Annals of Nuclear Medicine Vol. 10, No. 2, 193–200, 1996

A clinical evaluation of FDG-PET to assess the response in radiation therapy for bronchogenic carcinoma

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The clinical usefulness of FDG-PET in the prediction and assessment of response to radiation therapy in patients with bronchogenic carcinoma was evaluated. Thirty patients with untreated bronchogenic carcinoma were included in the study. All patients received FDG-PET before the initiation of radiation therapy, while 20 also received it after completing the therapy. The tumor to muscle ratio (TMR) was used as an index of the FDG uptake. The tumor response to therapy was classified as either a partial response (PR, n = 21) or no change (NC, n = 9) according to changes in the tumor size. Prognosis was made 6 months after the initiation of therapy, and was classified as either relapse (n = 19) or non-relapse (n = 9). The FDG uptakes both before and after therapy were compared with tumor response and prognosis. A high FDG uptake was noted in all 30 lesions before therapy. No significant differences in the uptake before therapy was observed according to the histological types nor T factors (UICC). The lesions with a higher uptake (TMR more than 7) responded better to therapy than those with a lower uptake ($p < 0.05$). The decrease in the uptake after therapy tended to be more prominent in the PR group than in the NC group. The rate of relapse was higher in lesions with a higher uptake before therapy (TMR more than 10) than in those with a lower uptake. The relapse group also showed a higher uptake after therapy than the non-relapse group. In addition, all 6 lesions showing a higher uptake (TMR more than 5) after therapy eventually relapsed ($p < 0.05$). Two lesions demonstrating a lower uptake both before and after therapy did not relapse, although no tumor regression due to the therapy was observed. These results indicate that FDG-PET plays a complementary role in both predicting and assessing the therapeutic response and prognosis in patients with bronchogenic carcinoma.

Key words: positron emission tomography, F-18 fluorodeoxyglucose, bronchogenic carcinoma, radiation therapy, therapeutic response

INTRODUCTION

EXTERNAL RADIATION THERAPY is often applied to patients with non-small cell bronchogenic carcinoma mainly in clinical stage III.[1,2] The therapeutic effect is usually evaluated by morphological examinations such as plain X-ray studies, CT or MRI, but it is well known that morphological changes do not necessarily correctly reflect the therapeutic effect. In clinical practice, we often encounter patients in which tumor regression after therapy did not correlate with the therapeutic effect.

The glucose metabolism in tumor tissue can be measured with F-18 2-fluoro-2-deoxy-D-glucose (FDG) and positron emission tomography (FDG-PET). Most human malignant tumors show a high FDG uptake, since in tumor tissue the metabolic rate of glucose is generally much higher than that in normal tissue. It has thus been shown that the glucose metabolism measured by FDG-PET provides valuable information in cancer diagnosis. Bronchogenic carcinoma has a high FDG uptake as do other malignant tumors. Several clinical applications of FDG-PET in the diagnosis of bronchogenic carcinoma have been reported in regard to the differential diagnosis between bronchogenic carcinoma and benign lung lesions[3–8] as well as the detection of metastases in the regional lymph node and distant organs.[9–11]

Received November 9, 1995, revision accepted January 22, 1996.

