

FDG-PET for the evaluation of tumor viability after anticancer therapy

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To evaluate positron emission tomography with ^{18}F -fluorodeoxyglucose (FDG-PET) as a diagnostic tool to determine tumor viability after anticancer therapy, fourteen patients were examined by FDG-PET after the end of the treatment. The lesions with residual viable tumor cells showed higher uptake of FDG than surrounding normal soft tissue. The lesions, in which tumor viability was lost or very low, showed higher uptake of FDG in four cases and similar uptake to normal soft tissue in three cases. The residual increased uptake of FDG was considered to be caused by remaining tumor cells and/or inflammatory reaction to anticancer treatment. FDG-PET after anticancer treatment should be interpreted by considering the reaction due to the treatment and the partial volume artifact of PET caused by the limited spatial resolution.

Key words: ^{18}F -fluorodeoxy glucose, positron emission tomography, anticancer therapy, oncology

INTRODUCTION

POSITRON EMISSION TOMOGRAPHY with ^{18}F -2-fluoro-2-deoxy-D-glucose (FDG-PET) has been studied in diagnosing various kinds of malignant tumors in the last decade. Tumor glucose metabolism can be observed by FDG-PET, and it is hopeful for imaging tumors, grading the malignancy and predicting the prognosis.^{1–3} FDG-PET was also used to monitor the early chemotherapeutic effect in tumors, including head and neck cancer, breast cancer and malignant lymphoma.^{4–6}

After a series of chemotherapy and/or radiotherapy applied to the tumor, the question whether viable tumor cells still remain or not, often becomes a grave clinical issue. When malignant cells survive, added treatment will be considered. X-ray CT and MRI are performed for the evaluation of the treated tumor. They demonstrate the morphological changes (e.g., tumor size), but there remains the possibility that active malignant tissue remains. In contrast, FDG-PET is useful for the observation of the metabolic state of the treated tumor, and it may be useful in assessing residual tumor activity. Haberkorn et al.

studied FDG-PET in patients with colorectal tumors after the end of radiotherapy. They reported that increased FDG uptake was not lost in most tumors after the treatment and the residual active tumor could not be distinguished from the inflammatory reaction caused by the radiation injury.⁷ FDG-PET study after the end of anticancer therapy has not been fully investigated, and studies on various kinds of tumors at other PET centers are considered to be valuable.

The aim of this study is to measure the glucose metabolism of the treated tumor by FDG-PET and evaluate FDG-PET as a diagnostic tool to determine tumor viability after anticancer therapy.

PATIENTS AND METHODS

Fourteen patients (age 16–80) with histologically proven tumors including non-Hodgkin's lymphoma ($n = 7$), lung cancer ($n = 2$), hypopharyngeal cancer ($n = 2$), malignant melanoma of sphenoid sinus ($n = 1$), rectal cancer ($n = 1$) and mediastinal germ cell tumor ($n = 1$), were studied. The patients were treated by means of systemic chemotherapy and/or radiotherapy with 10 MeV photons. Details of the treatment are shown in Table 1. From day 1 to day 30 after the end of the anticancer therapy, FDG-PET was performed at the site where the tumor had been observed before the treatment. X-ray CT was also performed on the same day and the cross section of the

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Table 1 Patient list

No.	disease*	treatment method**	mass diameter	FDG uptake (TCR)	period (day) from treatment to PET	tumor viability*** (clinical observa- tion period; month)
1	NHL	BACOD-VP16 5 cycle RT (40 Gy)	1.5 cm	+(2.68)	1	– (biopsy)
2	NHL	BACOD-VP16 5 cycle RT (30 Gy)	1.3 cm	+(2.74)	8	– (biopsy)
3	NHL	RT (66 Gy)	1.3 cm	+(2.25)	1	– (26)
4	NHL	BACOD-VP16 3 cycle RT (40 Gy)	1.3 cm	–	4	– (20)
5	NHL	BACOD-VP16 3 cycle RT (30 Gy)	1.3 cm	+(2.26)	4	– (16)
6	NHL	BACOD-VP16 2 cycle RT (38 Gy)	–	–	17	– (9)
7	melanoma	Carboplatin RT (50 Gy)	–	–	20	– (12)
8	NHL	RT (56 Gy)	5.5 cm	+(1.76)	23	+(10)
9	hypopharyn.	RT (76 Gy)	1.1 cm	+(2.34)	11	+(20)
10	hypopharyn.	RT (60 Gy)	3.0 cm	+(2.97)	10	+(6)
11	lung	RT (60 Gy)	4.0 cm	+(2.94)	1	+(11)
12	lung	RT (60 Gy)	4.0 cm	+(5.35)	15	+(8)
13	rectum	RT (60 Gy)	5.9 cm	+(3.11)	30	+(6)
14	germ-cell	RT (50 Gy)	8.8 cm	+(2.99)	6	+(6)

