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Acute effects of stereotactic radiosurgery on the kinetics of glucose metabolism in metastatic brain tumors: FDG PET study

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Hyperacute changes in the expression of glycolysis-associate gene products as well as FDG uptake in tumor cells after high-dose irradiation reflect response of the cells to noxious intervention and may be a potential indicator of the outcome of treatment. To understand acute effects on the kinetics of glucose metabolism of tumors *in vivo* after high-dose irradiation, we analyzed dynamic FDG PET data in patients with metastatic brain tumors receiving stereotactic radiosurgery. ***Materials and Methods:*** We studied 5 patients with metastatic brain tumors by means of dynamic FDG PET before and 4 hours after stereotactic radiosurgery. Rate constants of glucose metabolism ($K_1^* - k_3^*$) were determined in a total of 13 tumors by a non-linear least squares fitting method for dynamic PET and arterial blood sampling data. Rate constants after radiosurgery were compared with those before radiosurgery. Changes in the rate constants induced by the therapy were also correlated with changes in tumor size evaluated by CT and/or MRI 6 months later. ***Results:*** Four hours after radiosurgery, the phosphorylation rate indicated by k_3^* was significantly higher (0.080 ± 0.058) than that before radiosurgery (0.049 ± 0.023) ($p < 0.05$, paired t test), but there was no significant change in the membrane transport rates indicated by K_1^* and k_2^*. Although increases in the net influx rate constant $K^* (= K_1^* k_3^* / (k_2^* + k_3^*))$ were correlated with increases in k_3^*, K^* after radiosurgery (0.027 ± 0.011) was not significantly different from that before the therapy (0.024 ± 0.012). The reduction in the tumor size was correlated with k_3^* after radiosurgery. ***Conclusion:*** Acceleration of the phosphorylation process was demonstrated *in vivo* in metastatic brain tumors as early as 4 hours after stereotactic radiosurgery, as shown experimentally *in vitro* in a previous report. The phenomenon may be a sensitive indicator of cell damage.

Key words: PET, FDG, tumor, rate constants, radiosurgery

INTRODUCTION

EFFECTS of various treatments on [^{18}F]-2-fluoro-2-deoxyglucose (FDG) uptake by malignant tumors have been investigated.[1–5] Positron emission tomography (PET) and FDG provide information on the therapeutic effects based on the energy metabolism that is the biological basis of viability of the tumor and cannot be assessed by CT or MRI. Many reports showed that a reduction in FDG uptake after therapy was a good indicator of an effective treatment although it is necessary to wait for several weeks after completion of the therapy for a reliable assessment.[1,2] Also reported was an increase in FDG uptake soon after treatment including chemotherapy and radiation therapy.[3–5] The FDG uptake in brain tumors was reported to increase 24 hours after stereotactic radiosurgery and to decrease to below the baseline by 7 days after

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Table 1 Patient characteristics

Patient (Age/Sex)	Diagnosis (primary)	Study No.	tumors irradiated		plasmaglucose level (mg/dl) before RS	after RS
1 (49/F)	lung cancer	1	1		85	97
2 (61/M)	melamona	2	2		100	101
		3	2		124	108
3 (80/F)	lung cancer	4	2		102	139
4 (55/M)	lung cancer	5	2		102	78
		6	2		89	91
5 (83/M)	lung cancer	7	2		99	100
		total	13	mean	100.1	102
				SD	12.5	18.9

RS: radiosurgery

treatment.[3] A similar time course of metabolic changes was reported after chemotherapy.[4] In a case with metastatic lymph nodes of a papillary carcinoma, serial FDG PET scans showed an initial increase in FDG uptake after irradiation with 6 Gy, followed by a slow but constant decline in FDG uptake as the radiation dose was increased.[5] In our previous report,[6] we also showed an increase in FDG uptake as early as 4 hours after stereotactic radiosurgery and suggested a possible role of it in predicting therapeutic effects.