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Table 1 Patients

Case	Age/Sex	Histology	UICC		Therapy	Response	Relapse	TMR	
			Stage	TNM				Before	After
1	80/M	SqCC	IIIA	T2N2M0	R	PR	—	9.5	2.1
2	76/M	AC	IIIB	T4N0M0	R + C	PR	—	14.5	3.1
3	84/M	SqCC	IIIB	T4N2M0	R	PR	—	16.9	2.6
4	43/M	LCC	IV	T2N3M1	R + C	PR	—	8.7	4.7
5	64/M	LCC	IIIB	T4N2M0	R + C	PR	—	10.0	
6	37/M	ACC	IIIB	T4N2M0	R + C	PR	—	5.6	
7	67/M	SmCC	IIIB	T4N2M0	R + C	PR	—	8.8	
8	43/M	SqCC	IIIB	T1N3M0	R + C	PR	+	6.5	5.1
9	67/M	SmCC	IIIB	T2N3M0	R + C	PR	+	9.3	0.0
10	77/F	AC	IIIB	T2N3M0	R	PR	+	7.5	4.7
11	70/M	UCC	IIIB	T3N3M0	R + C	PR	+	13.5	6.4
12	67/M	SqCC	IIIB	T4N1M0	R + C	PR	+	20.8	7.8
13	52/M	SqCC	IIIB	T4N2M0	R + C	PR	+	10.7	5.1
14	61/M	SqCC	IIIB	T3N3M0	R	PR	D	9.6	2.2
15	52/M	AC	IIIB	T2N3M0	R + C	PR	D	7.9	
16	67/M	AC	IIIB	T2N3M0	R	PR	D	12.1	
17	68/M	SqCC	IIIB	T4N3M0	R	PR	D	10.4	
18	57/M	LCC	IIIB	T4N0M0	R	PR	D	22.4	
19	47/M	SqCC	IV	T4N3M1	R	PR	D	12.3	
20	75/M	SqCC	IIIB	T2N3M0	R	PR	#	10.6	5.3
21	77/M	SqCC	IIIB	T4N1M0	R	PR	#	13.6	4.0
22	75/M	UCC	I	T2N0M0	R + C	NC	—	6.1	2.6
23	62/M	AC	IIIA	T3N0M0	R + C	NC	—	5.8	3.6
24	50/F	AC	IIIA	T3N2M0	R + C	NC	+	20.9	13.6
25	62/M	PDC	IIIB	T3N3M0	R	NC	+	11.3	5.1
26	60/F	SqCC	IIIB	T4N2M0	R	NC	+	16.5	3.3
27	65/M	LCC	IV	T3N3M1	R + C	NC	+	9.9	2.9
28	72/F	SqCC	IV	T4N2M1	R	NC	D	4.7	4.0
29	58/M	AC	IIIB	T4N3M0	R	NC	D	11.2	
30	42/M	SqCC	IV	T3N3M1	R + C	NC	D	5.7	

SqCC: squamous cell carcinoma, AC: adenocarcinoma, LCC: large cell carcinoma, SmCC: small cell carcinoma, ACC: adenoid cystic carcinoma, PDC: poorly differentiated carcinoma, UCC: unclassified carcinoma, R: radiation therapy, C: chemotherapy, PR: partial response, NC: no change, —: no relapse, +: relapse, D: death, #: not followed up to 6 months

Regarding the evaluation of tumor response to therapy, it was observed in early experimental models that glucose metabolism can be used to monitor tumor response to therapy.[12,13] There have been several clinical reports on the use of FDG-PET for the evaluation of therapeutic response in bronchogenic carcinoma,[9,14] as well as in other tumors such as brain tumors,[15–17] head and neck tumors,[18–20] laryngeal cancer,[21] breast cancer,[20,22] liver tumors,[23–25] colon cancer,[26] malignant lymphoma[27] and miscellaneous cancers.[28] The purpose of this study is to clarify the role of FDG-PET in bronchogenic carcinoma to evaluate the therapeutic effect of radiation in predicting and assessing the therapeutic response and prognosis.

MATERIALS AND METHODS

Patients

The study covered 30 patients with bronchogenic carcinomas before the initiation of therapy (Table 1). Their histological diagnoses were finally obtained by a transbronchial lung biopsy in 8, a percutaneous lung biopsy in 8, sputum cytology in 4, transbronchial brushing in 3, a transbronchial biopsy in 2, an autopsy in 3, a lymph node biopsy in 1 and an exploratory thoracotomy in 1, and the histological types were classified as squamous cell carcinoma in 12, adenocarcinoma in 8, large cell carcinoma in 4, small cell carcinoma in 2, adenoid cystic carcinoma in 1, poorly differentiated carcinoma in 1 and unclassified carcinoma in 2. The clinical stages based on the UICC classification (1987) were stage I in 1, stage IIIA in 3, stage IIIB in 21 and stage IV in 5, and the T factors were T1 in 1, T2 in 8, T3 in 7 and T4 in 14.

