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Original

Prediction on Recurrence for Stage I Non-Small Cell Lung Carcinoma by Tl-SPECT and FDG-PET

Licht Tominaga[1)], Hiroshi Onishi[1)], Kengo Kuriyama[1)], Masayuki Araya[1)], Shinichi Aoki[1)], Ryo Saito[1)], Yoshiyasu Maehata[1)], Mitsuhiko Oguri[1)], Yoko Sato[2)] and Satoshi Kato[2)]

[1)] Department of Radiology, University of Yamanashi, Chuoshi, Yamanashi, Japan

[2)] Kofu neurosurgical hospital, Kofushi, Yamanashi, Japan

Abstract: Background: The purpose of this study is to clarify the utility of thallium-201 single photon emission tomography (Tl-SPECT) for predicting local recurrence after stereotactic radiotherapy (SRT) by comparing it with ^{18}fludeoxyglucose-positron emission tomography (FDG-PET). Since Tl-SPECT can be performed at general hospitals, the ability of Tl-SPECT to predict local recurrence after SRT is clinically important.
Methods and materials: Between January 2007 and December 2011, 78 patients with stage I non-small cell lung carcinoma underwent Tl-SPECT and FDG-PET before SRT. The median follow-up period was 28 months (range, 6 to 66 months), and the subjects' median age was 80-years-old (range, 50 to 90-years-old).
Results: During the analysis of factors associated with recurrence outside of the radiation field and all recurrent lesions, correlations were detected between recurrence and the early and delayed standardized uptake values obtained during FDG-PET. Although it is not possible to predict the local effects of radiation based on a tumor's FDG uptake, the latter parameter is useful for predicting the overall risk of recurrence. This indicates that the recurrence rate could be reduced by performing chemotherapy after radiotherapy in cases exhibiting strong FDG uptake. It is suggested that tumors that exhibit a retention index of >50.68 on Tl-SPECT often recur.
Conclusion: Local recurrence after SRT can be predicted by Tl-SPECT. Therefore, it is expected that the use of Tl-SPECT will lead to the identification of patients that are at high risk of local recurrence. Such patients could be given more intensive treatment, which would lead to an improvement in the local control rate.

Key Words: lung cancer, stereotactic radiotherapy, FDG-PET, TL-SPECT

Introduction

In Japan, the prevalence of lung cancer has recently been increasing in both men and women[1)], and the mortality rate of the condition has also been rising since 1950. In 1998, lung cancer accounted for about 18% of all cases of malignant tumors and caused the deaths of 50,871 people in Japan. In 1993, lung cancer surpassed gastric cancer and became the most common malignant tumor in Japanese males[2)]. In 2008, 66,849 males developed lung cancer in Japan[3)], and lung cancer also became the most common malignant tumor in females.

Recently, as medical check-ups have become more common cases of early stage (c-stage I and

[1)] 1110 Shimokato, Chuo city, Yamanashi, 409-3898, Japan.
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II) non-small cell lung carcinoma that require surgical resection have been identified with increasing frequency. However, many patients are not able to undergo surgery because of concerns about their age or concurrent illnesses. Moreover, some elderly patients reject surgery despite their condition being operable.

Radiotherapy is based on the difference in radiation sensitivity between tumor cells and healthy cells; i.e., a dose of radiation that can be tolerated by healthy cells, but not by tumor cells is administered in order to exterminate the tumor cells. For this purpose, it is necessary that the radiation must be focused on the tumor cells and that healthy cells are not exposed to it. Thus, stereotactic body radiation therapy, in which the radiation is focused on the tumor in a multi-directional non-coplanar manner, was developed. The ability of stereotactic body radiation to concentrate a high dose of radiation on the tumor field means that it can improve the local control rate and reduce toxicities. Stereotactic body radiotherapy was first applied to brain tumors. Increases in the accuracy of tumor field delineation led to its use being expanded to include tumors of the trunk, and it was later used to treat lung cancer.

As stereotactic radiotherapy is a minimally invasive therapy it has started to be employed as a therapeutic option for c-stage non-small cell lung carcinoma. Patients with c-stage I disease account for about 20% of all non-small cell lung cancer patients (and about 15% of all lung cancer patients[4]).

Onishi H *et al.*[5] reported the results of clinical cases from 13 Japanese institutions in which stereotactic radiotherapy was used to treat lung cancer. According to the latter study, the 5-year survival rate of non-small cell lung cancer was 72% (58-82%) at stage IA and 64% (38-78%) at stage IB. While in operable cases in which the tumor was irradiated with a biologically effective dose (BED) of >100 Gy the 5-year survival rates of patients with stage IA and stage IB disease were 90% and 84%, respectively, both of which are good.

In our hospital, both ^{18}fludeoxyglucose-positron emission tomography (FDG-PET) and thallium-201 single photon emission tomography (Tl-SPECT) are performed before stereotactic radiotherapy. Since these imaging modalities cannot provide the pathological findings obtained by surgery, Tl-SPECT is performed in addition to FDG-PET in order to increase the specificity of the imaging findings and eliminate false-positives due to inflammation.

FDG-PET, which is used to diagnose malignant tumors, depicts FDG uptake. In examinations of Japanese individuals aimed at determining whether lung tumors were benign FDG-PET displayed sensitivity and specificity values of 74% (95% confidence interval (CI): 59.7-85.4%) and 50% (95%CI: 31.3 to 68.7%), respectively.

