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Thallium-201 SPECT in advanced non-small cell lung cancer: In relation with chemotherapeutic response, survival, distant metastasis and p53 status

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Purpose: The aim of this study was to evaluate the relationship between ^{201}Tl tumor uptake, chemotherapeutic response, metastasis, p53 status and survival in non-small cell lung cancer (NSCLC). ***Methods:*** A total of 23 patients underwent ^{201}Tl SPECT. In 9 patients, 2nd ^{201}Tl SPECT study were performed 1 week after the 3rd cycle of chemotherapy (ChT), and early (ER) and delayed (DR) tumor/normal lung ratios and retention indices (RI) were obtained. In 15 patients p53 status was assayed with immuno-histochemical staining. The patients were divided into subgroups after the 3rd cycle of ChT; responders [R(+) (n = 10)] and non-responders [R(−) (n = 13)], distant metastasis [(M_1) n = 11] and [(M_0) n = 12], and mutant p53 status [p(+) n = 7, p53(−) n = 8]. ***Results:*** The differences for ER, DR and RI values between all of the subgroups were not statistically significant. ER and DR of responders decreased significantly after ChT; from to 2.46 to 1.36 ($p = 0.04$) and 2.29 to 1.53 ($p = 0.04$), respectively. In the non-responder group, both ER and DR slightly increased after ChT ($p > 0.05$). ***Conclusion:*** Our results suggest that in NSCLC, there was a weak correlation between higher ^{201}Tl ratios and positive response to chemotherapy, absence of distant metastasis, and p53(−) status. Significant ^{201}Tl uptake decrease after chemotherapy indicates that delayed ^{201}Tl uptake can be used in evaluating the chemotherapeutic response.

Key words: non-small cell lung cancer, ^{201}Tl SPECT, chemotherapy, survival, metastasis, p53

INTRODUCTION

Non-small cell carcinomas (NSCLC) account for 75–80% of all lung cancer, and surgical cure is achieved in only 15–20% of the patients.[1] Chemotherapy may be applied as a palliative treatment in patients with advanced disease (stage III and IV). Chemotherapeutic failure and development of resistance are significant problems in patients with NSCLC. Thus, predicting chemotherapeutic response of NSCLC is important in clinical practice in order to determine further management of the patients.

The response of the therapy is evaluated on the basis of physical examination and radiological imaging. However, these morphological assessment methods do not sufficiently reflect the metabolic changes. Currently, ^{18}F-FDG-PET is a commonly used imaging tool for diagnosing, staging and recurrence detecting in primary lung cancer,[2,3] but is still an expensive and not widely available imaging tool in most nuclear medicine clinics. This imaging modality has limited usage in routine practice. Additionally, FDG accumulates not only in malignant tumors but also in many benign conditions, such as active inflammatory or infective lesions.[4–6]

^{201}Tl is a potassium analogue; it is, therefore, transported into the cell in a competitive way with potassium regulated by Na-K ATPase. This transport system is related to tumor uptake.[7] In the detection of primary lung cancer and mediastinal lymph node metastases ^{201}Tl was used first by Salvatore et al.[8] and Tonami et al.[9]

Mutation of the p53 tumor suppressor gene is found in

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about 50% of all types of lung cancer.[10,11] Recent studies indicate that p53 protein is involved in several vital functions, such as gene transcription, DNA synthesis and repair cell cycle arrest, and programed cell death (apoptosis). Mutation of p53 gene can abrogate these functions and may contribute to genomic instability and progression of cancer.[12–16]

The purpose of this study was to assess the value of the ^{201}Tl SPECT in predicting the chemotherapeutic response, and its relationship with the metastatic potential, p53 status and survival in untreated advanced NSCLC.