All 30 patients received radiotherapy from 30 to 60 Gray in 150 cGy fractions by 6 MV X-ray with a linear accelerator Nelac 1600X (Nippon Electric Corp., Japan), and 17 patients also received chemotherapy. The therapeutic response after the therapy was evaluated by both plain chest X-rays and CT within one week after the

completion of radiotherapy, and they were classified as follows: complete response (CR): disappearance of the tumor, partial response (PR): a decrease in the tumor size of more than 50%, no change (NC): less than a 50% decrease, or less than a 25% increase, progressive disease (PD): more than a 25% increase. The prognosis was made at 6 months after the initiation of therapy in 28 patients who were followed up for more than 6 months after the initiation of therapy, and all were classified into either the relapse or non-relapse group. Nine patients who died within 6 months were also included in the relapse group.

The investigation was approved by the committee of medical application of the cyclotron-produced radionuclides in Kyushu University Hospital, and informed consent was obtained from all patients.

FDG-PET studies

All 30 patients underwent FDG-PET studies within 1 week before the initiation of the therapy, and 20 patients also received it within 3 weeks after the completion of the therapy. FDG was prepared as described previously.[28] A positron scanner SET130W (Shimadzu Corp. and Akita Noken, Japan) was used for the scanning, which has 3 detector rings providing 5 contiguous slices at 15 mm intervals. The effective spatial resolution used in the study was 14 mm in FWHM. Transmission scanning was performed with a Ge-68 ring source for attenuation correction. 111–296 MBq (3–8 mCi) of FDG was administered intravenously in the fasting state. Static scanning was done for 15 minutes from 45 to 60 minutes following the injection of FDG. Matrices of 128 × 128 were used, with each pixel measuring 3 mm × 3 mm.

Data analysis

The regions of interests (ROIs), which ranged from 15 mm × 15 mm to 27 mm × 27 mm in size, were set on the primary tumor and muscles. The area showing the highest FDG uptake was chosen as the ROI of the tumor. The ROIs of the muscle were set on 5 or 6 different parts, and their mean values were used. The tumor to muscle ratio (TMR) was calculated from the mean counts per pixel in the tumor and the muscles, and was used as an index of the FDG uptake. The ratio of TMR after therapy to that before therapy was then used as the residual uptake ratio. The cut off levels of the TMR used for the evaluation of the therapeutic response and prognosis were selected to obtain the respective optimal differentiations. One way factorial ANOVA and multiple comparison test, Fisher's exact method and paired t-test were all used for the statistical analysis.

RESULTS

Difference in the FDG uptake among histological types and T factors

All 30 lesions had a high FDG uptake before therapy and were clearly visualized. Their mean and standard deviation of the TMR was 11.1 ± 4.7 (n = 30, ranging from 4.7 to 22.4). No significant differences were observed in the TMRs among the various histological types of bronchogenic carcinoma (Fig. 1). Regarding the correlation between the TMR and T factors, it was observed that the higher the grades of the T factors, the higher the TMRs were, but no significant differences were noted (Fig. 2). Due to these two results, the following analyses were made while taking no account of either the histological types or the T factors.