Tl-SPECT is a tumor imaging modality based on the affinity of 201Tl-chloride for tumor cells[6–8]. Some reports have indicated that Tl-SPECT is useful for detecting residual and recurrent tumors after radiotherapy or surgery. Other studies have suggested that it is useful for assessing the curative effects of treatment[9] and prognostic prediction in lung cancer[10]. In addition, Tl-SPECT is widely employed for tumor scintigraphy. A previous study found that Tl-SPECT exhibited sensitivity and specificity values of 71.4% and 80%, respectively, for detecting lung cancer[11].

However, FDG-PET is very expensive (it costs 8,635 points in the Japanese national insurance system), and many general hospitals do not have FDG-PET imaging devices.

On the other hand, Tl-SPECT can be carried out using normal radioisotope examination ap-

paratus and is performed in a relatively high number of hospitals. In the Japanese national insurance system, Tl-SPECT costs 1,800 points, which is less than a quarter of the cost of FDG-PET, and Tl-SPECT imaging is also relatively easy to perform.

The utility of FDG-PET for predicting local recurrence after stereotactic radiotherapy is currently under investigation in various studies. However, the results reported so far have been mixed[12,13]. On the other hand, the utility of Tl-SPECT for predicting local recurrence after stereotactic radiotherapy has not been examined.

The present investigation was carried out in order to clarify the utility of Tl-SPECT for cancer staging and predicting local recurrence after stereotactic radiotherapy for stage I non-small cell lung cancer. In order to do this, we compared Tl-SPECT with FDP-PET. In addition, we also attempted to identify Tl-SPECT-derived parameters that are associated with local recurrence after stereotactic radiotherapy. As many general hospitals do not have FDG-PET devices, the ability of Tl-SPECT to predict local recurrence is clinically significant.

Subjects

The subjects were 78 patients who underwent stereotactic radiotherapy at the Department of Radiology, Yamanashi University, Chuoshi, Yamanashi. The subjects (1) were diagnosed with malignant lung tumors by transbronchial biopsy or computed tomography (CT)-guided biopsy; (2) underwent 201Tl-SPECT and FDG-PET within the three months before they received stereotactic radiotherapy (from January 2007 to December 2011); and (3) were diagnosed with stage I non-small cell lung cancer based on tumor viability evaluations performed before the radiotherapy and the detection of lymph node metastasis.

Follow-up evaluations were carried out after the radiotherapy according to a predefined schedule: Physical examinations and CT imaging scans were performed every two months until 6 months after the radiotherapy, every 3 months from 6 months to 2 years after the radiotherapy, and every 6 months from then on.

Methods

In FDG-PET, after the injection 3 MBq per kg body weight the early standardized uptake value (SUV) was measured after 1 hour, and the delayed SUV was assessed after 2 hours. In addition, the retention index (RI) was calculated using the following equation: RI = 100 x {(delayed SUV - early SUV)/(early SUV)}. The FDG-PET scans were obtained with a matrix size of 128 x 128 using a Biograph DUO LSO scanner (Siemens) in 3D mode.

In Tl-SPECT, after the injection of 111 MBq per kg of body weight (for subjects who weighed <65 kg) or 148 MBq (for those who weighed ≥65 kg) the early ratio was measured after 15 minutes, and the delayed ratio was measured after 3 hours, and the RI was calculated using the following formula: RI = {100 x (delayed ratio - early ratio)/(early ratio)}.

The radiotherapy protocol was as follows: In order to minimize the respiratory motion of the lung nodules, a respiratory monitoring device (Abches ®, APEX medical, Tokyo, Japan) was used during the pre-treatment imaging, and breath holding was enforced at least twice during the use of the fluoroscopic apparatus. When the patient was not very good at holding their breath, they were asked to practice it further until their breath holding improved. After the pre-treatment CT scans had been obtained using a Hi-speed DX/l (GE Yokogawa Medical Systems,

Tokyo, Japan), the tumor was imaged a further 3 times at 5-minute intervals, and the accuracy of the tumor positioning measurements obtained during breath holding was assessed. The radiotherapy involved non-coplanar multi-field irradiation or rotational conformal therapy delivered by a linear accelerator (EXL-15DP, Mitsubishi Electric, Tokyo, Japan).

The gross tumor volume (GTV) was extracted from the tumor outline on lung field CT (window width: 2000, window level: -700 HU). The clinical target volume (CTV) was defined as follows: CTV = GTV + the internal target volume (ITV), and the ITV was defined as: ITV = CTV + breath holding accuracy in all directions (which was measured 3 times during the abovementioned CT imaging). The planning target volume (PTV) was defined as PTV = ITV+5 mm, and the leaf margin was set at 0 to 5 mm.

Local recurrence was defined as (1) an increase of ≥20% in the major axis of the tumor compared with that seen before radiotherapy or (2) an increase of <20% in the major axis of the tumor and the detection of an SUVmax of ≥3 on FDG-PET.

Unfortunately, there are no definite clinical SUVmax criterion for detecting tumors on FDG-PET, and each facility has their own threshold. In the present study, malignant tumors were detected using an SUVmax value of ≥3, which was chosen based on the findings of a previous report[14].

A relapse-free state was defined as follows: (1) the abovementioned criteria had not been met at more than two years after the last observation or (2) the abovementioned criteria had not been met by September 2012. Out of field recurrence was defined as follows: (1) an increase in the major axis of the tumor of ≥20% that resulted in the tumor extending outside of the radiation field or (2) an increase in the major axis of the tumor of <20% that resulted in the tumor extending outside of the radiation field and the detection of an SUVmax of ≥3 on FDG-PET.

In the present study, "all recurrence" included both local recurrence and out of field recurrence.

This study was approved by the ethical review board of Yamanashi University medical department.