MATERIALS AND METHODS

This study included 23 NSCLC patients (stage III or IV) without any previous treatment by any therapeutic approach. Their age ranged from 40 to 79 years (mean age: 62.34 ± 10.54 yr). All patients underwent a detailed physical examination, chest X-ray and thoracic CT scan. Diagnosis was made by cytological or histopathological analysis of sputum and/or specimens taken with bronchoscopy or CT-guided needle biopsy samples. 21 patients had squamous cell cancer and 2 had adenocarcinoma. The lung lesions were staged according to TNM classification. The local ethical committee had approved this study, and all patients gave their informed consent prior to participation.

Chemotherapy: All patients were treated using etoposide and cisplatin for ChT, but none were treated with radiation therapy. They were divided into two groups,

Table 1 Demographic data, ^{201}Tl uptake and p53 results of all patients

Pt. no	Age (y)	Size (mm × mm)	Response	Stage	Survey (week)[a]	ER	DR	RI	p53 status[b]
1	51	30 × 40	PR	IV	32	3.71	2.70	−27.22	+
2	68	70 × 90	PR	IIIA	40	3.67	4.21	14.71	+
3	65	35 × 40	PR	IV	?	2.50	4.86	94.40	−
4	71	50 × 60	PR	IIIB	76	5.70	6.47	13.51	−
5	45	45 × 40	PR	IIIB	44	2.05	2.85	39.02	+
6	70	60 × 80	PR	IV	64	2.46	3.08	25.20	?
7	68	30 × 30	CR	IIIA	120	2.52	2.08	−17.46	?
8	68	30 × 30	PR	IIIB	?	3.82	4.21	10.21	?
9	61	20 × 30	PR	IV	20	2.94	2.29	−22.11	?
10	57	30 × 30	PR	IV	32	1.18	1.59	34.75	?
11	71	50 × 50	NC	IIIA	32	2.60	3.54	36.15	+
12	57	25 × 30	PD	IIIB	32	3.44	3.84	11.63	−
13	70	40 × 50	NC	IIIB	96	4.02	4.38	8.96	−
14	67	45 × 60	PD	IV	8	4.11	4.22	2.68	−
15	65	50 × 50	NC	IIIA	76	2.98	3.24	8.72	−
16	79	40 × 40	PD	IIIB	4	1.89	2.54	34.39	+
17	40	50 × 60	PD	IV	8	2.12	3.65	72.17	+
18	65	20 × 30	PD	IV	24	2.91	2.71	−6.87	−
19	46	70 × 80	PD	IV	48	2.31	2.61	12.99	+
20	69	50 × 30	PD	IV	12	2.00	2.12	6.00	−
21	43	110 × 70	PD	IV	68	2.62	3.02	15.27	?
22	70	60 × 50	NC	IIIB	?	1.61	1.51	−6.21	?
23	68	100 × 80	PD	IIIB	8	1.76	2.22	26.14	?

ER: Early ratio; DR: Delayed ratio; RI: Retention index; PR: Partial response; CR: Complete response; PD: Progressive disease; NC: No change. [a]? = survival could not be obtained. [b]? = not assayed due to limited biopsy material.

Table 2 ER, DR and RI values respecting the response to ChT, distant metastasis and p53 status

	ER	DR	RI
Non-responder (n = 13)	2.64 ± 0.82	3.04 ± 0.86	−17.0 ± 21.2
Responder (n =10)	3.05 ± 1.24	3.43 ± 1.49	−16.5 ± 35.8
M_0 (n = 12)	3.00 ± 1.19	3.42 ± 1.33	14.9 ± 16.8
M_1 (n = 11)	2.62 ± 0.80	2.98 ± 0.94	18.8 ± 37.1
P53(−) (n = 8)	3.45 ± 1.15	3.98 ± 1.35	17.3 ± 31.7
P53(+) (n = 7)	2.62 ± 0.76	3.15 ± 0.64	26.0 ± 30.5

ChT: Chemotherapy; M_0: no distant metastasis; M_1: distant metastasis

responders (n = 10) and non-responders (n = 13) according to morphological changes on CT scan taken 2 weeks after the 3rd cycle of ChT. Response to ChT [R(+)] was defined as a disappearance of the tumor or reduction in its size by >50% on CT scan. No change in tumor size or an increase in tumor size or decrease in tumor size of <50% was considered to indicate absence of response to ChT [R(−)].