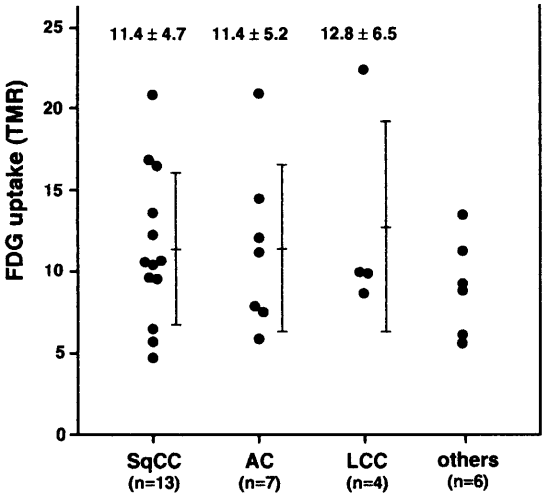


Fig. 1 FDG uptake before therapy according to histological types. (SqCC: squamous cell carcinoma, AC: adenocarcinoma, LCC: large cell carcinoma)

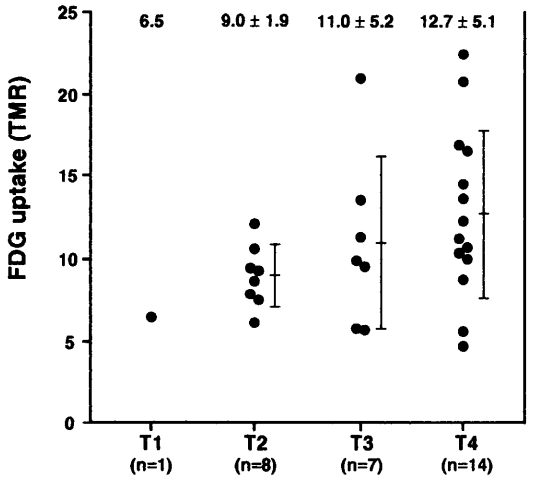


Fig. 2 FDG uptake before therapy according to T factors by UICC classification.

FDG uptake before therapy and the therapeutic response

PR was observed in 21 lesions, and NC in 9, and there was no lesion with either CR or PD. The lesions with a higher FDG uptake (a TMR of more than 7) before therapy showed a higher PR ratio than those with a lower uptake