Statistical Analysis

All statistical analyses were carried out using the Statistical Package for Social Science (SPSS) ver.21 (IBM, N.Y., USA). Analyses of the differences in the various FDG-PET or Tl-SPECT parameters between the patients that did and did not develop recurrent lesions were carried out using the Mann-Whitney U test, and multivariate analysis was performed using the Cox regression analysis method.

Since the multivariate analysis detected correlations between tumor diameter and confounding factors, tumor diameter was not included in the multivariate analysis. Instead, age, sex, and histological type were entered into the Cox regression analysis.

Results

The patients' characteristics are shown in Table 1. The data regarding the associations between FDG or ^{201}Tl-chloride uptake and local recurrence, out of field recurrence, or all recurrence are shown in Table 2.

(1) Our findings regarding the relationships between local recurrence and the various FDG-PET and TI-SPECT parameters are shown in Table 2. In Tl-SPECT, the delayed ratio and the RI differed significantly between the recurrence

Table 1. Patients' characteristics

	Local recurrence		Out of field recurrence		All recurrence		Overall
	no recurrence	recurrence	no recurrence	recurrence	no recurrence	recurrence	
Age (years)	79.3 ± 6.2	78.9 ± 6.5	79.1 ± 6.8	79.6 ± 5.0	79.2 ± 6.5	79.3 ± 6.0	79.2 ± 6.3
median	80	80	81	80	81	80	80
range	58 – 90	60 – 86	58 – 90	65 – 87	58 – 90	60 – 87	58 – 90
Gender							
male	40	10	33	17	28	22	50
female	21	7	20	8	15	13	28
Histology							
adenocarcinoma	33	11	28	16	22	22	44
squamous cell carcinoma	17	4	15	6	12	9	21
unclassified non-small cell lung cancer	5	1	5		4	2	6
unknown	6	1	5	2	5	2	7
Tumor diameter(mm)	25.2 ± 8.2	29.1 ± 6.3	26.7 ± 7.4	24.8 ± 9.04	26.3 ± 7.7	25.9 ± 8.4	27 ± 8.84
median	25	28	27	25	26	27	26
rangeg	10 – 43	14 – 39	10 – 40	10 – 43	10 – 40	10 – 43	10 – 43
Median follow-up (months)	28 (6 – 66)	30 (14 – 60)	24 (6 – 66)	40 (7 – 61)	24 (6 – 66)	36 (7 – 61)	28 (6 – 66)

Table 2. Associations between Tl-SPECT or FDG-PET parameters and recurrence

		Uptake parameters	No recurrence	Recurrence	Mann-Whitney U test p-value	Cox regression analysisg		
						p-value	HR	95%CI
Local recurrence	FDG-PET	early SUV	5.40 ± 4.5	7.27 ± 4.9	0.175	0.125	1.083	(0.978 – 1.199)
		delayed SUV	6.83 ± 5.8	9.35 ± 6.3	0.191	0.132	1.063	(0.982 – 1.150)
		RI	22.4 ± 18.5	26.8 ± 24.8	0.342	0.937	1.001	(0.980 – 1.022)
	Tl-SPECT	early ratio	2.28 ± 0.97	2.6 ± 1.1	0.245	0.558	1.139	(0.737 – 1.761)
		delayed ratio	3.02 ± 2.1	3.86 ± 2.1	0.025 *	0.134	1.154	(0.957 – 1.393)
		RI	27.0 ± 32.6	48.5 ± 41.1	0.037 *	0.013 *	1.015	(1.003 – 1.027)
Out of field recurrence	FDG-PET	early SUV	5.74 ± 4.9	5.95 ± 4.1	0.250	0.116	1.080	(0.981 – 1.761)
		delayed SUV	7.23 ± 6.3	7.72 ± 5.5	0.265	0.149	1.055	(0.981 – 1.134)
		RI	20.8 ± 15.6	28.7 ± 26.6	0.134	0.410	1.009	(0.988 – 1.029)
	Tl-SPECT	early ratio	2.35 ± 1.0	3.13 ± 2.1	0.898	0.895	0.974	(0.661 – 1.435)
		delayed ratio	3.13 ± 2.1	3.36 ± 2.1	0.835	0.702	1.034	(0.872 – 1.226)
		RI	29.5 ± 34.8	36.3 ± 37.0	0.330	0.408	1.005	(0.994 – 1.015)
All recurrence	FDG-PET	early SUV	5.21 ± 4.7	6.18 ± 4.1	0.077	0.022 *	1.102	(1.014 – 1.197)
		delayed SUV	6.53 ± 6.1	8.00 ± 5.3	0.057	0.031 *	1.070	(1.006 – 1.139)
		RI	18.9 ± 16.4	28.8 ± 22.6	0.023	0.167	1.012	(0.995 – 1.030)
	Tl-SPECT	early ratio	2.20 ± 0.9	2.53 ± 1.1	0.220	0.134	1.263	(0.930 – 1.715)
		delayed ratio	2.88 ± 2.0	3.60 ± 2.1	0.075	0.116	1.106	(0.976 – 1.254)
		RI	26.4 ± 33.3	38.1 ± 37.3	0.118	0.109	1.007	(0.998 – 1.017)

*: $p<0.05$

Table 3. Correlations between the Tl-SPECT and FDG-PET parameters

		Tl early ratio	Tl delayed ratio	Tl RI
FDG-PET early SUV	Correlation coefficient	0.158	0.208	0.147
	P-value (two-sided)	**0.041** *	**0.007** **	0.057
FDG-PETdelayed SUV	Correlation coefficient	0.130	0.176	0.130
	P-value (two-sided)	0.092	0.023 *	0.092
FDG-PET RI	Correlation coefficient	−0.011	0.013	0.003
	P-value (two-sided)	0.887	0.866	0.972

*: $p<0.05$ **: $p<0.01$

and no recurrence groups. Moreover, in Cox regression analysis the Tl-SPECT RI was found to be significantly higher in the recurrence group. None of the FDG-PET parameters differed significantly between the groups.