As a possible mechanism of decreased FDG uptake after the effective therapy, damage to glucose transport and/or membrane integrity were suggested. A recent study on cultured tumor cells showed that both glucose transporter-1 mRNA expression and the enzymatic activity of hexokinase was increased 4 hours after a single high-dose irradiation.[7] Therefore, an increase in FDG uptake soon after radiosurgery may be attributable to an increase in both membrane transport of glucose and hexokinase activity. Nevertheless, *in vivo* change in the kinetics of glucose metabolism after radiosurgery had remained largely unknown and studies on acute changes after treatment focused on the rate constants are rare. In this report, to understand the acute effects of treatment on the kinetics of glucose metabolism of the tumor, we analyzed dynamic FDG PET data obtained in patients with metastatic brain tumors, who received stereotactic radiosurgery.

MATERIALS AND METHODS

Patients

We studied 5 patients with metastatic brain tumors (3 males and 2 females, age 65.6 years old ± 15.2, Table 1) by means of FDG PET before and 4 hours after stereotactic radiosurgery. Four patients had a primary lesion in the lung and one patient had one in the skin (melanoma). Two patients had received whole-brain irradiation (one of them also had the tumor resected), one patient had tumor resection only and two other patients never had been treated for brain lesions before the present radiosurgery. Three patients received radiosurgery twice. In accordance with the criteria for radiosurgery in our hospital, none of the patients had active extracranial disease, and all expected to survive for at least 6 months after treatment. None of the patients received chemotherapy during the study.

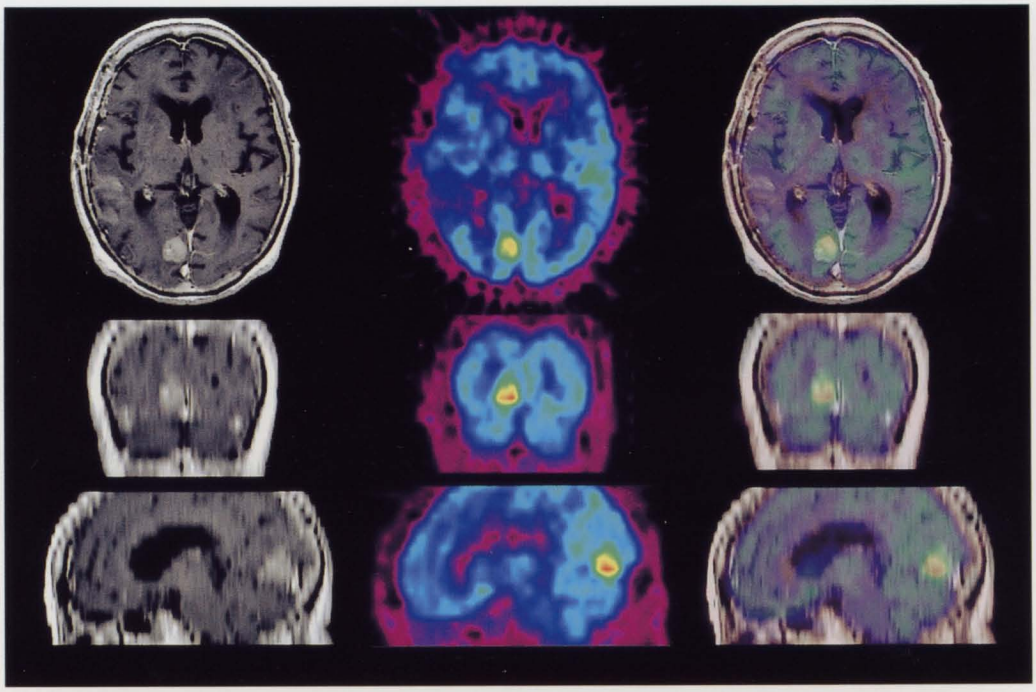
The study was approved by the Ethical Committee of Fukui Medical University, and all patients gave their written informed consent.