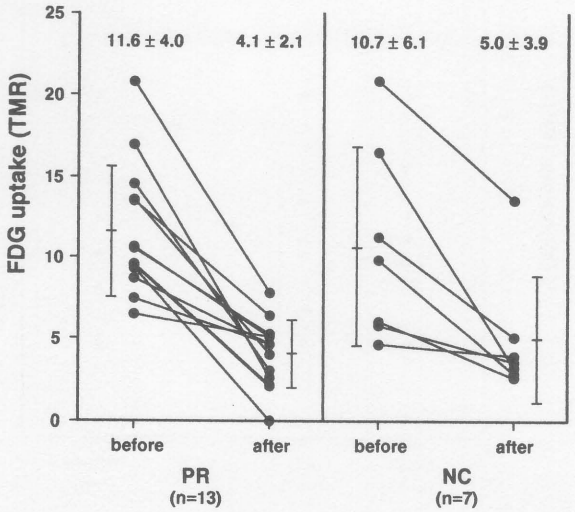


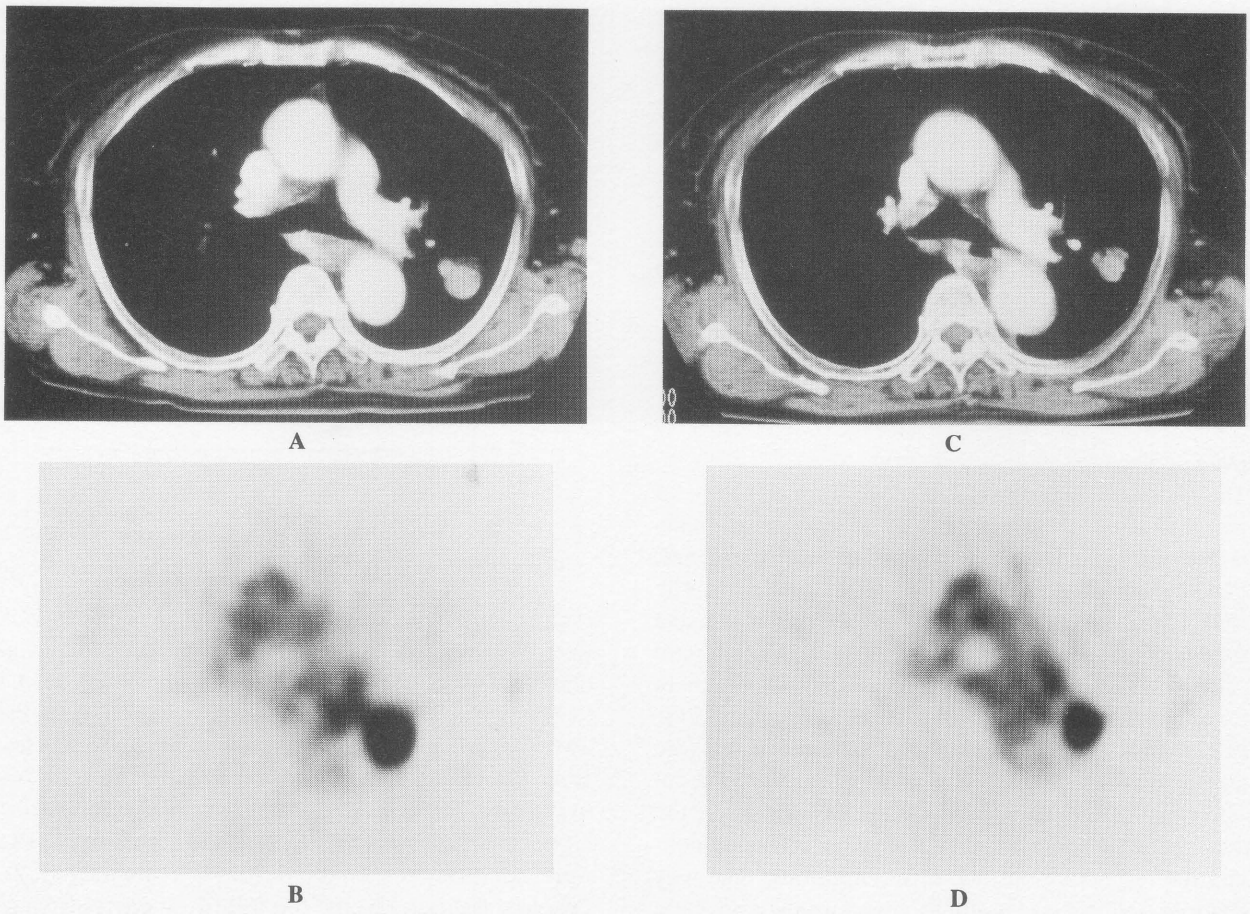
Fig. 3 Change in the FDG uptake by therapy and therapeutic response.

Table 2 Comparison of therapeutic response between lesions with a low and high FDG uptake before therapy

TMR before therapy	PR	NC
Less than 7 (n = 6)	2	4
More than 7 (n = 24)	19	5

$p < 0.05$, Fisher's exact method

▼ **Fig. 4** 77-year-old-female. Adenocarcinoma, stage IIIB, T2N3M0 (case 10). CT before therapy (A) showed a mass density in the left lung field, and high FDG uptake was noted in this lesion and mediastinal lymph node metastases (B). After radiation therapy of 60 Gy, the tumor decreased in size on CT (C), and FDG uptake also decreased (D).



(19/22 (79%) versus 2/6 (33%), $p < 0.05$) (Table 2). The 2 lesions with a TMR less than 7 in which a PR was obtained were a lesion of adenoid cystic carcinoma (case 6), which is generally thought to be a low-grade malignancy, and a small lesion (case 8, 2.5 cm in size), in which TMR was probably underestimated due to a partial volume effect. The mean TMR before therapy in the PR and NC groups was 11.5 ± 4.3 (n = 21) and 10.2 ± 5.5 (n = 9), respectively (n.s.).