(2) As for out of field recurrence, none of the examined FDG-PET or Tl-SPECT parameters differed significantly between the recurrence and no recurrence groups.

(3) Table 2 also shows our findings concerning the relationships between all recurrence and the FDG-PET or Tl-SPECT parameters. The RI obtained with FDG-PET differed significantly between the groups. Moreover, Cox regression analysis demonstrated that the early and delayed SUV were both significantly higher in the recurrence group. None of the Tl-SPECT parameters differed significantly between the groups.

(4) Correlations between the FDG-PET and Tl-SPECT parameters (Table 3).

As for the relationships between the FDG-SPECT and Tl-SPECT parameters, the early SUV was correlated with the early and delayed ratios, and a correlation was also detected between the delayed SUV and the delayed ratio.

(5) To detect factors associated with local recurrence, the FDG-PET and Tl-SPECT parameters were subjected to a Cox regression analysis involving fluorescent marker uptake, sex, age, and histological type, and the results are shown in Table 4. In the multivariate analysis, only the RI obtained with Tl-SPECT was found to be correlated with local recurrence ($p = 0.010$, HR: 1.020).

(6) To identify factors associated with out of field recurrence, the FDG-SPECT and Tl-SPECT parameters were subjected to a Cox regression analysis involving fluorescent marker uptake, sex, age, and histological type, and the results are shown in Table 5. A significant relationship was detected between the early SUV and out of field recurrence ($p=0.048$, HR: 1.111). However, no such relationship was detected for the delayed SUV ($p=0.058$, HR: 1.079). Overall, a strong tendency was observed between FDG uptake and out of field recurrence. None of the Tl-SPECT parameters exhibited significant relationships with out of field recurrence.

(7) To detect factors that are associated with all recurrence (Table 6), the FDG-PET and Tl-SPECT parameters were subjected to a Cox regression analysis involving fluorescent marker uptake, age, sex, and histological type.

The early ($p=0.013$, HR: 1.025) and delayed SUV ($p=0.018$, HR: 1.084) both demonstrated significant associations with all recurrence. None of the Tl-SPECT parameters displayed significant relationships with all recurrence.

(8) In the multivariate analysis, no significant relationships between recurrence and age, sex,

Table 4. Multivariate Cox regression analysis of local recurrence

	FDG-PET early SUV		FDG-PET delayed SUV		FDG-PET RI		Tl SPECT early ratio		Tl SPECT delayed ratio		Tl SPECT RI	
	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)
Fluorescent marker uptake	0.095	1.105 (0.983 – 1.243)	0.098	1.080 (0.986 – 1.182)	0.796	1.003 (0.980 – 1.026)	0.635	1.120 (0.701 – 1.792)	0.116	1.209 (0.954 – 1.533)	0.010 *	1.020 (1.005 – 1.035)
Age	0.765	1.012 (0.983 – 1.243)	0.746	1.013 (0.936 – 1.096)	0.916	1.004 (0.386 – 3.608)	0.985	0.999 (0.923 – 1.082)	0.966	0.998 (0.922 – 1.081)	0.965	0.998 (0.918 – 1.086)
Sex	0.983	1.012 (0.338 – 3.027)	0.990	1.007 (0.333 – 3.042)	0.771	1.181 (0.386 – 3.608)	0.834	1.128 (0.365 – 3.484)	0.901	1.071 (0.360 – 3.185)	0.873	1.094 (0.366 – 3.265)
Histology	0.819		0.819		0.927		0.945		0.816		0.591	
AC histology	0.628	1.674 (0.208 – 13.467)	0.643	1.638 (0.204 – 13.150)	0.758	1.387 (0.173 – 11.102)	0.767	1.128 (0.365 – 3.484)	0.474	2.387 (0.221 – 25.820)	0.320	3.188 (0.325 – 31.273)
NSCLC histology	0.714	1.722 (0.094 – 31.615)	0.761	1.577 (0.084 – 29.771)	0.628	2.044 (0.114 – 36.792)	0.655	1.931 (0.107 – 34.718)	0.414	3.742 (0.221 – 25.820)	0.183	9.246 (0.351 – 243.78)
SCC histology	0.957	0.939 (0.093 – 0.485)	0.935	0.908 (0.089 – 9.275)	0.962	1.057 (0.105 – 10.644)	0.942	1.088 (0.112 – 10.552)	0.658	1.759 (0.145 – 21.392)	0.472	2.775 (0.224 – 34.407)

