocarcinoma	T3N3M0	30/—	1150	1221	2.87	2.24	3.38	2.61	17.7	16.5	67/270	1046	NC
24.	79 M	Adenocarcinoma	T4N2M1	34/90 (VDS 12)	2342	2318	2.66	2.68	3.84	3.32	44.2	23.8	78/260	1452 (VDS 18)	NC
25.	65 M	Adenocarcinoma	T3N1M0	28/—	1457	1875	2.87	2.47	3.95	3.35	37.5	35.6	60/—	1194	NC
26.	56 M	Adenocarcinoma	T2N2M1	28/120	528	532	3.20	3.02	4.00	3.70	24.7	22.5	54/260	1462	PD

Squamous cell = Squamous cell carcinoma, Large cell = Large cell carcinoma. RT/Chemo dose = Radiotherapy / Chemotherapy (cisplatin) dose, Final tumor volume: Tumor volume measured about 9 weeks after the accomplishments of therapy. VDS = Vindesine, MMC = Mitomycin, CR = Complete response, PR = Partial response, NC = No change, PD = Progressive disease

MATERIALS AND METHODS

Between September 1993 and April 1998 a total of 32 patients with non-small cell lung cancer (adenocarcinoma, 16; squamous cell carcinoma, 14; large cell carcinoma, 2) underwent ^{201}Tl SPECT and CT scans before and approximately halfway through radiationtherapy (accumulated tumor dose: 27.4 ± 4.5 Gy) with or without adjuvant chemotherapy (cisplatin mainly; 1 course = 70–120 mg). The adjuvant chemotherapy was concomitantly performed during radiationtherapy. Local tumor response to therapy was assessed by follow-up CT scan about 9

Table 2 Comparison of parameters on Tl-201 SPECT between responders and non-responder groups

	Early ratio		Delayed ratio		Retention index (%)	
	Pre	Post	Pre	Post	Pre	Post
Responders (n = 13)	2.8 ± 0.8	2.6 ± 0.6	3.9 ± 1.0	2.4 ± 0.7*	37.4 ± 17.8	−2.3 ± 25.5*
Non-responders (n = 13)	2.7 ± 0.6	2.9 ± 0.9	3.8 ± 1.1	3.7 ± 1.0**	36.8 ± 22.4	26.8 ± 16.7**

* The delayed ratios and retention index significantly decreased compared to the pretreatment values in the responder group ($p = 0.01$ and $p < 0.0001$, respectively), but these did not significantly change in the non-responder group (N.S.).

** The delayed ratios and retention index following treatment were significantly lower in the responder group than those in the non-responder group (both, $p < 0.01$).