Changes in the FDG uptake after therapy and the therapeutic response

The TMRs after therapy decreased in all 20 lesions, when compared to the TMR before therapy (Figs. 3 and 4). One

Table 3 Comparison between tumor response and prognosis

Tumor response	Non-relapse	Relapse
PR (n = 19)	7	12
NC (n = 9)	2	7

n.s., Fisher's exact method

Table 4 Comparison of prognosis between lesions with a low and high FDG uptake before therapy

TMR before therapy	Non-relapse	Relapse
Less than 10 (n = 15)	7	8
More than 10 (n = 13)	2	11

n.s., Fisher's exact method

Table 5 Comparison of prognosis between lesions with a lower and higher FDG uptake after therapy

TMR before therapy	Non-relapse	Relapse
Less than 5 (n = 12)	6	6
More than 5 (n = 6)	0	6

$p < 0.05$, Fisher's exact method

lesion (case 9) could not be visualized on the FDG-PET image after therapy, although a residual mass was noted on CT. The mean TMRs before and after therapy in all 20 lesions were 11.3 ± 4.7 and 4.4 ± 2.8, respectively ($p < 0.001$). The mean TMR after therapy was 4.1 ± 2.1 ($n = 13$) in the PR group and 5.0 ± 3.9 ($n = 7$) in the NC group (n.s.). The mean residual uptake ratio was 0.38 ± 0.22 in PR and 0.50 ± 0.22 in NC (n.s.) (Fig. 5), and there was a tendency for the decrease in the uptake to be more prominent in the PR than in the NC group.

Changes in the tumor size and prognosis

In 28 patients who were followed up for more than 6 months after the initiation of therapy, 9 lesions had no relapse, and 19 lesions were either not controlled by therapy or relapsed. Relapse was noted in 12 out of 19 lesions (63%) with a PR and 7 out of 9 (78%) in NC (n.s.) (Table 3).

FDG uptake before therapy and prognosis

When the lesions with a lower and higher uptake (TMR less or more than 10) before therapy were compared, a relapse was noted in 8 out of 15 lesions (53%) in the lower uptake group, and in 11 out of 13 lesions (85%) in the higher uptake group (n.s.) (Table 4). The prognosis tended to be more favorable in the lower uptake group, but no apparent difference between the non-relapse and relapse groups was noted in the mean TMR before therapy (9.5 ± 3.9 versus 11.7 ± 5.1).

Changes in the FDG uptake after therapy and prognosis

In 18 patients who received FDG-PET both before and after therapy and who were followed up for more than 6 months, 12 patients relapsed, while 6 patients did not relapse. The TMRs after therapy in the non-relapsed group were confined to the lower ranges, and the highest value was 4.7, whereas those in the relapsed group showed a wide distribution from 13.6 to 0 (Fig. 6). The mean TMR in the non-relapsed group was lower than that in the relapsed group (3.1 ± 0.9 versus 5.0 ± 3.4, n.s.). The difference between the two groups in the mean residual uptake ratios (0.36 ± 0.19 versus 0.45 ± 0.25, n.s.) was less prominent than that in the mean TMR after therapy. No relapse was observed in 6 lesions with a lower uptake (TMR less than 5), whereas 6 out of 12 (50%) relapsed in the lesions with a higher uptake ($p < 0.05$) (Table 5).

In 9 lesions with NC, 2 lesions (cases 22 and 23) did not relapse, and they had low TMRs both before therapy (6.1 and 5.8) and after therapy (2.6 and 3.6).