Scintigraphy: All patients underwent ^{201}Tl SPECT before the ChT. In addition, 9 patients underwent a 2nd ^{201}Tl SPECT study one week after the 3rd cycle of ChT. SPECT images were acquired 15 min (early) and 3–4 hours (delayed) after IV injection of ^{201}Tl (148–185 MBq). For SPECT images 64 projections were taken by using 64 × 64 matrixes each for 30 sec with a large field-of-view gamma camera (Philips Gamma Diagnost Tomo), with low energy high-resolution collimator. Raw SPECT data were reconstructed using Butterworth and Ramp filters, and transverse, coronal and sagittal slices were obtained. No attenuation correction was performed.

Data analysis: Reconstructed SPECT images were analyzed visually with respect to CT images. Over the tumor area (T) and on the contralateral side over the normal lung area (N) regions of interest (ROI) were drawn in all transverse images. Using the mean per pixel obtained from these ROIs, early (ER) and delayed (DR) T/N ratios and retention indices [RI = (DR – ER) × 100/ER] were calculated.

Immuno-histochemical staining: Sections with a size of 5 μm were obtained from paraffin-embedded tissue blocks, and stained by immuno-staining streptavidin-biotin peroxidase complex method.[17] The sections for p53 were judged positive when 5% or more tumor nuclei were stained.

Table 3 Survival rate respecting to response to ChT, distant metastasis and p53 status

	Survival rate (week)
Non-responders (n = 12)	34.6 ± 30.8
Responders (n = 8)	53.5 ± 32.4
M_1 (n = 10)	31.6 ± 21.9
M_0 (n = 10)	52.8 ± 37.9
P53(+) (n = 7)	29.7 ± 17.3
P53(−) (n = 6)	46.2 ± 35.5

Statistical analysis: All quantitative data were expressed as the mean ± standard deviation. Comparison of the ER and the DR ^{201}Tl uptake and the values before and after therapy were assessed using the Wilcoxon matched test for paired data. Comparison of the uptake ratios and survival rate between responders and non-responders, between no-distant metastasis (M_0) and distant metastasis (M_1), and between p53 status (−) and (+) were performed using the two tailed Student's t-test for unpaired data. The relationship between the survival and ^{201}Tl uptake values were compared with Pearson correlation test. Probability values below 0.05 were considered statistically significant.

RESULTS

Distribution of patients according to tumor stage was as follows: 4 in stage IIIA, 8 in IIIB, 11 in IV. Demographic data, Tl-201 tumor uptake and p53 status of all patients were shown in Table 1. The smallest tumor size was 20 × 30 mm. In all patients uptake of ^{201}Tl was clearly demonstrated in lung lesion. The mean ± SD values of ER, DR and RJ were 2.82 ± 1.02, 3.21 ± 1.16, and 16.8 ± 27.8, respectively. DR was significantly higher than ER ^{201}Tl ($p = 0.01$). ER, DR and RI values with respect to the chemotherapeutic response, distant metastasis status and p53 status were shown in Table 2. Although in the responder group ER and DR were higher than those of the non-responder group, there was no significant difference between the responder and non-responder groups in ER or DR. Both ER and DR in M_0 were slightly higher than those of in M_1 group. Although both ER and DR values tended to be higher in p53(−) group than in p53(+) group, there was no significant difference in ER, DR or RI between these two groups (Table 2). Survival ratio (SR) of responder group was longer, but statistically insignificant, than that of the non-responder group (Table 3). Similarly M_0 group had longer, but statistically insignificant, SR than the M_1 group (Table 3). No significant correlations were found between SR of either ER or DR ($r = 0.40$, $p = 0.07$, $r = 0.33$, $p = 0.14$, respectively). ER and DR of the responder group decreased significantly after ChT (AT) to before ChT (BT); from 2.46 to 1.36 ($p = 0.04$) and 2.29 to 1.53 ($p = 0.04$), respectively (Table 4). In the non-responder group, there were slight increase in ER and DR after ChT ($p > 0.05$). There were no significant