*: $p<0.05$

Table 5. Multivariate Cox regression analysis of out of field recurrence

	FDG-PET early SUV		FDG-PET delayed SUV		FDG-PET RI		Tl SPECT early ratio		Tl SPECT delayed ratio		Tl SPECT RI	
	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)
Fluorescent marker uptake	0.048*	1.111 (1.001 – 1.232)	0.058	1.079 (0.997 – 1.167)	0.204	1.014 (0.992 – 1.036)	0.808	0.953 (0.647 – 1.405)	0.802	1.024 (0.849 – 1.236)	0.500	1.004 (0.992 – 1.016)
Age	0.211	1.041 (0.978 – 1.108)	0.204	1.042 (0.978 – 1.167)	0.219	1.042 (0.976 – 1.114)	0.348	1.031 (0.968 – 1.098)	0.357	1.030 (0.967 – 1.097)	0.363	1.030 (0.966 – 1.099)
Sex	0.572	0.761 (0.295 – 1.962)	0.545	0.746 (0.288 – 1.930)	0.501	0.717 (0.272 – 1.891)	0.640	0.640 (0.302 – 2.089)	0.604	0.775 (0.296 – 2.029)	0.590	0.768 (0.294 – 2.005)
Histology	0.675		0.662		0.749		0.874		0.890		0.922	
AC histology	0.993	1.007 (0.220 – 4.601)	0.970	0.971 (0.213 – 4.417)	0.883	0.983 (0.199 – 4.016)	0.796	0.818 (0.178 – 3.748)	0.903	0.904 (0.179 – 7.017)	0.991	0.991 (0.203 – 4.830)
NSCLC histology	0.393	0.330 (0.026 – 4.187)	0.365	0.306 (0.024 – 3.974)	0.494	0.420 (0.035 – 5.059)	0.582	0.497 (0.041 – 5.979)	0.639	0.541 (0.042 – 3.847)	0.723	0.627 (0.048 – 8.279)
SCC histology	0.581	0.617 (0.112 – 3.416)	0.555	0.597 (0.108 – 3.310)	0.544	0.544 (0.099 – 2.981)	0.533	0.579 (0.104 – 3.219)	0.625	0.639 (0.106 – 3.847)	0.717	0.718 (0.120 – 4.314)

*: $p<0.05$ significant differences

Table 6. Multivariate Cox regression analysis of all recurrence

	FDG-PET early SUV		FDG-PET delayed SUV		FDG-PET RI		Tl SPECT early ratio		Tl SPECT delayed ratio		Tl SPECT RI	
	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)
Fluorescent marker uptake	0.013 *	1.120 (1.025 – 1.225)	0.018 *	1.084 (1.014 – 1.159)	0.073	1.018 (0.998 – 1.037)	0.155	1.275 (0.912 – 1.783)	0.101	1.147 (0.974 – 1.352)	0.109	1.009 (0.998 – 1.020)
Age	0.169	1.038 (0.984 – 1.096)	0.165	1.039 (0.984 – 1.097)	0.157	1.042 (0.984 – 1.103)	0.360	1.025 (0.972 – 1.082)	0.357	1.026 (0.971 – 1.084)	0.387	1.025 (0.969 – 1.084)
Sex	0.376	1.417 (0.655 – 3.069)	0.402	1.394 (0.641 – 3.032)	0.419	1.387 (0.628 – 3.064)	0.403	1.388 (0.644 – 2.994)	0.415	1.380 (0.635 – 2.999)	0.450	1.353 (0.617 – 2.968)
Histology	0.824		0.842		0.818		0.764		0.642		0.669	
AC histology	0.494	1.683 (0.379 – 7.472)	0.525	1.620 (0.366 – 7.165)	0.604	1.477 (0.338 – 6.463)	0.471	1.768 (0.375 – 8.331)	0.319	2.454 (0.419 – 14.365)	0.424	1.876 (0.401 – 8.782)
NSCLC histology	0.746	1.412 (0.175 – 11.382)	0.833	1.256 (0.151 – 10.434)	0.654	1.602 (0.204 – 12.599)	0.408	2.410 (0.300 – 19.336)	0.252	3.858 (0.382 – 38.921)	0.235	3.863 (0.416 – 35.867)
SCC histology	0.803	1.228 (0.245 – 6.159)	0.829	1.195 (0.238 – 6.005)	0.955	1.047 (0.209 – 5.260)	0.722	1.345 (0.263 – 6.883)	0.483	1.929 (0.308 – 12.101)	0.531	1.730 (0.312 – 9.605)

*: $p<0.05$ significant differences

or histological type were detected.

Fig. 1 shows the FDG and ^{201}Tl-chloride uptake detected in one of our cases and the radiotherapy dose distribution map for the same patient.

DISCUSSION

Previous reports have examined whether it is possible to differentiate between benign and malignant tumors[15] using FDG-PET and Tl-SPECT or whether these modalities can be used to predict recurrence[16]. Recent studies have produced contradictory results regarding whether FDG-PET is useful for predicting recurrence after stereotactic radiotherapy. However, this is the first detailed report about local recurrence in patients who undergo both Tl-SPECT and FDG-PET before stereotactic radiotherapy.

Previous studies have found that prognosis can be predicted based on the results of Tl-SPECT and FDG-PET scans performed before surgical resection[13,15–17], but these studies only examined the correlations between the subjects' imaging findings and the frequency of metastasis and did not analyze the relationships between Tl-SPECT/FDG-PET findings and local recurrence.

Although FDG-PET is very useful for searching for metastasis during lung cancer staging, it has been reported to exhibit sensitivity and specificity values of 92% and 67.4%, respectively, for differentiating between benign and malignant lung tumors in Japanese individuals, which indicates that there is a high risk of false-positives.