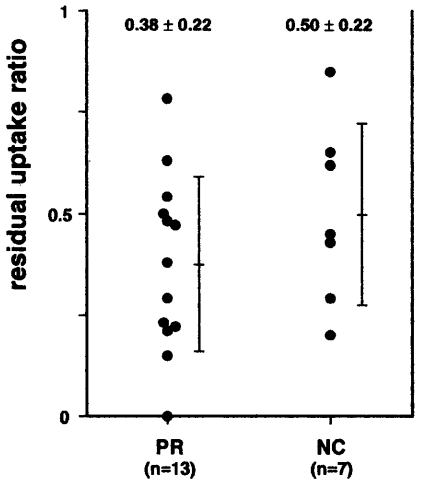


Fig. 5 The residual uptake ratio and therapeutic response. (The residual uptake ratio: TMR after therapy/TMR before therapy)

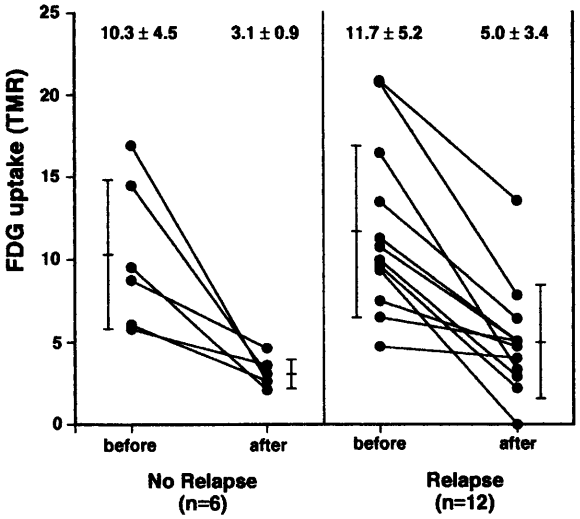


Fig. 6 Change in the FDG uptake by therapy and prognosis.

DISCUSSION

In this series all 30 lesions showed a high FDG uptake before therapy. Concerning the correlation between the FDG uptake before therapy and histological types, no correlation has been observed in bronchogenic carcinoma,[4,9,29] and similar results was observed in this series. Tumor size has a direct influence on the FDG uptake measured by PET due to the partial volume effect. In this study, the uptake measured in small lesions especially those less than 3 cm in diameter was thought to be underestimated, since the spatial resolution of the PET scanner used in this study was 14 mm in FWHM, but no significant correlation was noted between the T factors and FDG uptake. The reason for this was considered to be that most lesions were relatively large.

Haberkorn et al.[19] reported that lesions with a higher FDG uptake before therapy had a higher regression in tumor volume caused by chemotherapy in 18 patients with head and neck tumors. Their results are in agreement with the data showing that the FDG uptake correlated with the proliferative activity of the tumor cells, which was assessed either by DNA flow cytometry or the proportion of mitotic cells in head and neck tumors[30–32] and malignant lymphoma.[33] Rapidly growing cells generally are highly sensitive to radiation. In this series, a similar finding was also obtained: a lesion with a higher FDG uptake before therapy was found to be more responsive to therapy as to tumor regression. This finding thus indicates that FDG uptake before therapy is useful in predicting tumor regression due to the therapy as well as in bronchogenic carcinoma.

