Carbon-11-Methionine PET Imaging of Choroidal Melanoma and the Time Course after Carbon Ion Beam Radiotherapy*

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Abstract. *The aim of this study was to assess the feasibility of MET-PET as an evaluation method of the therapeutic effect of carbon ion beam radiotherapy. Patients and Methods: Twenty-four choroidal melanoma patients who were treated with a carbon ion beam underwent at least three MET-PET scans before and after therapy. The uptake was visually and semiquantitatively evaluated on the basis of the tumor-to-brain ratio (TBR). Results: The accumulation was significantly decreased at 6 months or more after therapy and disappeared in 50% of the patients at 12 months after therapy. The baseline TBR, 1, 6, 12 and 24 months after therapy averaged 1.88±0.65, 1.73±0.52, 1.08±0.42, 0.67±0.27 and 0.65±0.30, respectively. TBR was significantly decreased at 6 months or more after therapy. Conclusion: MET-PET may be an alternative method for evaluating the effect of radiotherapy.*

Choroidal melanoma is the second most common intraocular malignant tumor after metastasis. The incidence of choroidal melanoma in Japan is far less than in United States and Europe, and is approximately 0.0025 in 100000 (1). Various forms of radiation therapy have been used for the treatment of choroidal melanoma as eye preservation modalities (2-6). The optimum form of radiation therapy has not been discovered yet. At the Research Center Hospital, Japan, treatment for choroidal melanoma with carbon ion beam from the Heavy Ion Medical Accelerator in Chiba (HIMAC) has been offered since 2001. HIMAC is the first heavy ion accelerator complex in the world established for use in a hospital environment (7).

In general, choroidal melanomas shrink very slowly after radiotherapy but do not disappear completely. Moreover, histological evaluation after therapy cannot be made unless enucleation is performed. These two problems are different from most malignant tumors. Gragoudas *et al*. reported that 8 of 70 (11%) tumors that showed no evidence of growth after irradiation presented some mitotic figures (8). From this point of view, another evaluation method in addition to the measurement of tumor size is desirable.

Positron emission tomography (PET) has made non-invasive tumor imaging possible based on tumor metabolism. PET has been reported to be useful for making a distinction between malignant and benign tumors, for the detection of metastases, and for the staging and monitoring of therapeutic effects (9-13). Most clinical PET studies have been conducted with fluorine-18-fluorodeoxyglucose (FDG) PET. FDG is a tracer for determining glucose metabolism. L-[methyl-11-C] methionine (MET) is another tracer for PET that can be used to assess the metabolism of amino acids. Methionine is needed for protein synthesis, and in cancer cells the rate of protein synthesis and transmethylation is high (14, 15). Further, an imbalance of DNA methylation has been reported in melanoma cells that need large amounts of methionine for cell growth (16-18). L-[methyl-11-C] methionine PET (MET-PET) has been reported to be useful in various tumors including melanoma (19-22). Moreover, methionine uptake has been reported to decrease rapidly after radiation therapy as found in an experimental tumor model (23, 24).

To the authors knowledge, there have been no PET studies on choroidal melanoma. The purpose of this study is to assess the ability of MET-PET to detect choroidal melanoma lesions and the feasibility of MET-PET as an evaluation method for the therapeutic effect in carbon ion beam radiotherapy (CIRT).

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Patients and Methods

Patients. Twenty-four consecutive patients with choroidal melanoma who had been referred to the Research Center Hospital, Japan, for CIRT and undergone MET-PET both before and after therapy in 2001-2003 were prospectively studied. None of the patients had undergone any therapy before CIRT. Diagnosis of choroidal melanoma was confirmed using clinical, fundus photography, fluoroscein angiography and ultrasonography.

Carbon ion beam radiotherapy (CIRT). All patients were treated with a carbon ion beam from the Heavy Ion Medical Accelerator in Chiba (HIMAC) at the hospital. The HIMAC system and the biophysical characteristics of the carbon ion beam have been described previously (7). The total dose ranged from 70 to 85 GyE in five fractions (the fraction size ranged from 14 to 17 GyE). The total dose was 70 GyE in 11 patients, 77GyE in 8 patients and 85GyE in 5 patients. Local control was defined as any degree of decrease of tumor size or no evidence of re-growth compared with previous examination.