Table 4 ER, DR and RI values before and after ChT

	Non-responders (n = 4)		Responders (n = 5)	
	BT median [range]	AT median [range]	BT median [range]	AT median [range]
ER	3.02 [1.89–4.02]	3.59 [2.23–5.58]	2.46 [1.94–2.94]	1.36 [1.04–2.12]*
DR	3.69 [2.54–4.38]	4.62 [3.10–6.54]	2.29 [1.78–3.08]	1.53 [0.98–2.28]*
RI	18.0 [8.2–26.5]	18.4 [6.7–35.6]	5.6 [−41.5–20.1]	5.3 [−6.1–17.1]

*p = 0.04 BT: Before therapy, AT: After therapy

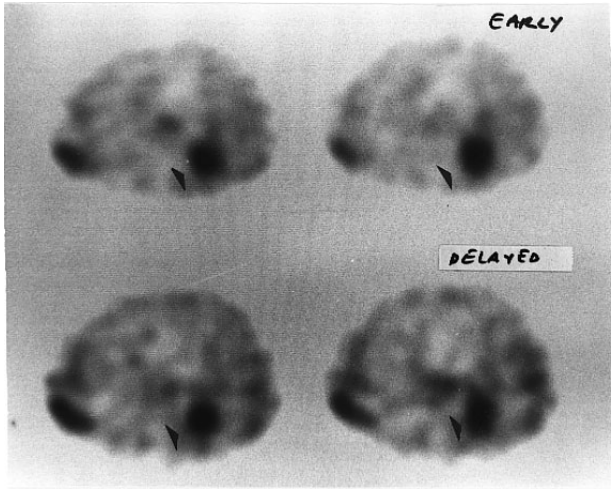

Fig. 1 Transverse ^{201}Tl SPECT images of R(+) and p53(+) patient 1 with a tumor (▶) in the left middle lung area: early (*upper row*) and delayed (*below row*) images.

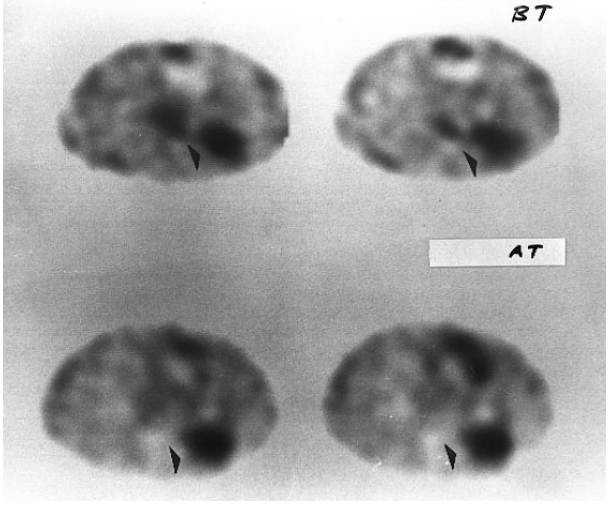

Fig. 2 Transverse ^{201}Tl SPECT images of R(−) and p53(−) patient 15 with a tumor (▶) in the left middle lung area: BT (*upper row*) and AT (*below row*) images.

differences between BT RI and AT RI for the responder and non-responder groups (Table 4). Figure 1 shows early and delayed Tl-201 transverse SPECT images of R(+) and p53(+) patient 1. Figure 2 shows before and after ChT Tl-201 transverse SPECT images of R(−) and p53(−) patient 15.