On the other hand, Tl-SPECT demonstrates sensitivity and specificity values of 71.4% and

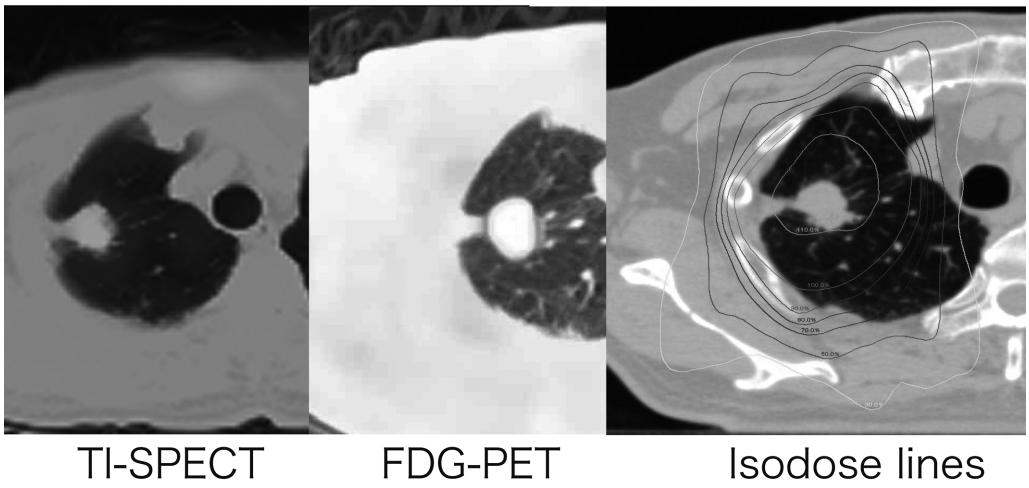

Fig. 1. Tl-SPECT and FDG-PET scans of the radiation field and a stereotactic radiotherapy dose map obtained in an actual case
Strong accumulation was observed on the Tl-SPECT and FDG-PET scans, and the radiation dose distribution during stereotactic radiotherapy was as shown on the right.

80%, respectively, for differentiating between benign and malignant tumors[9].

Unlike surgery, radiotherapy does not allow a definitive pathological diagnosis to be obtained. Therefore, in the present study both FDG-PET and Tl-SPECT were performed before radiotherapy in order to improve diagnostic accuracy.

During FDG-PET scans, patients are exposed to radiation doses as low as 3.5 mSv[18]. It has previously been reported that a dose of about 500 mSv is required to reduce a patient's white blood cell count. In an epidemiological survey, it was unclear whether the administration of <100 mSv influenced the risk of cancer. In Tl-SPECT scans involving a radiation dose of 111 MBq per kg body weight the patient is exposed to 15.54 mSv of radiation (calculated using the MIRD method: ICRP publication). The radiation dose delivered during a simple CT scan is about 10 mSv, whereas that delivered during contrast-enhanced CT is about 20 mSv. Thus, the combined use of TL-SPECT and FDG-PET is very significant from a clinical point of view because it provides more information than CT at a comparable radiation dose.

(I) The correlations between the findings of FDG-PET and Tl-SPECT

It has been reported that FDG uptake via the Glut-1 receptor is correlated with the degree of cancer cell specialization. On the other hand, it has been reported that Tl is taken up into cells by Na+/K+-ATPase. Although FDG-PET and Tl-SPECT involve different absorption mechanisms, FDG and Tl both accumulate in viable malignant tumor cells. Therefore, it is supposed that the findings obtained with these methods will be correlated to some degree.

(II) Relationships between FDG-PET parameters and recurrence

In the present study, none of the examined FDG-PET parameters were found to be related

to local recurrence after stereotactic radiotherapy. As for out of field recurrence and all recurrence, significant relationships were observed between all recurrence and the early SUV or delayed SUV during an analysis in which only time and FDG uptake were considered as factors. Moreover, multivariate analysis detected significant relationships between the early SUV and out of field recurrence (HR: 1.111, p=0.048) or all recurrence (HR: 1.120, p=0.013). As for the delayed SUV, FDG uptake was strongly associated with out of field recurrence (HR: 1.079, p=0.058) and all recurrence (HR: 1.084, p=0.018), which indicates that FDG uptake is related to recurrence. This shows that FDG uptake during FDG-PET can be used to predict metastasis outside of the radiation field.

It has been demonstrated that strong FDG uptake during FDG-PET is associated with a high grade of malignancy and a poor prognosis [19–25]. A high grade of malignancy is a risk factor for metastasis, which explains why strong FDG uptake can be used to predict metastasis. As for local recurrence, it has been suggested that high local FDG uptake might be indicative of increased cell turnover. According to Bergonie-Tribondeau's law (the radiosensitivity of a tissue is affected by (1) its mitotic activity, (2) the duration of active cell proliferation, and (3) the proportion of undifferentiated cells), it is supposed that local recurrence can not be predicted from FDG uptake because of the interaction between the grade of malignancy and the markedly increased radiosensitivity of locally recurrent lesions.

Although in the present study the delayed SUV did not exhibit a significant relationship with out of field recurrence, as the associated p-value was high (p=0.058) it is considered that this relationship might become significant if the number of cases was increased.

(III) Tl-SPECT and recurrence

No previous studies have examined the relationship between Tl-SPECT parameters and local recurrence after stereotactic radiotherapy. Although in Tl-SPECT ^{201}Tl produces a strong focus with a large RI, and higher RI values indicate more malignant lesions, the significance of ^{201}TL-chloride uptake during Tl-SPECT has not been fully elucidated. Based on assumption that Tl-chloride uptake exhibits a similar relationship with the degree of malignancy to FDG uptake, it is considered that radiotherapy has a marked effect on cells that exhibit strong Tl-chloride uptake. However, the mechanism responsible for Tl uptake is different from that of FDG because Tl is transported by the Na+/K+ pump, whereas FDG is subjected to sugar metabolism.

Since the RI reflects the amount of the fluorescent marker left in a cell, a high RI is indicative of low outflow of the marker from the cell. This suggests that fluorescent markers remain within malignant cells due to a reduction in the amount of blood flowing to such cells. For this reason, malignant cells are considered to receive less oxygen than normal cells.