MET-PET and MRI examination. All patients underwent at least three MET-PET scans: before therapy, at one month after therapy (averaged 31.2 days) and at about 6 months (averaged 6.6 months) after therapy. Furthermore, some patients underwent repeated follow-up MET-PET scans. Sixteen patients underwent a fourth MET-PET at about 12 months (averaged 12.8 months) after therapy and 7 patients underwent a fifth (one patient, forth) MET-PET at about 24 months (averaged 22.9 months) after therapy. MRI was performed one week after each MET-PET scan. Written informed consent was obtained from all patients, and the research protocol was approved by the institution's Ethical Board.

PET imaging was performed with an ECAT 47 or ECAT HR+ scanner (Siemens CTI, Knoxville, TN, USA). The ECAT 47 and ECAT HR+ allow simultaneous collection of 47/63 transverse slices over a span of 16.2-15.5 cm with a slice thickness of 3.4-2.5 mm and a transaxial resolution of 6.3-4.8 mm at 10 cm offset from the center of the field of view using a Nyquist frequency Ramp filter. All data were reconstructed in a 128×128 image matrix. The final in-plane resolution in reconstructed and Ramp-filtered (cut-off frequency: 0.4 cycle/pixel) images of the ECAT 47 and the ECAT HR+ in FWHM were 10.5 mm and 7.5 mm, respectively.

Patients were fasted for at least 6 hours before PET scans. A transmission scan for attenuation correction was acquired for 10 minutes for the ECAT 47 and 20 minutes for the ECAT HR+ to the primary tumor region. Twenty three minutes after intravenous administration of approximately 740 MBq ^{11}C-MET, a static emission scan was acquired for 15 minutes for the ECAT 47 and 30 minutes for the ECAT HR+.

Evaluation and quantification. First, the uptake was visually evaluated. The degree of MET uptake was categorized into four grades according to the following scale: Grade 0: no visible uptake; Grade 1: uptake in tumor lower than in the cerebellar cortex or occipital cortex on the same slice; Grade 2: the uptake in tumor is similar to cerebellum cortex or occipital cortex on the same slice; Grade 3: uptake in tumor higher than in the cerebellar cortex or occipital cortex on the same slice (Figure 1). Second, the uptake was semiquantitatively evaluated on the basis of the Tumor-To-Brain Ratio (TBR) obtained as follows. The regions of interest (ROIs) were placed in the choroidal melanoma lesion, including the highest uptake area (circle ROI, about 1cm in diameter) and the largest possible bilateral cerebellar or occipital areas on the same slice. TBR was calculated by dividing the mean radioactivity of the tumor ROI by that of the bilateral brain ROIs. Residual uptake ratio (RUR) was defined as the ratio of the TBR divided by the TBR before therapy. Reference to MRI, CT and transmission scanning images was made to confirm precisely the location of the choroidal lesion. The static images were displayed as transaxial slices, and coronal and sagital slices were added as necessary.

To establish the size of the tumor, the maximum size which could be the diameter or thickness of the tumor, as the case might be, was measured using an MRI T2 weighted image acquired one week within each MET-PET scan. Residual tumor ratio (RTR) was defined as the ratio of the maximum tumor size divided by the tumor size before therapy.

Statistical analysis. A p-value <0.05 indicated a statistically significant difference when comparing the two groups. The data in this paper was presented as value±SD.

Table I. *Patient characteristics*.

Pt. no.	Age/ Gender	CIRT dose (GyE)	Maximum size (mm)	Follow-up time (mo)
1	69/M	70	12	34
2	45/M	70	13	22
3	53/F	77	13	12
4	39/M	70	18	24
5	38/M	85	14	7
6	60/M	70	12	24
7	62/F	85	13	9
8	54/F	85	15	8
9	25/F	70	12	18
10	66/M	77	15	14
11	82/F	70	12	19
12	64/M	77	15	16
13	67/M	77	14	12
14	63/F	70	13	30
15	51/F	85	9	9
16	38/M	70	13	25
17	33/F	70	13	30
18	44/M	85	18	7
19	46/M	77	16	13
20	68/M	77	8	14
21	56/M	77	14	10
22	36/F	70	14	36*
23	78/M	77	15	12
24	70/M	70	11	16
mean±SD	55.5±15	75.5±5.9	13.4±2.3	17.3±8.2

*Died of metastatic disease. Mo, month.