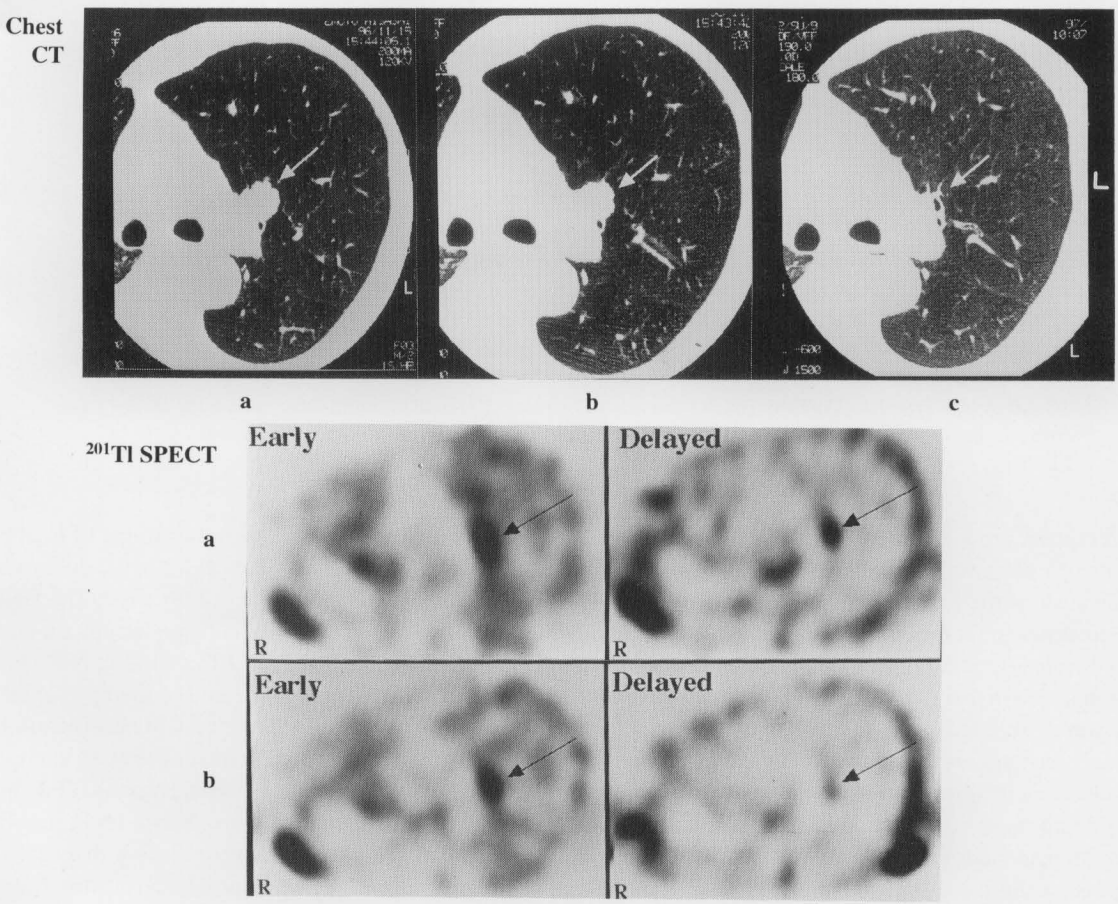

Fig. 1 Chest CT and ^{201}Tl SPECT scans in a case of complete response (CR), a 65-yr-old male with squamous cell carcinoma (# 1 in Table 1). Chest CT scan showing a tumor measuring 23 × 24 mm in the left hilum before radiationtherapy (a; arrow). At an accumulated tumor dose of 22 Gy, the tumor size had not changed noticeably (b; arrow); however, it completely disappeared 19 weeks after the end of radiationtherapy with a total dose of 54 Gy (c; arrow). On ^{201}Tl SPECT, delayed uptake ratio (DUR) and retention index (RI) in the tumors (arrows) were decreased at the time of 22 Gy-dose (b) compared to pretreatment (a) (DUR; from 3.7 to 2.6, RI; 12.7% to −40.0%).