DISCUSSION

Positive chemotherapeutic response is a very important prognostic indicator in the follow up of lung cancer patients. Although several studies investigated the use of ^{201}Tl SPECT in the evaluation and staging of lung cancer,[18–21] evaluation of limited number of studies used it for the chemotherapeutic effects in a limited number of studies.[22,23] ^{201}Tl SPECT imaging compared to ^{18}F-FDG-PET imaging is cheaper, but it has a limited role in evaluating lesions measuring less than 2 cm. However, a malignant lesion over 2 cm could be evaluated with close sensitivity and specificity to ^{18}F-FDG-PET.[21] Hanada et al.[24] found a significant inverse correlation between cisplatin 50% inhibitory concentration values and thallium cellular accumulation. On the other hand, they did not find significant correlation between the cellular accumulation of cisplatin and thallium. Ishibashi et al.[25] showed that while delayed ^{201}Tl uptake was correlated with the cancer cell proliferation ratio in patients with SCLC, there was no correlation in patients with NSCLC. Nishiyama et al.[23,26] reported that no significant correlation was present between the ^{201}Tl ratio and the ChT response in NSCLC. Similarly, in our study although in the responder group ER, DR and SR were higher than in the non-responder group, the differences were not significant.

Some authors assessed the role of ^{201}Tl SPECT before and after therapy in evaluating the treatment response. Shimizu et al.[27] concluded that this method could be very useful as their complete remission group showed significantly lower uptake ratios after radiotherapy than the groups with partial response or no change. Yamaji et al.[28] showed a significantly lower RI in patients without recurrence compared to the patients with early recurrence, but no significant difference was found in ER and DR. They suggested that RI after treatment was useful for the evaluation of the therapeutic effect in primary lung cancer. Suga et al.[29] reported that a significant decrease in DR and RI halfway through the therapy was observed compared to pre-therapy in the responder group. In contrast, there was no significant change in the non-responder group for any of these parameters. In the present study, we evaluated only the ChT response in the early stage (after 3rd course of ChT), and found that only DR decreased significantly after ChT in responder. However, after therapy ER tended to decrease, and RI did not change. In the non-responder group, although ER and DR increased after ChT, these increases were statistically insignificant. Similarly, RI did not change.

Takekawa et al.[30] found that higher retention index of ^{201}Tl is a useful indicator for lymph node metastasis in patients with adeno-carcinoma, and therefore, it facilitates the prediction of prognosis. Yamamoto et al.[31] found that patients with distant metastasis had significantly higher ER and DR values for ^{201}Tl, but not for ^{99m}Tc-MIBI. They suggested that ^{201}Tl is more effective than ^{99m}Tc-MIBI in predicting the metastatic potential in NSCLC. Takekawa et al.[32] noted that patients with lower ^{201}Tl uptake survived longer than those with higher ^{201}Tl uptake, and added that ^{201}Tl uptake is an independent factor. In conflict with the above-mentioned studies, we found no significant difference between RI values of M_0 and M_1 groups. Moreover, M_0 group had higher, but statistically insignificant, ER and DR values as well as

survival rate than those of M_1 group. Additionally, in conflict with Yamamoto et al. we could not find any relationship between high ^{201}Tl uptake and distant metastasis. Henceforth, in respect to the results of the abovementioned studies, and ours we thought that although higher ^{201}Tl uptake is associated with higher intracellular accumulation of chemotherapeutic agents, it does not reflect the tumor aggressivity.

The relationship between p53 status and ChT is conflicting in NSCLC. Brattstrom et al.[33] noted that tumors with p53 mutation were more resistant to cisplatin and cyclophosphamide. Additionally, a p53 alteration was frequently found in close association with the topoisomerase II alpha expression.[34] Since etoposide is a topoisomerase II alpha inhibitor, its intracellular concentration might be affected by p53 status. There was no study in which the relationship between p53 types and ^{201}Tl was evaluated, and to our knowledge this was the first study on this topic. We found that in p53(+) group ^{201}Tl uptake was lower than the p53(−) patients and the p53(+) group tended to have shorter SR than the p53(−) group. The lower uptake of ^{201}Tl in p53(+) group supports our suggestion that higher ^{201}Tl uptake does not reflect the tumor aggressivity.