Stereotactic Radiosurgery

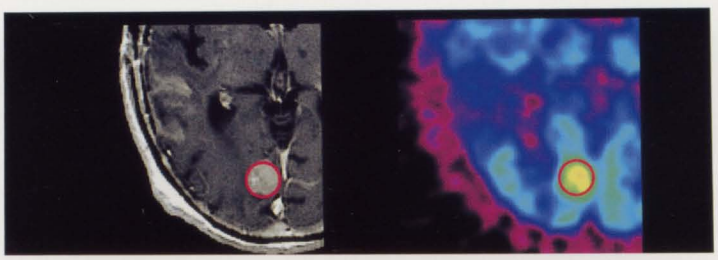
All the patients were treated with 10-MV photons from a linear accelerator by a multiple-arc non-coplanar method in which irradiation accuracy was estimated to be within ± 1 mm.[8,9] The mechanical details of the stereotactic radiosurgery have been described previously.[10] Leksell's stereotactic frame was applied to the patient's head and fixed to the treatment bed under local anesthesia and intravenous analgesics. Axial contrast-enhanced CT was performed to obtain sequential slices that were 1 mm thick at the target point and 5 mm thick through the entire head. Treatment planning software (Marui Medical Inc., Tokyo, Japan) was used to select the center of the tumor and to calculate the number of treatment arcs, start and stop angles for the linear accelerator gantry and couch angles. The 50% isodose line covered the periphery of the tumor, which was delineated by contrast-enhanced CT. All treatment procedures took about 2 hours and another hour was required to treat an additional tumor. We irradiated no more than 3 tumors at a time. Stereotactic radiosurgery with a sharp peripheral dose falloff resulted in minimal exposure of surrounding tissue. The central target point in the tumor received a dose, which ranged from 24 to 32 Gy.

PET Procedure

Patients underwent a set of two dynamic FDG PET scans, one before and the other after stereotactic radiosurgery. The first FDG PET scan was performed within a week before radiosurgery and the second study was done 4



a



b

Fig. 1 (a) FDG PET images (middle) are co-registered on MR images (left). Co-registered FDG PET images overlaid on MR image are shown (right). Metastatic brain tumor is visualized in the right occipital lobe on the both FDG PET and MR image. The tumor is well demarcated on the MR images. (b) A region of interest (ROI) is defined on the MR image (left) and transferred onto the FDG PET image (right).

hours after the therapy. Three patients received radiosurgery twice. Two of them also underwent a set of two FDG PET scans at the time of the second radiosurgery but one did not, so that seven sets of FDG PET data on five patients were available in this study. To reduce statistical errors caused by a small ROI size, we chose 13 solid tumors out of 14 with a diameter of more than 1 cm (1.7 ± 0.4 cm, ranging from 1.0 to 2.4 cm).

FDG was produced by the method of Hamacher et al.[11] with an automated FDG synthesis system (NKK, Tokyo, Japan) and a small cyclotron (OSCAR3; Oxford Instruments, Oxford, UK). A dynamic PET scan was performed with a GE Advance system (General Electric, Milwaukee, WI). The physical characteristics of the scanner have been described in detail elsewhere.[12] This system permits the simultaneous acquisition of 35 transverse slices with interslice spacing of 4.25 mm with septa (two-dimensional mode). Images were reconstructed to a full width at half maximum of 4.2 mm in both transaxial and axial directions. The field of view (FOV) and the pixel size of the reconstructed images were 256 and 2 mm, respectively. Transmission scan was performed for 10 minutes with a standard pin source of $^{68}Ge/^{68}Ga$ for attenuation correction of the emission images. A dose of FDG (244–488 MBq/10 m*l*) was administered through the antecubital vein in 10 seconds. Dynamic scan data were acquired for up to 60 minutes after the injection. The dynamic scan consisted of four 30-second, eight 1-minute and five 10-minute frames. The plasma glucose concentration was measured during the scan. In all patients, arterial blood samples were drawn from a thin catheter placed on the radial artery every 15 seconds in the first 2 minutes and at 3, 5, 7, 10, 15, 20, 30, 45 and 60 minutes after the injection. The plasma radioactivity was measured by a scintillation counter, against which the PET camera was calibrated, with a cylindrical phantom filled with the ^{18}F solution.