* NHL; non-Hodgkin's lymphoma, hypopharyn.; hypopharyngeal cancer, lung; lung cancer, rectum; rectal cancer, germ-cell; germ-cell tumor

**BACOD-VP16; day 1—Belomycin 4 mg/m², Vincristine 1 mg/m², Cyclophosphamide 600 mg/m², Adriamycin 60 mg/m²
day 1–5—Dexamethasone 6 mg/m²
day 6–8—Etoposide 200

***tumor viability; It was diagnosed by pathological examination (cases 1 and 2) and clinical observation (cases 3–14)

residual tumor size was measured. The mean diameter of the residual mass, $\sqrt{\text{long axis} \times \text{short axis}}$, is shown in Table 1.

Tumor viability after the anticancer treatment was diagnosed by pathological examination of the biopsied specimens ($n = 2$) and by clinical observation longer than six months ($n = 14$). The observation period is shown in Table 1.

FDG was produced by CYPRIS and CUPID, a cyclotron system made by Sumitomo Heavy Industries. After transmission scan, about 148 MBq (4 mCi) of FDG was injected intravenously in the fasting state. Starting 60 minutes after the injection, a 5 minute scan was performed with a Shimadzu-SET 130W (HEADTOME III) PET scanner. The reconstructed image was compared with the CT images. First, the FDG uptake of the treated tumor was visually evaluate to see whether it was higher than that of the surrounding normal soft tissue or not. Next, when higher uptake was observed, quantitative evaluation was performed by means of the ROI technique. Two 10×10 mm square ROIs were put into position, one in the area where FDG uptake was highest in the treated tumor, and one in the normal soft tissue (mainly muscle). The tumor to normal soft tissue contrast ratio (TCR) was obtained by means of the next following equation:

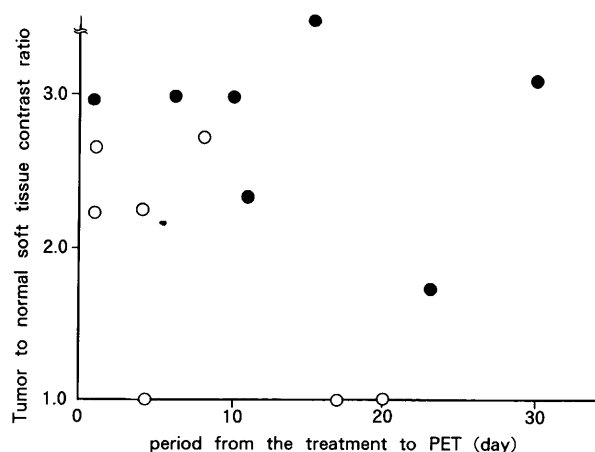


Fig. 1 Plot of all patients. The horizontal axis shows the period (day) from the end of the anticancer therapy to FDG-PET. The vertical axis shows TCR. A treated tumor, viability of which was considered to be lost or very low, was shown as an open circle (○). A treated tumor with evident tumor viability was shown as a closed circle (●).

$$\text{TCR} = \text{tumor activity} / \text{normal soft tissue activity}$$

TCR of tumors, in which FDG uptake was lower than surrounding normal soft tissue, was plotted as TCR = 1.