Regarding the correlation between the regression of tumor size due to the therapy and changes in the FDG uptake before and after therapy, Abe et al.[14] reported a good correlation between them in 4 patients with bronchogenic carcinoma who received radio- and/or chemotherapy. In tumors other than bronchogenic carcinoma, it is also reported that the decreases in FDG uptake in the response group were more prominent than those in the no response group in head and neck tumors,[18,19] colon cancer,[26] liver tumors[24,25] and miscellaneous cancers.[28] The same tendency was also noted in this series, but it was less clear, i.e., little difference was noted between PR and NC groups in the mean FDG uptake after therapy, but the decrease in FDG uptake after therapy was more prominent in the PR group. The following three possibilities can be suggested to explain our findings. First, advanced stage III bronchogenic carcinomas, which included most patients evaluated in our study, are intractable to radiation and/or chemotherapy, and a sufficient therapeutic effect is rarely obtained. Such tumors are usually either not controlled by therapy or recur within 1 year, and the mean survival time is around 1 year.[1,2] It is therefore possible that the difference between PR and NC in respect to changes in the tumor metabolism is minor, when compared to other well-controllable cancers. The second possibility is an uptake in the co-existent inflammatory process. FDG accumulates not only in tumor tissue but also in inflammatory lesions.[34] The lung is the most common site in which to demonstrate infection. Pneumonia or pneumonitis is often noted by a histological examination of the surrounding or peripheral area of a tumor lesion, even when a chest X-ray or CT shows no such findings. FDG uptake measured by PET may therefore be overestimated by the superimposed uptake in the inflammatory process. The third possibility is related to the timing of the second PET study after therapy. We usually performed it immediately after the completion of therapy. A high FDG uptake immediately after therapy due to the effect of radiation or unknown causes has been noted.[7,26,28,35] Infiltrating cells such as macrophages or newly formed granulation tissues, which are abundant around the necrotic tissue, have a high FDG uptake.[36] FDG-PET studies 1 or 2 months after therapy may thus afford more precise information concerning this point. A further evaluation is required to determine the optimal timing of the second PET study.

As for the correlation between the FDG uptake before therapy and prognosis, it has been reported that lesions with a higher FDG uptake had a poorer prognosis than those with a lower uptake in cerebral glioma,[15,16] meningioma,[17] malignant lymphoma[27] and in some miscellaneous cancers.[28] The prognosis in advanced bronchogenic carcinoma after radiation therapy is generally poor, and most lesions relapse within 1 year. Therefore, in this study an evaluation was made 6 months after therapy to establish a short-term prognosis. In this series, we also found that that prognosis was more favorable in the lower uptake group than in the higher uptake group, although no statistical significance was noted. This was thought to be useful in making a prognosis before therapy. Further evaluation is needed, however, in a large population.

The therapeutic effect is usually evaluated by morphological changes in the tumor size. Lesions with no change in tumor size are therefore thought to have undergone ineffective therapy, but in this series it was also shown that morphological changes alone were not satisfactory in making a prognosis. It has been shown that FDG-PET after therapy is predictive in the prognosis of bronchogenic carcinoma.[7,14] Strauss et al.[9] suggested that the FDG uptake is therefore a more reliable and sensitive method for evaluating the therapeutic outcome than the change in tumor volume. In this series, we also noted that the mean TMR after therapy was higher in the relapsed group than in the non-relapsed group. Furthermore, all TMRs in the non-relapsed group were less than 4.7, while the TMRs in the relapsed group were widely distributed. This meant that lesions with a high uptake after therapy relapse early, but the prognosis for lesions with a low uptake varies. We also noted two patients who had no tumor regression and did not relapse. They had a low FDG uptake both before

and after therapy. Our findings therefore suggest that FDG-PET plays an important role in making a prognosis, but regarding the role of FDG-PET after therapy, further evaluation is needed, because in the FDG uptake after therapy the difference between the non-relapsed and relapsed groups was minor, and it also remained unclear as to whether or not the FDG uptake after therapy correctly reflects tumor metabolism.[36]

We therefore conclude that FDG-PET plays a complementary role in the prediction and assessment of therapeutic response in bronchogenic carcinoma, but a further evaluation in a large tumor population is needed. Comparative studies of FDG and other metabolic tracers such as C-11 methionine, C-11 tyrosine or F-18 fluorouracil are also called for.

ACKNOWLEDGMENTS

The authors thank Mr. Brian T. Quinn for editorial support and Ms. Miwa Watanabe for secretarial assistance. This work was supported in part by a grant-in-aid for Cancer Research from Fukuoka Cancer Society, Japan and a grant-in-aid for Cancer Research No. 06282110 from the Ministry of Education, Science and Culture, Japan.

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