Table 2 Net influx rate constant, rate constants and SUV before and after radiosurgery

Study No.	Tumor No.	Before Radiosurgery					After Radiosurgery				
		K* (ml/g/min)	K_1* (ml/g/min)	k_2* (min^{-1})	k_3* (min^{-1})	SUV	K* (ml/g/min)	K_1* (ml/g/min)	k_2* (min^{-1})	k_3* (min^{-1})	SUV
1	1	0.012	0.045	0.052	0.020	3.0	0.013	0.052	0.104	0.034	3.3
2	2	0.043	0.053	0.009	0.039	11.6	0.037	0.064	0.066	0.090	10.5
	3	0.036	0.146	0.228	0.075	8.2	0.033	0.077	0.105	0.077	8.3
3	4	0.029	0.073	0.103	0.067	9.3	0.031	0.071	0.179	0.139	10.0
	5	0.045	0.076	0.064	0.094	7.3	0.040	0.091	0.098	0.077	7.7
4	6	0.033	0.065	0.028	0.029	13.6	0.039	0.073	0.070	0.079	12.0
	7	0.024	0.065	0.084	0.050	5.3	0.016	0.050	0.074	0.034	4.3
5	8	0.020	0.076	0.144	0.052	5.8	0.039	0.117	0.449	0.222	8.7
	9	0.021	0.041	0.078	0.078	7.0	0.036	0.060	0.099	0.146	9.0
6	10	0.018	0.041	0.057	0.043	4.4	0.020	0.040	0.046	0.046	4.6
	11	0.013	0.051	0.075	0.025	4.4	0.016	0.047	0.038	0.019	4.5
7	12	0.012	0.019	0.019	0.034	6.5	0.011	0.028	0.047	0.031	6.2
	13	0.012	0.049	0.095	0.030	6.7	0.017	0.052	0.102	0.051	7.2
	Mean	0.024	0.062	0.080	0.049	7.2	0.027	0.063	0.114	0.080[a]	7.4
	SD	0.012	0.030	0.058	0.023	3.0	0.011	0.023	0.107	0.058	2.7

[a]: significantly different from value before radiosurgery at $p < 0.05$

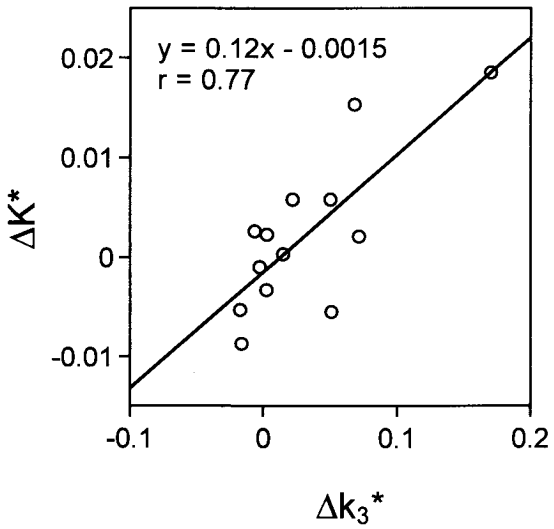


Fig. 2 The plot of ΔK^* against Δk_3^* is shown. There is a significant correlation between ΔK^* and Δk_3^*.

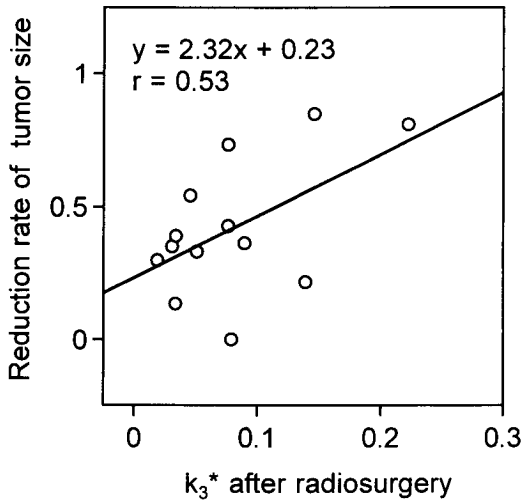


Fig. 3 The reduction of the tumor is correlated only with k_3^* after radiosurgery. Neither ΔK^* nor Δk_3^* are correlated with the reduction of the tumor (not shown).