The therapeutic effect of radiation is based on the damage to DNA caused by X-rays. There are two mechanisms of X-ray damage, the direct effects of X-rays, where the X-rays directly destroy the DNA molecule, and the indirect effects of X-rays, where active oxygen destroys the DNA molecule. It is known that the indirect effects of X-rays have a greater curative impact on tumor cells than their direct effects. Therefore, it is considered that the therapeutic effect of radiation is weak because the low oxygen density in malignant cells reduces the amount of active oxygen that can be synthesized.

In this study, we found that the RI data obtained during Tl-SPECT can be used to predict local recurrence (HR: 1.020, p=0.010), so we

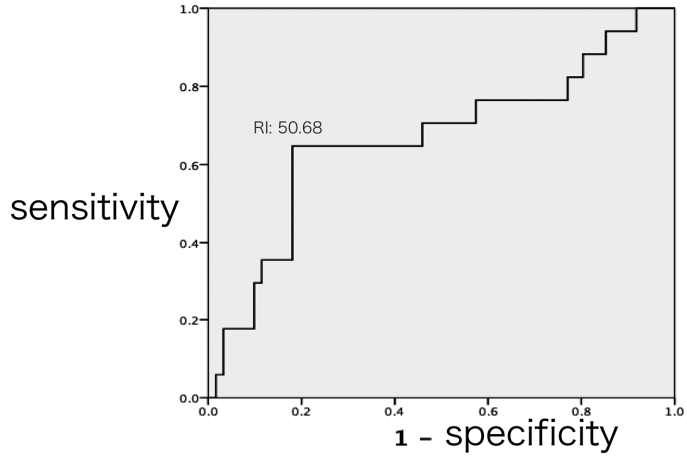

Fig. 2. ROC curve of the utility of Tl-SPECT RI values for detecting local recurrence

produced a receiver operating characteristic (ROC) curve in order to determine the optimal Tl-SPECT RI cut-off level for this purpose (Fig. 2). As a result, we found that local recurrence can be predicted with 64.7% sensitivity and 82% specificity at an RI cut-off level of 50.68. The findings of the present study suggest that it might be possible to increase the local control rate of patients that exhibit RI of greater than 50.68.

Unfortunately, however, Tl-SPECT was not able to predict out of field recurrence or all recurrence. Thus, it is possible that the reduction in blood flow associated with a high RI on Tl-SPECT also results in a lower risk of metastasis.

In the JCOG0403 study, the local control rate of lung tumors that were treated with BED of <100 was 71.8% (20/28). Therefore, it is necessary to increase the local control rate of lung cancer patients who undergo stereotactic radiotherapy. The local control rate can be improved by: (1) increasing the radiation dose and/or (2) intensifying the curative effect of radiation by combining it with chemotherapy. Regardless of which method is chosen, it is necessary to select patients that are at high risk of local recurrence and intensify their treatment. Therefore, a method that can be used to predict local recurrence before treatment is required.

The current standard operation for lung cancer is a pulmonary lobectomy. The validity of this limited procedure for early stage lung cancer was recently examined in the JCOG0802 and JCOG0804 studies. If such local treatment is determined to be appropriate by these studies, stereotactic radiotherapy, which is also a local treatment, could become more established. The curative effect of local treatment is considered to be a prognostic predictor, and local therapy is only appropriate in cases in which the lymph nodes, which can not be treated with stereotactic radiotherapy, do not require treatment. So, the use of Tl-SPECT to predict the local effects of treatment could have beneficial effects on the local control rate. Specifically, our findings suggest that by using RI data obtained with Tl-SPECT and the cut-off level mentioned above it would be possible to increase the local control rate of stereotactic radiotherapy by intensifying the treatment administered to the local site in appropriate cases. Thus, stereotactic radiotherapy

Table 7. Comparison of the outcomes of stereotactic radiotherapy and surgery (5-year survival rate)

	Pathologicalstage		(Clinical stage)	
	Mountain*a (n=5319)	NCCH*b (n=1545)	National survey*c (n=13010)	SBRT**d (n=87)
Stage IA	67% (61%)	79% (71%)	84% (77%)	72% (58-82%)
Stage IB	57% (40%)	60% (44%)	66% (60%)	64% (38-78%)

* Surgery ** Stereotactic radiotherapy
a: Mountain, CF. Semin. Surg. Oncol. 18: 106–115, 2000.
b: Naruke T. Ann Thorac Surg. 71: 1759–1764, 2001.
c: Asamura H. JTO 3: 46–52, 2007.
d: Onishi H. JTO 2:supple 3 94-100 2007 Onishi H. IJROBP 2011; 81: 1352–8.

is considered to be clinically important.

However, since it would be risky to only apply local therapy in cases that exhibit strong FDG uptake on FDG-PET, the use of stereotactic radiotherapy requires careful consideration. Accordingly, chemotherapy might be a better choice in some cases.

(IV) Relationships between uptake and recurrence due to differences in age, sex, and histological type

In the analysis of the relationships between recurrence and FDG or ^{201}Tl-chloride uptake, no clear relationship was detected between recurrence and the uptake of either marker according to age, sex, or histological type. In lung cancer, the degree of FDG uptake during FDG-PET is considered to decrease in the following order: squamous cell carcinoma > large-cell cancer > adenocarcinoma > alveolus epithelial cancer, and it has been reported that during Tl-SPECT adenocarcinoma exhibits stronger ^{201}Tl-chloride uptake than squamous cell carcinoma. However, in the present study Cox regression analysis did not detect any differences in uptake according to histological type[9].

(V) Recurrence rate

A comparison between the outcomes of surgery and radiotherapy is shown in Table 7. The local control rate in the present study was 55.1% (43/78), which seems slightly low. In most cases in the JCOG0403 study, small tumors (<1 cm in diameter) with a ground glass appearance were subjected to active treatment. However, follow-up is the standard strategy for such tumors, and in the present study a greater number of cases involved solid tumors of ≥1 cm in diameter, which would explain why the local control rate of the current study population was lower.