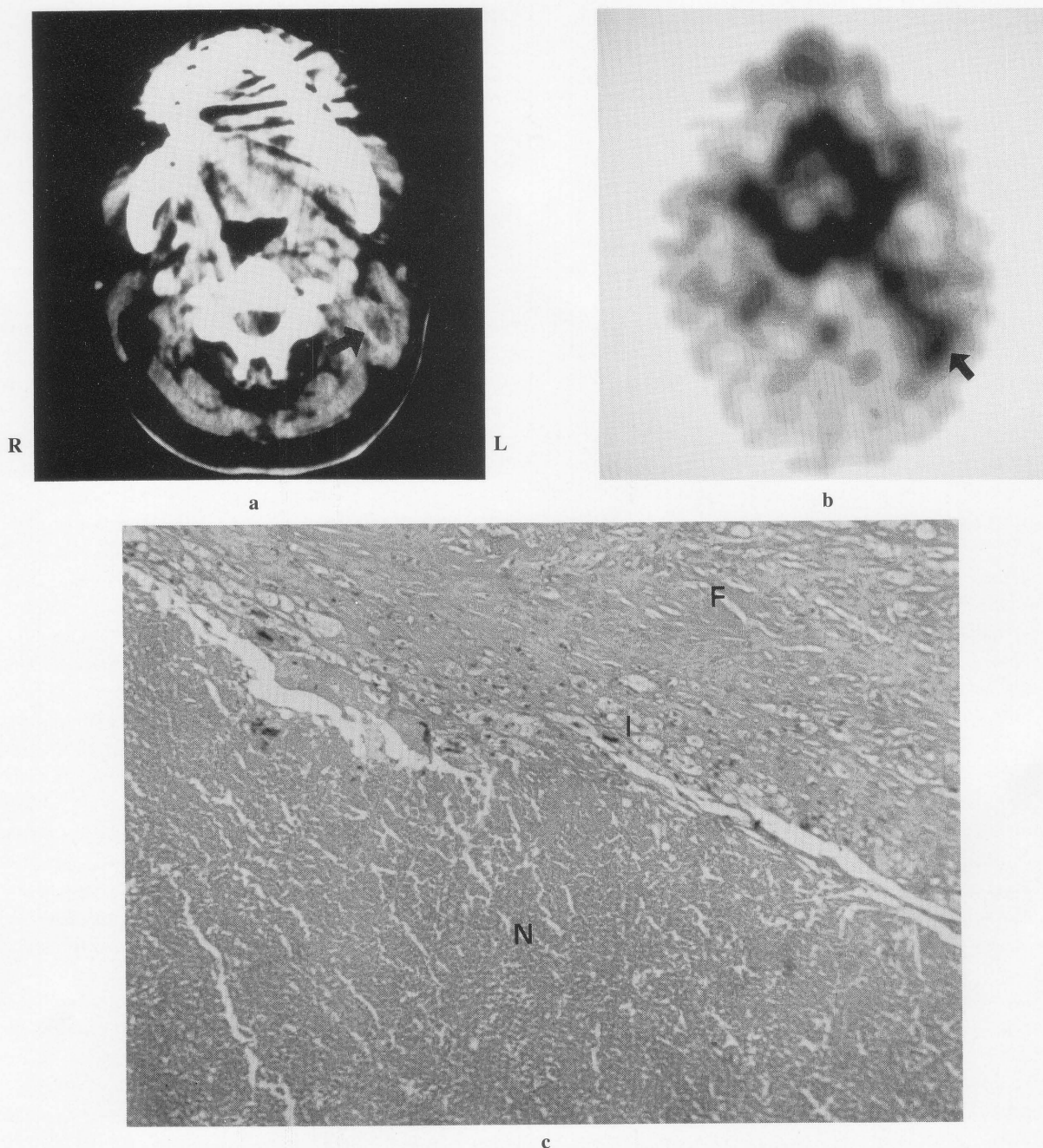


Fig. 2 Case 1. 52 year old female with NHL of left jugular area. At the end of the treatment, mass remained at the original tumor site (Fig. 2a, arrow). FDG-PET performed one day after the end of treatment showed higher FDG uptake, TCR = 2.68 (Fig. 2b, arrow). Pathological study showed that fibrotic change (F) and infiltrate of inflammatory cells (I) was observed surrounding central necrosis (N). Malignant cells were not observed (Fig. 2c).

RESULTS

In two patients (cases 1 and 2), tumor volume was decreased by the treatment, but small masses less 2 cm in diameter remained. The masses were resected after FDG-PET, and they were examined pathologically. There were no live malignant cells in the masses (Table 1). In two patients (cases 6 and 7), the tumor disappeared from X-ray

CT images following the anticancer therapy. No increase in the uptake of FDG was found. They have been followed up for longer than nine months, but no tumor relapse has been observed. Their prognosis shows that tumor viability was lost or was very low at the time of the FDG-PET study. In the other ten patients, the treated tumors did not disappear and observation of the tumors was continued. During the observation period, the volume of the treated

tumor in cases 3 to 5 did not increase, and tumor viability was considered to be not evident or very low. On the other hand, in cases 8 to 14, an increase in tumor volume was observed. Tumor viability was considered to remain at the time of the FDG-PET study.

In three tumors (cases 4, 6, and 7), FDG uptake disappeared following the anticancer therapy. On the other hand, in the other tumors, FDG uptake was higher than in surrounding normal soft tissue. TCRs of all patients are plotted against the period from the end of the treatment to FDG-PET in Figure 1.

In treated tumors with viable malignant tumor cells (closed circles), TCR was higher than 1.76. Treated tumors with low viability (open circle) had a tendency to have lower TCRs than treated tumors with evident tumor viability. However, four treated tumors with no evidence of viable cells (cases 1, 2, 3 and 5) had higher FDG uptake than surrounding normal soft tissue. They were studied by PET from day one to day eight after the end of the treatment.