Data Analysis

FDG PET images before and after radiosurgery were co-registered onto MRI images with a software package (Dr. View; Asahi Kasei Joho system, Tokyo, Japan) by a method described by Kapouleas et al.[13] and Uematsu et al.[14] (Fig. 1a). The final voxel sizes of the MR and FDG PET images were $0.86 \times 0.86 \times 4$ mm and $2 \times 2 \times 4.25$ mm, respectively. Circular regions of interest (ROIs) were placed over the tumor on the MR images and transferred onto the dynamic PET images to obtain time-radioactivity data on the tumor (Fig. 1b). All tumors examined were solid on CT and MR images and no cystic and/or necrotic region was included in the analysis. The size of the ROI drawn over the tumor was larger than 1 cm^3.

Rate constants of the 2-tissue compartment model of glucose metabolism before and after radiosurgery were estimated by a non-linear least squares fitting procedure for the time-radioactivity data of the tumor and plasma. We estimated the rate constants for the transport of FDG from blood to tissue (K_1^*: ml/g/min) and from tissue to blood (k_2^*: 1/min), for the phosphorylation of FDG (k_3: 1/min), and the intravascular plasma volume (V_0: ml/g). We ignored k_4^* because of the known slow dephosphorylation rate in the tumor and the short scan duration employed in this study. The net influx rate constant (K*) was calculated as $K_1^* k_3^* / (k_2^* + k_3^*)$. Standardized uptake

values (SUVs), which were the simplest quantitative parameters, were included in the analysis for comparison.

Rate constants after radiosurgery were compared with those before the therapy to assess if high dose irradiation had some effects on a specific process of glucose metabolism. We also assessed if acute changes in the net influx rate (ΔK^* = second K^* – first K^*) and/or rate constants (Δk_j^* = second k_j^* – first k_j^*; j = 1–3) induced by radiosurgery correlated with the reduction in the tumor size evaluated by CT or MRI 5 to 6 months later. The reduction of the tumor size was expressed as a reduction rate of a volume of the tumor ([pre-treatment volume – post-treatment]/pre-treatment volume).

RESULTS

The results of the net influx rate constant and rate constants were summarized in Table 2. Four hours after radiosurgery, the phosphorylation rate indicated by k_3^* was significantly higher (0.080 ± 0.058) than that before radiosurgery (0.049 ± 0.023) ($p < 0.05$, paired t test), but there was no significant change in the membrane transport rates indicated by K_1^* and k_2^*. Although significant correlation was found between ΔK^* and Δk_3^* ($\Delta K^* = 0.12\Delta k_3^* - 0.0015$, $r = 0.77$, $p < 0.01$, Fig. 2), K^* after radiosurgery (0.027 ± 0.011) was not significantly different from K^* before radiosurgery (0.024 ± 0.012). There was no significant difference between SUVs before and after radiosurgery. The reduction in the tumor 6 months later showed a weak correlation with k_3^* after the therapy (Fig. 3). There were no correlations between the reduction in tumor size and ΔK^*, ΔK_1^*, Δk_2^* or Δk_3^*.

DISCUSSION

In the present study, a significant increase in k_3^*, suggesting acceleration of the phosphorylation process, was noted in metastatic brain tumors as early as 4 hours after stereotactic radiosurgery. Fujibayashi et al.[7] reported a transient increase in the uptake of deoxyglucose (DG) and glycolysis associated gene products in cultured tumor cells immediately after single-dose 30 Gy irradiation. In their report, an increase in the hexokinase activity of the cells was also demonstrated 3 hours after irradiation, which was consistent with our finding an increase in k_3^*. They also demonstrated an increase in the glucose transporter-1 mRNA expression, suggesting an increase in glucose transporters after treatment. In our analysis, however, no significant effect on K_1^* was observed. There might be a chronological gap in an increase in glucose transporters between cultured tumor cells and *in vivo* tumor cells, or glucose transporters might not be induced on the cell surface. The tumors analyzed in this study might lack glucose transporters, as Guerin et al.[15] showed that metastatic brain tumors from the lung in their study were negative for glucose transporters. Damage to the cell membrane might impair the function of glucose transporters, but this is not the case because cell death or giant cell formation[16] as well as abnormalities in the level of membrane degeneration products[17,18] was found more than 1 day after exposure to ionizing radiation. Although a transient increase in glucose uptake was demonstrated in cultured tumor cells[7] and *in vivo* brain tumors[3,6] after a single high dose irradiation, we could not show any increase in K^* after the treatment, but we noted a significant correlation between Δk_3^* and ΔK^*, suggesting that an increase in k_3^* should be associated with an increase in K^*. Because of the small number of subjects, the effect on K^* might not reach statistical significance. We could not find a significant change in SUV after radiosurgery. Although SUV was the simplest semi-quantitative indicator of glucose uptake and metabolism, it was not a good indicator of such a subtle change in the kinetics of glucose metabolism after radiosurgery.