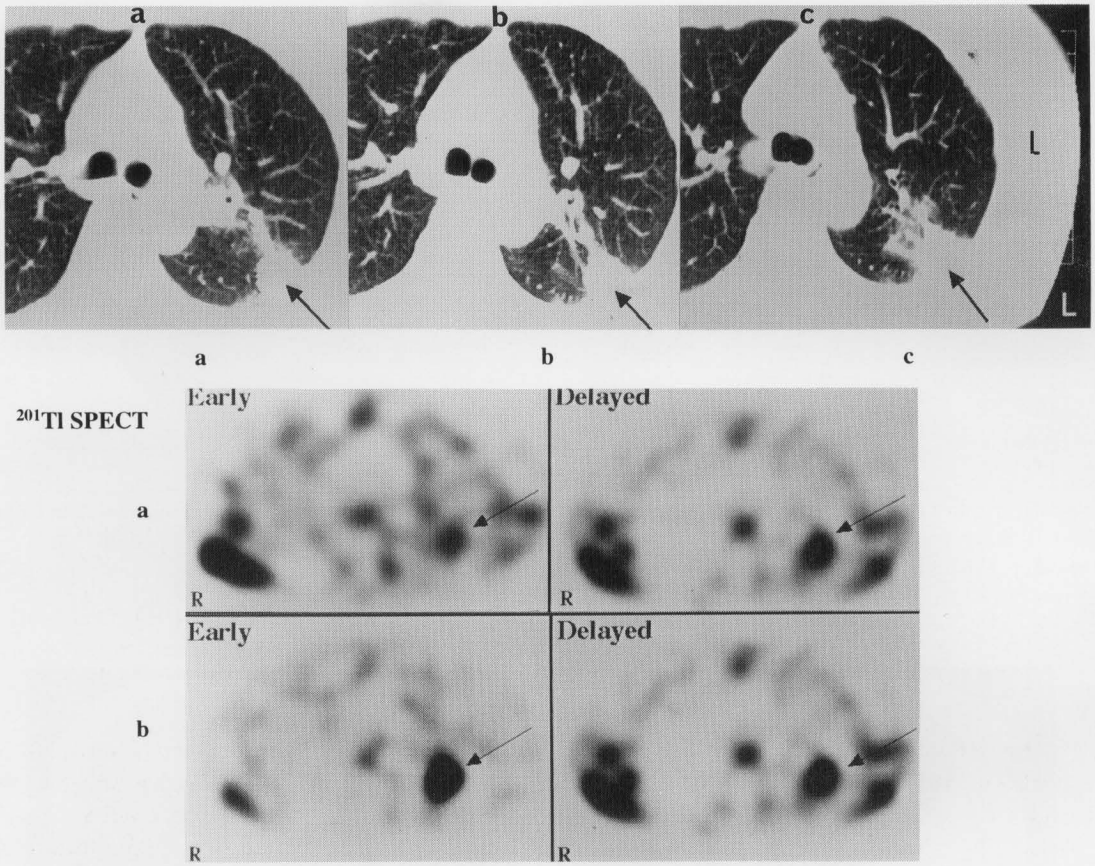

Fig. 2 Chest CT and ^{201}Tl SPECT scans in a case of progressive disease (PD), a 56-yr-old male with adenocarcinoma (# 20 in Table 1). Chest CT scan showing a tumor measuring 22 × 24 mm in the left dorsal lung before therapy (a; arrow). At the accumulated tumor dose of 28 Gy combined with one course of chemotherapy (cisplatin), the tumor size had not changed noticeably (b; arrow); the tumor subsequently increased to 34 × 43 mm 21 weeks after the end of radiationtherapy with a total dose of 54 Gy and 2 additional courses of chemotherapy (c; arrow). On ^{201}Tl SPECT, there was only slight reduction of delayed uptake ratio (DUR) and retention index (RI) in the tumors (arrows) after a 28 Gy-dose irradiation (b) compared to the pretreatment values (a) (DUR; from 4.0 to 3.7, RI; from 24.7% to 22.5%).

weeks (average; 9.2 ± 1.3 weeks) after the therapy. The assessments of mediastinal and hilar lymph nodes were omitted because of the lack of histologic confirmation before the treatments. Of the 32 patients, a total of 26 (22 males and 4 females, average age, 65.3 yrs) were retrospectively analyzed in this study (Table 1). The remaining 6 patients were excluded because of difficulty in accurately defining the tumor borders due to secondary changes such as atelectasis or obstructive pneumonia or marked radiation pneumonitis. The 26 patients consisted of 13 patients in the responder group who had more than 50% tumor regression compared to pretreatment (12 males and 1 female; squamous cell carcinoma 7, adenocarcinoma 4 and large cell carcinoma 2), and 13 patients in the non-responder group who had less than 50% tumor regression (10 males and 3 females; adenocarcinoma 11, squamous cell carcinoma 2). Between these two groups there were no significant differences in tumor size before treatment (1948 ± 1475 mm^2 vs. 2091 ± 1571 mm^2; N.S.), in the radiation doses halfway through the course of treatment (26.9 ± 4.3 Gy vs. 28.0 ± 4.7 Gy; N.S.) or the doses added until the end of therapy (23.2 ± 4.2 Gy vs. 27.0 ± 5.3 Gy; N.S.), in the doses of cisplatin halfway through the course of treatment (114 ± 29 mg vs. 107 ± 10 mg; N.S.) or the total doses of cisplatin until the end of therapy (231 ± 18 mg vs. 241 ± 21 mg; N.S.). The standard classifications of tumor response are: complete response (CR; complete disappearance of the tumor), partial response (PR; more than 50% tumor regression), no change (NC; less than 50% tumor regression), and progressive disease (PD; tumor enlargement). The responder group included 2 patients with CR and 11 with PR, whereas the non-responder group included 8 patients with NC and 5 with PD. Separate informed consent was obtained prior to each SPECT study from all the patients.