Case 1 was a 52-year-old female with NHL of the left jugular area. She received one course of chemotherapy with 5 cycles of BACOD-VP16 and 40 Gy radiotherapy. But at the end of the treatment, a mass 1.5 cm in average diameter remained at the original tumor site (Fig. 2a). FDG-PET was performed one day after the end of the treatment. The PET showed high FDG uptake with TCR of 2.68 in the remaining mass (Fig. 2b). After the PET, the remaining mass was totally resected and pathologically examined. The central area of the mass was occupied by necrosis without cell components. Surrounding the necrosis, fibrotic change and infiltration of inflammatory cells was observed. No malignant cells were observed (Fig. 2c).

DISCUSSION

Some kinds of malignant tumors were investigated by FDG-PET before treatment, and high glucose metabolism was observed in most of them.¹⁻³ To monitor tumor treatment response, FDG-PET was also applied. Its usefulness in assessing early treatment effect has been reported.⁴⁻⁶ In this study, we performed FDG-PET from day one to day 30 after the end of the anticancer therapy and evaluated the efficacy of FDG-PET in monitoring tumor viability.

In this paper, TCR was used as an index of the glucose metabolism of the tumor. In a previous study⁸ by us, TCR closely correlated with the influx constant given by the kinetic rates of glucose metabolism, $k_1k_3/(k_2 + k_3)$, which was calculated by the graphic method reported by Patlak and Gjedde et al.^{9,10} The value was closely connected with glucose metabolism.¹¹ Consequently, TCR was considered to correlate with glucose metabolism and it could be obtained without arterial blood sampling.⁸

In this study, masses remained on X-ray CT in the seven

tumors with viable malignant cells at the end of the anticancer therapy. The FDG uptake was increased and TCRs were higher than 1.76.

On the other hand, in the other seven patients, no tumor viability was evident or was very low after the anticancer therapy. Two tumors disappeared from X-ray CT images, and the FDG uptake was not increased. In the other five tumors, the volume was decreased but small masses remained on X-ray CT. The FDG uptake of one residual mass was not increased. The other four residual masses showed increased FDG uptake, $2.25 < \text{TCR} < 2.74$. One of the two masses was histologically examined. Fibrosis and infiltration by inflammatory cells surrounding the central necrosis was observed, but no malignant cells were found.

Colorectal tumors were studied by FDG-PET⁷ after radiotherapy. In the study, FDG uptake did not disappear in most tumors. Although no pathological examinations were performed, the authors speculated that the FDG uptake might be explained by inflammatory reactions caused by radiation injury. Intra-tumoral distribution of FDG in mice was studied by microautoradiography. Macrophages and granulation tissues surrounding the necrotic area of the tumors showed higher uptake of FDG than the viable tumor cells.¹²

In this study, the pathological findings in one patient (case 1) showed that the FDG uptake after the anticancer therapy was caused by the inflammatory and fibrotic changes. In the other three remaining mass, the FDG uptake was also high, but no tumor viability was apparent. The four patients were examined by FDG-PET soon after the end of the treatment (Fig. 1). The treated sites had not yet fully recovered from the acute reaction caused by the treatment in the early period. The FDG uptake was considered to be explained by the reaction caused by the treatment.

Another problem in the evaluation of treated tumors by means of PET was a partial volume artifact caused by the limited spatial resolution of PET. The volume of malignant tumors is decreased by anticancer therapy in most cases. Especially in malignant lymphoma, the decrease is sometime dramatic. When a tumor is examined by PET after the anticancer therapy, the partial volume artifact cannot be ignored. The in-plane-spatial resolution of our PET machine was 1.08 cm (FWHM). The recovery coefficient (RC)¹³ caused by the partial volume artifact was measured by means of a spherical phantom in our PET system. When the diameter of the phantom was 2 cm. The RC was 0.64.¹⁴ This means that the radioactivity of a residual tumor 2 cm in diameter must be corrected by dividing by 0.64. In our study, the average diameter of the six residual tumors was less than 2 cm. If the tumors are spherical, the RCs are less than 0.64. In clinical practice, the shape of the residual tumor is not spherical, and the RC cannot be measured. We cannot correct the partial volume effect exactly, but we must not forget the artifact.

In summary, we studied FDG uptake in fourteen lesions after anticancer therapy. The lesions in which viable tumor cells remained showed higher uptake of FDG than surrounding normal soft tissue. The lesions in which tumor viability was lost or very low showed higher uptake of FDG in four cases, and similar uptake to normal soft tissue in three cases. The high uptake of FDG was considered to be caused by remaining tumor cells and/or the reaction to the anticancer treatment. The aim of this study was to evaluate FDG-PET as a diagnostic tool for monitoring tumor viability after anticancer therapy. The inflammatory effect of radiotherapy may last for the first half year after the end of the therapy.¹⁵ FDG-PET after anticancer treatment should be interpreted by taking into account the reaction due to the treatment. We should also consider the partial volume artifact of PET caused by limited spatial resolution. When the size of the residual mass after the treatment is small, the radioactivity will be underestimated, i.e. less than the true value.

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