CONCLUSION

Our results suggest that in NSCLC, higher ^{201}Tl tumor uptake had a weak correlation with positive response to chemotherapy, absence of distant metastasis, and p53(−) status. With respect to the pre-therapeutic ER and DR values ^{201}Tl could not be used as an efficient method for predicting the response to ChT. Significant decrease of DR value after chemotherapy indicated that delayed ^{201}Tl uptake could be used in the evaluation of the chemotherapeutic response, but this needs to be confirmed in larger series of patients.

REFERENCES

1. Bernard JP, Louie O, Altorki N. Staging and the surgical management of lung cancer. *Radiol Clin North Am* 2000; 38: 545–561.
2. Chiti A, Schreiner FA, Crippa F, Pauwels EK, Bombardieri E. Nuclear medicine procedures in lung cancer. *Eur J Nucl Med* 1999; 26: 533–555.
3. Coleman E. PET in Lung cancer. *J Nucl Med* 1999; 40: 814–820.
4. Lowe VJ, Duhaylongsod FG, Patz EF, et al. Pulmonary abnormalities and PET data analysis: a retrospective study. *Radiology* 1997; 202: 435–439.
5. Bakheet SM, Saleem M, Powe J, Al-Amro A, Larsson SG, Mahassin Z. F-18 fluorodeoxyglucose chest uptake in lung inflammation and infection. *Clin Nucl Med* 2000; 25: 273.
6. Ichiya Y, Kuwabara Y, Sasaki M, Yoshida T, Akashi Y, Murayama S, et al. FDG-PET in infectious lesions: The detection and assessment of lesion activity. *Ann Nucl Med* 1996; 10: 185–191.
7. Sehweil AM, MeKillop JH, Milroy R, Wilson R, Abdel-Dayem HM, Omar YT. Mechanism of ^{201}Tl uptake in tumours. *Eur J Nucl Med* 1989; 15: 376–379.
8. Salvotore M, Caratu L, Porta E. Thallium-201 as a positive indicator for lung neoplasm: preliminary experiments. *Radiology* 1976; 121: 487–488.
9. Tonami N, Shuke N, Yokoyama K, et al. Thallium-201 Single photon emission computed tomography in the evaluation of suspected lung cancer. *J Nucl Med* 1989; 30: 997–1004.
10. Iggo R, Gatter K, Bartek J, Lane D, Harris AL. Increased expression of mutant form of p53 oncogene in primary lung cancer. *Lancet* 1990; 335: 675–679.
11. Takahashi T, Nau MM, Chiba I, et al. P53: a frequent target for genetic abnormalities in lung cancer. *Science* 1989; 246: 491–494.
12. Kawasaki M, Nakanishi Y, Kuwano K, Takayama K, Kiyohara C, Hara N. Immunohistochemically detected p53 and p-glycoprotein predict the response to chemotherapy in lung cancer. *Eur J Cancer* 1998; 34: 1352–1357.
13. Gottlieb TM, Oren M. p53 in growth control and neoplasia. *Biochim Biophys Acta* 1996; 1287: 77–102.
14. Ko LJ, Prives C. p53: puzzle and paradigm. *Genes Dev* 1996; 10: 1054–1072.
15. Levine AJ. The cellular gatekeeper for growth and division. *Cell* 1997; 88: 323–331.
16. Polyak K, Xia Y, Zweier JL, Kinzler KW, Vogelstein B. A model for p53-induced apoptosis. *Nature* 1997; 389 (6648): 300–305.
17. Yüksel M, Çermik TF, Candan L, et al. ^{99m}Tc-MIBI SPET in non-small cell lung cancer in relationship with Pgp and prognosis. *Eur J Nucl Med Mol Imaging* 2002; 29: 876–881.
18. Flores LG, Ochiai E, Nagamachi S, et al. The diagnostic role of ^{201}Tl SPECT imaging in patients with lung tumours: comparison with computed tomography. *Nucl Med Commun* 1996; 17: 493–499.
19. Tonami N, Yokoyama K, Shuke N, et al. Evaluation of suspected malignant pulmonary lesions with ^{201}Tl single photon emission computed tomography. *Nucl Med Commun* 1993; 14: 602–610.
20. Arbab AS, Koizumi K, Toyama K, Arai T, Yoshitomi T, Araki T. Detection of lung lesions and lymph nodes with ^{201}Tl SPET. *Nucl Med Commun* 1998; 19: 411–416.
21. Higashi K, Nishikawa T, Seki H, et al. Comparison of fluorine-18-FDG PET and thallium-201 SPECT in evaluation of lung cancer. *J Nucl Med* 1998; 39: 9–15.
22. Fukumoto M, Yoshida D, Hayase N, Kurohara A, Akagi N, Yoshida S. Scintigraphic prediction of resistance to radiation and chemotherapy in patients with lung carcinoma: technetium 99m-tetrofosmin and thallium-201 dual single photon emission computed tomography study. *Cancer* 1999; 86: 1470–1479.
23. Nishiyama Y, Yamamoto Y, Satoh K, et al. Comparative study of Tc-99m MIBI and Tl-201 SPECT in predicting chemotherapeutic response in non-small-cell lung cancer. *Clin Nucl Med* 2000; 25: 364–369.
24. Hanada T, Isobe H, Saito T, et al. Intracellular accumulation of thallium as a marker of cisplatin cytotoxicity in nonsmall cell lung carcinoma: an application of inductively coupled plasma mass spectrometry. *Cancer* 1998; 83: 930–935.