^{201}Tl SPECT was conducted 15 min (early scan) and 120 min (delayed scan) after intravenous injection of approximately 148 MBq (4 mCi) of ^{201}Tl chloride, using

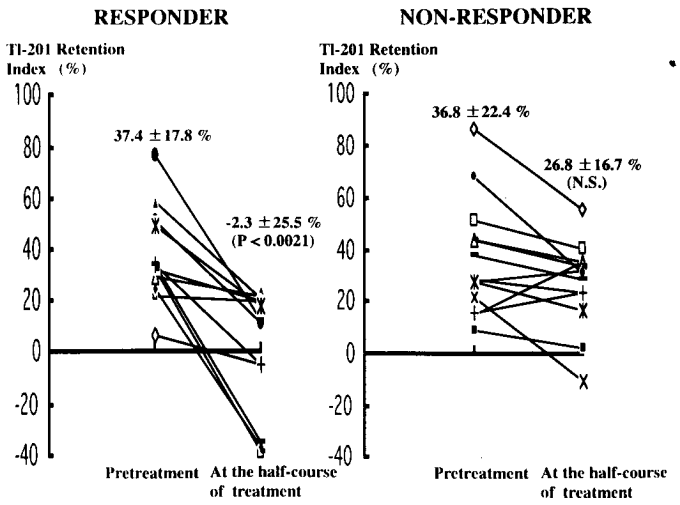

Fig. 3 Alterations of ^{201}Tl retention indices (RIs) between the responder and non-responder groups. In the responder group (left graph), the RIs measured halfway through the course of treatment were significantly decreased compared to those of pretreatment (−2.3 ± 25.5% vs. 37.4 ± 17.8%; p = 0.0001). By contrast, in the non-responder group, the RIs were not significantly changed compared to pretreatment values (26.8 ± 16.7% vs. 36.8 ± 17.8%; N.S.). Each of the different markers represents an individual patient.

a three-detector gamma camera (Toshiba 9300A/HG, Tokyo, Japan) equipped with a low-energy collimator in a 64 × 64 matrix, and with 20%-windows centered over an 80 keV energy peak. A 360° SPECT of the chest was performed with an acquisition time of 20 sec/view for 64 steps. Contiguous transaxial images were reconstructed at 6.4 mm-thickness. No attenuation or scatter correction was performed.

Chest CT scan was performed 2 or 3 days after ^{201}Tl SPECT, with a Toshiba-900-S scanner at 5-mm slice sections and intervals. Tumor sizes were measured by the maximal tumor areas on sequential CT scans, and the product of width × length was designated as the tumor size. Geographic localization of ^{201}Tl uptake by the tumor was determined by visual estimation, taking into account the location and intensity of abnormal tumor activity in comparison with the background of normal lung with reference to findings on CT scan. Quantitative analysis of tumor ^{201}Tl uptake was determined by the regions of interest (ROIs) drawn manually inside the outer border of the tumors with positive accumulation of this agent.[12] An identical ROI was drawn over the contralateral lung field, which was presumed to be normal on CT scan. The mean pixel counts for ROIs were measured, and the ratios of the lesion to contralateral lung tissue on both early and delayed scans were obtained, yielding early and delayed ^{201}Tl uptake ratios (EUR and DUR) in the tumor.[12,13] The ^{201}Tl retention index (RI) was also calculated in order to evaluate the degree of ^{201}Tl retention in the tumors, according to the following formula: RI = (delayed uptake ratio − early uptake ratio)/early uptake ratio × 100%.[12] These measurements were performed without prior knowledge of treatment. To assess the correlation between tumor response and the parameters measured on ^{201}Tl SPECT, group comparisons were performed by means of Student's t-test. Differences were considered significant when the p-value was less than 0.05. Linear regression analysis was performed with commercially available software (StatView 4.02 SE + Graphics; Abacus Concepts, Berkeley, Calf) to assess the linear dependency between tumor reduction after therapy and the changes in the parameters measured by ^{201}Tl SPECT.