It is also known that changes in the physiological environment caused by sedation and the plasma glucose level also affect the kinetics of glucose metabolism. Therefore, in previous reports, FDG uptake in tumors was normalized by FDG uptake in the white matter[3] or cerebellum,[6] and the ratio of FDG uptake was used in the analysis. But in this study, we did not normalize the net influx rate constant or the other rate constants of the tumor by those of normal cerebral structures. It was reported that the effects of sedation and the plasma glucose level on FDG uptake and kinetic constants were different in tumors and the normal brain, and FDG uptake was less affected in tumors than in normal cerebral tissues.[19,20] The second FDG PET in this study was always performed under intravenous analgesics that may suppress glucose metabolism more in the normal brain than in tumors. The net influx rate constant and rate constants would be also affected. If ratio of the rate constants in the tumor to that in normal brain was utilized in the analysis, errors may become large. Although the plasma glucose level was not always in a normoglycemic range, there was no significant difference between the average plasma glucose levels before and after treatment. We therefore assumed that the effects of plasma glucose level were almost canceled out and effects of sedation were smaller without normalization. In the second FDG PET under analgesics, the net influx rate constant and rate constants without normalization are probably smaller than those with normalization. This may be the reason why we could not find an increase in K^* or K_1^* after the therapy because K^* and K_1^* as well as k_3^* might be underestimated in our analysis. Therefore, among these kinetic constants, k_3^* which showed a significant increase after the therapy may be the most sensitive marker of the initial cell response to the therapy.

Prognostic significance of acute changes in FDG uptake in the tumor after the therapy was suggested previously.[6,21] In the analysis of serial FDG PET scans before and 24 hours to 30 days after complex multi-drug chemo-

therapy, Rozental et al.,[21] examining the ratio of FDG uptake of the tumor to the contralateral white matter, showed that patient survival was inversely related to the magnitude of the increase in the ratio at 24 hours after the therapy. They speculated that accelerated glucose metabolism might represent a repair response by the tumor to the therapy. Maruyama et al.,[6] analyzing FDG PET 4 hours after radiosurgery and CT and/or MRI 5 to 6 months later, demonstrated that the magnitude of increase in the K_i ratio (ratio of the net influx rate constant in the tumor to that in the contralateral cerebellum) correlated with the reduction in tumor size, and the tumor without an increase in the K_i ratio was not reduced in size. They speculated that the tumor cells required more glycolytic metabolism for energy-consuming processes such as DNA repair and apoptosis. DNA damage leads to programed cell death and to G_1 arrest to inhibit the replication of damaged DNA. In this preliminary study of a limited number of patients, we could not find any relationship between changes in rate constants and therapeutic effects, but an increase in k_3*, as suggested previously,[6,7] seemed to represent an accelerated phosphorylation process in glucose metabolism that was needed for a repair process. The reduction in tumor size had a tendency to correlate with k_3* after the therapy. Although malignant potentials may be indicated by increased k_3* before the therapy,[22] effects of the therapy may be predicted by an increase in k_3* after the therapy. We speculate that k_3* is a potential and sensitive marker of cellular damage, although it was not determined whether the damage was fatal or not in this study. Further study of a large number of patients is needed to clarify the implications of the acute increase in k_3* after the therapy.

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