25. Ishibashi M, Fujii T, Yamana H, Fujimoto K, Rikimaru T, Hayashi A, et al. Relationship between cancer cell proliferation and thallium-201 uptake in lung cancer. *Ann Nucl Med* 2000; 14: 255–261.
26. Nishiyama Y, Yamamoto Y, Fukunaga K, et al. Evaluation of radiotherapeutic response in non-small cell lung cancer patients by technetium-99m MIBI and Tl-201 chloride SPET. *Eur J Nucl Med* 2000; 27: 536–541.
27. Shimizu M, Seto H, Kageyama M, Wu Y, Morijiri M, Watanabe N, et al. Assessment of treatment response in irradiated lung cancer by sequential thallium-201 SPECT: comparison with tumor volume change and survival time. *Radiat Med* 1996; 14: 7–12.
28. Yamaji S. Usefulness of ^{201}Tl SPECT in the evaluation of treatment effect for primary lung cancer. *KAKU IGAKU (Jpn J Nucl Med)* 1995; 32: 1333–1340.
29. Suga K, Kume N, Nishigauchi K, Ogasawara N, Hara A, Miura G, et al. ^{201}Tl SPECT as an indicator for early prediction of therapeutic effects in patients with non-small cell lung cancer. *Ann Nucl Med* 1998; 12: 355–362.
30. Takekawa H, Itoh K, Abe S, et al. Retention index of thallium-201 single photon emission computerised tomography (SPECT) as an indicator of metastasis in adenocarcinoma of the lung. *Br J Cancer* 1994; 70: 315–318.
31. Yamamoto Y, Nishiyama Y, Satoh K, et al. Comparative evaluation of Tc-99m MIBI and Tl-201 chloride SPECT in non-small-cell lung cancer mediastinal lymph node metastases. *Clin Nucl Med* 2000; 25: 29–32.
32. Takekawa H, Takaoka K, Tsukamoto E, Kanegae K, Miller F, Kawakami Y. Thallium-201 single photon emission computed tomography as an indicator of prognosis for patients with lung carcinoma. *Cancer* 1997; 80: 198–203.
33. Brattstrom D, Bergqvist M, Lamberg K, et al. Complete sequence of p53 gene in 20 patients with lung cancer: comparison with chemosensitivity and immunohistochemistry. *Med Oncol* 1998; 15: 255–261.
34. Galimberti S, Marchetti A, Buttitta F, et al. Multidrug resistance related genes and p53 expression in human non small cell lung cancer. *Anticancer Res* 1998; 18: 2973–2976.