RESULTS

The changes in EUR, DUR and RI halfway through the therapy are summarized in Table 1. Before treatment all of the tumors showed positive ^{201}Tl uptake, and there were no significant differences in these parameters for the responder and non-responder groups (N.S.). All the tumors also remained positive for ^{201}Tl uptake halfway through the therapy. In the responder group, EUR tended to decrease compared to pretreatment, but without significance difference (N.S.), whereas DUR and RI significantly decreased (both; $p < 0.01$) (Table 1, Figures 1, 3). When normalizing DUR and RI compared to the pretreatment values (100%), these parameters decreased to 68.4 ± 17.9% and −16.9 ± 17.8%, respectively. By contrast, in the non-responder group, none of these parameters was significantly changed compared pretreatment (N.S.) (Table 1, Figures 2, 3). When comparing DUR and RI halfway through the therapy for the two groups, these parameters were significantly lower in the responder group (both; $p < 0.01$), but no significant difference was noted in EUR (N.S.) (Table 1). A linear regression analysis showed that the percent reduction in tumor size halfway through the

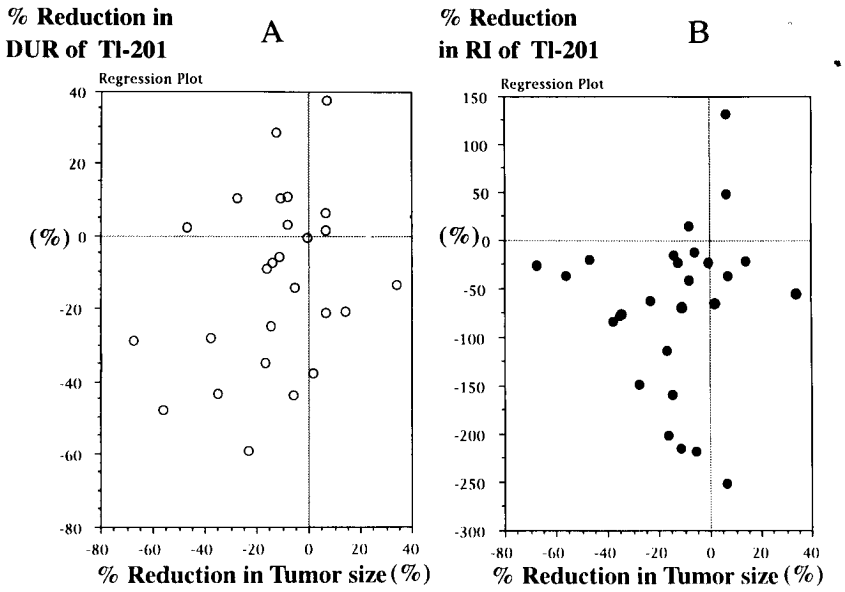

Fig. 4 Relationship between tumor reduction and DUR (A) or RI (B). The extent of tumor reduction in size did not correlate with and DUR or RI, either (N.S.).

therapy was not correlated with the percent decrease in DUR or RI (N.S.) (Figure 4).