In addition, since the aim of the present study was to analyze the utility of Tl-SPECT-based staging prior to stereotactic radiotherapy from the viewpoint of predicting recurrence, risk factors such as anamnesis and performance status were not considered. In some previous cases, tumors that exhibited strong FDG-PET uptake and a tendency to grow subsequently reduced in size during follow-up[26]; thus, FDG-PET-based predictions of local recurrence can result in false-positives.

When local recurrence develops after radiotherapy, re-irradiation or a salvage operation is the next option, and even when out of field recurrence occurs it is possible to control the patient's symptoms to some extent using chemotherapy.

Recently, it has been reported[27] that FDG-PET is superior to Tl-SPECT for preoperative screening. According to MacManus MP *et al.*, FDG-PET is able to detect more distant metastas-

es than Tl-SPECT. Moreover, since the contrast between the background and the tumor is high on FDG-PET it possesses greater sensitivity.

It is important to perform FDG-PET when searching for distant metastasis before treatment because staging has a significant impact on decision-making regarding treatment. However, it is also important to perform Tl-SPECT in order to reduce the false-positive rate and increase diagnostic accuracy because FDG-PET displays low specificity in Japanese patients. Based on these considerations, it is considered that FDG-PET and Tl-SPECT have a complementary relationship.

However, PET/CT (cost in Japanese national health insurance system: 8,635 points) is much more expensive than Tl-SPECT (cost in Japanese national health insurance system: 1,800 points). In addition, many hospitals do not have FDG-PET scanners, whereas Tl-SPECT is widely available in general hospitals. Therefore, the ability of Tl-SPECT to predict local recurrence after stereotactic radiotherapy is of great clinical significance because it makes it possible to customize the treatment delivered to each patient, even in general hospitals that do not have FDG-PET scanners.

In particular, if a group of patients that would not benefit from surgery were identified Tl-SPECT could be used to estimate the therapeutic effects of potential therapies on local tumors during treatment modification. On the other hand, it is considered that out of field recurrence and all recurrence can be predicted based on FDG-PET uptake. Thus, in cases involving high FDG-PET uptake the therapeutic effect of stereotactic radiotherapy could be increased by adding chemotherapy-based maintenance treatment.

(VI) Study limitations

The main limitations of the present study are related to the disadvantages of stereotactic radiotherapy.

(1) The treatment range cannot be examined pathologically unlike during surgery; i.e., it is not possible to identify whether the whole tumor is included within the treatment range.

(2) As lymphadenectomy cannot be carried out during radiotherapy (unlike during surgery), micrometastasis to the lymph nodes cannot be detected. Therefore, it is difficult to predict metastasis to regions outside of the radiation field.

(3) Since most patients that undergo stereotactic radiotherapy have inoperable conditions or refuse surgery, suspected recurrence often can not be confirmed pathologically. Therefore, some of the recurrent lesions in the present report might have been false-positives.

Terashima K *et al.* reported that in some cases, the uptake of FDG and the patient's carcinoembryonic antigen level increase after stereotactic radiotherapy, but these symptoms subsequently subside during follow-up.

In addition, in some of the cases examined in the present study the tumor could not be biopsied because it increased in size after stereotactic radiotherapy. These cases have not been published yet, but were included in the present study because the recurrence was not confirmed pathologically. This is considered to be a limitation of the present study.

Since it is difficult to pathologically confirm out of field recurrence, all tumors that increased in size and whose borders extended outside of the irradiation field were considered to be out of field recurrences in the present study. However, when a mass develops outside of the irradiation field, a definitive diagnosis can be obtained by

biopsy if the lesion is located near to the skin surface, but the risk of performing a biopsy is too high when the mass occurs deep inside the liver or a lymph node.

In addition, most patients who receive radiotherapy are old, and many have other complications so surgery is not an option. In these cases, a therapeutic method will be chosen based on the attending physician's clinical judgment. Therefore, in some cases primary malignant neoplasms are not distinguished from out of field recurrences because of a lack of a confirmed pathological diagnosis based on a biopsy. Thus, some of the recurrent lesions examined in the present study might actually have been malignant tumors that arose outside of the radiation field. This is also a limitation of the present study.

(VII) Future problems

In future, we will try to evaluate the vasculature of suspicious lung masses using contrast-enhanced CT and dynamic CT. In addition, we will examine whether Tl-SPECT could be used to predict local recurrence in patients that are able to undergo limited surgery.

Further study is necessary to determine the how radiation doses should be altered based on the findings of Tl-SPECT. In addition, we will investigate the utility of FDG uptake on FDG-PET for aiding decision-making regarding treatment selection and identifying suitable candidates for maintenance chemotherapy.

CONCLUSION

It is possible to predict local recurrence by carrying out Tl-SPECT before stereotactic radiotherapy for stage I non-small cell lung carcinoma. Therefore, it is expected that by using Tl-SPECT patients who are at risk of recurrence will be identified, and the treatment given to such patients will be improved, leading to an increase in the local control rate.

On the other hand, it might be possible to predict out of field recurrence and all recurrence by performing FDG-PET before stereotactic radiotherapy although this technique is unable to predict local recurrence. Therefore, in cases involving high FDG-PET uptake careful pretreatment examinations are necessary to aid decision-making regarding the use of stereotactic or whole body radiotherapy.

The ability of Tl-SPECT to predict local recurrence is clinically significant because Tl-SPECT is inexpensive, and the required apparatus are widely available.

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