DISCUSSION

This retrospective study indicates that the delayed uptake ratio (DUR) and retention index (RI) can be changed rather soon after starting therapy in patients with non-small cell lung cancer, and that the extent of decrease in these two parameters can be predictive indicators for tumor response to therapy. Although several investigators have previously shown that DUR and RI were significantly decreased after completion of therapy in lung cancer patients with a good response to therapy,[3,6–8] our results indicate that the reduction can occur soon after therapy. Furthermore, our results showed that DUR and RI changed independently of tumor volume after therapy, as indicated by no correlations with the reduction in tumor size. This indicates the superiority of ^{201}Tl SPECT to morphologic CT scan in assessing therapeutic effects. The non-invasiveness and high sensitivity of this method in visualizing relatively small tumors also seems beneficial for early evaluation of therapeutic effects.[13]

Since ^{201}Tl retention in tumors on delayed SPECT scan may depend on the clearance of ^{201}Tl from tumor tissues, the reduction in DUR and RI in our responder group indicates that ^{201}Tl may result in a faster washout when the tumors respond well to therapy. If therapy is assumed to reduce tumor cell viability and the grade of malignancy, reduction of these parameters is consistent with a previously reported finding that ^{201}Tl washed out more rapidly from benign tumors than from malignant tumors.[13,14] There is also considerable evidence that these parameters are associated with malignant potential or tumor proliferative activity in lung cancer. Takekawa et al.[15,16] demonstrated the association of tumor ^{201}Tl uptake and intensity of Na-K ATPase staining in lung adenocarcinomas, and slower washout or increased retention of ^{201}Tl in these neoplasms with high metastatic potential or poor differentiation. These investigators also showed that DUR was a reliable prognostic factor for survival in patients with various types of lung cancer.[17] Yamaji et al.[8] reported a significantly lower RI in patients with early recurrent lung cancer than in patients without recurrence after completion of therapy. Tonami et al.[14] showed that this index was highest for small-cell lung carcinoma with early lymph node metastasis. In various malignant tumors other than lung cancer, the degree of ^{201}Tl retention in tumors was also reported to be associated with the malignant potential or tumor proliferative activity.[18–21]

Although a significant reduction in EUR compared to pretreatment was not observed in our patients in the responder group, this parameter might also have decreased significantly if the responder group had included a greater number of patients with complete response (CR). Although after accomplishment of radiationtherapy, Shimizu et al.[6] demonstrated that EUR significantly decreased in the patients with lung cancer in the CR group compared to that in patients in the partial response (PR) + no change (NC) group. Their study included a greater number of patients in CR than in our study. Our previous animal study,[11] although with a planar scintigram, revealed a dose-dependent reduction in EUR in VX-2 tumors soon (7 days) after irradiation with a concomitant reduction in Bromodeoxyuridine (BrdU) uptake (proliferative activity indicator) in tumor tissues. Other animal

and clinical studies demonstrated that hardly any ^{201}Tl was taken up by nonviable or necrotic tissues in treated tumors.[5,22–26] Although a transient increase in EUR soon after radiationtherapy despite subsequent tumor regression has been reported in a limited number of patients with intracranial tumor,[10] this phenomenon was not observed in any of our patients with CR response, as shown in Figure 1. Intracranial tumors may have different ^{201}Tl kinetics after therapy because of the presence of the blood-brain barrier.

In some patients with lung cancer, early evaluation of tumor response during therapy may be beneficial when devising an efficient approach to treatment or adjuvant therapeutic regimens such as bronchial arterial infusion therapy. The importance of early evaluation of tumor response will increase in the strategies of recently developing stereotactic radiationtherapy and radiosurgery. A limitation of our study is the lack of histologic proof of tumor response to treatment. Pathological assessment by biopsy during the course of treatment is the only definitive examination to confirm tumor response to treatment. Obtaining sequential biopsies is usually difficult and even dangerous in patients with lung cancer. As demonstrated in this preliminary study, ^{201}Tl SPECT with measurements of EUR and RI at accumulated radiation doses of approximately 27 Gy can be a non-invasive procedure for assessing therapeutic effects, but concerning the best timing for ^{201}Tl SPECT during treatment, further study is needed. A further long-term follow-up study or a prospective study is also needed to validate our interpretation of ^{201}Tl SPECT.

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