Results

Patient characteristics. Of the 24 patients, 15 were male and 9 female. The average patient age was 55.5±15 years (range 25-82 years). The average maximum tumor size measured

Table II. *Time course of visual grade, TBR, and tumor size before and after CIRT.*

	Visual Grade					TBR					Tumor size				
Pt. no	Before CIRT	1mo after CIRT	6mo after CIRT	12mo after CIRT	24mo after CIRT	Before CIRT	1mo after CIRT	6mo after CIRT	12mo after CIRT	24mo after CIRT	Before CIRT	1mo after CIRT	6mo after CIRT	12mo after CIRT	24mo after CIRT
1	3	1	1	1	1	2.27	1.37	0.94	0.56	0.51	12	10	10	9	7
2	2	3	1	1	0	1.18	1.47	0.87	0.50	0.45	13	13	12	12	9
3	3	3	3	2	-	2.92	2.44	2.02	1.12	-	13	13	10	9	-
4	3	3	1	0	0	2.59	1.47	0.68	0.74	0.42	18	18	17	18	19
5	1	2	1	-	-	1.19	1.37	0.96	-	-	14	13	12	-	-
6	2	1	1	1	-	1.13	1.01	0.91	0.70	-	12	13	8	9	-
7	3	3	0	-	-	3.17	2.54	1.04	-	-	13	15	15	-	-
8	3	3	2	-	-	2.06	1.72	1.31	-	-	15	13	9	-	-
9	3	3	2	1	-	1.32	1.65	1.08	0.91	-	12	12	12	9	-
10	3	2	1	0	-	1.52	2.01	1.44	0.58	-	15	15	14	15	-
11	3	2	0	0	-	1.69	1.70	0.15	0.22	-	12	12	12	12	-
12	3	3	3	0	-	2.06	1.50	1.29	0.39	-	15	15	13	12	-
13	2	3	3	-	-	2.35	2.38	1.80	-	-	14	13	11	-	-
14	3	3	1	0	0	1.31	1.64	0.61	0.35	0.29	13	12	12	12	12
15	1	0	0	-	-	0.63	0.33	0.44	-	-	9	9	9	-	-
16	3	3	2	1	1	1.78	2.01	1.26	1.23	0.84	13	13	13	12	13
17	3	3	1	-	1	2.14	2.23	1.17	-	0.99	13	13	13	-	14
18	3	3	2	-	-	2.16	2.11	1.46	-	-	18	19	17	-	-
19	3	3	1	0	-	2.74	2.31	1.04	0.52	-	16	15	13	14	-
20	1	1	0	0	-	1.03	1.02	0.63	0.57	-	8	8	8	8	-
21	2	3	1	1	-	1.31	1.65	0.94	0.78	-	14	14	13	12	-
22	3	3	2	2	2	2.33	1.76	1.63	0.82	1.05	14	14	12	8	*
23	3	2	2	-	-	2.01	1.59	1.13	-	-	15	15	15	-	-
24	3	3	1	0	-	2.13	2.14	1.03	0.73	-	11	11	11	9	-
mean±SD	2.6± 0.2	2.5± 0.2	1.3± 0.9	0.6± 0.7	0.7± 0.8	1.88± 0.65	1.73± 0.52	1.08± 0.42	0.67± 0.27	0.65± 0.30	13.4± 2.3	13.3± 2.5	12.1± 2.4	11.3± 2.8	12.3± 4.2

CIRT: Carbon ion beam radiotherapy; mo: month; TBR: Tumor-to-brain ratio.

by MRI was13.4±2.3 mm (range 8-18 mm). The mean follow-up time was 17.3±8.2 months (range 7-36 months). None was lost to follow-up. There were no evidences of tumor re-growth or local recurrence on the MRI to date. One patient (Case 22) died of metastatic disease about 36 months after therapy. One eye in another case needed to be enucleated due to complication. The patient characteristics are summarized in Table I.

Time course of visual grade. Table II and Figure 2A summarize the time course of visual grade and the mean grade in all follow-up periods for all patients, respectively. All choroidal lesions were detected (100%, visual grade≥1) on MET-PET before CIRT. The visual grade was Grade 3 in 17 (70.8%) patients, Grade 2 in 4 (16.7%) patients and Grade 1 in 3 (12.5%) patients. No patient had Grade 0. The mean visual grade before therapy was 2.6±0.2. At one month after therapy, visual grade changed from high to low as compared with that before therapy. The visual grade at one month after therapy was not significantly different from that before therapy (p=0.42). At 6 months and 12 months after therapy, visual grade became low compared with the previous MET-PET in general. The visual grade became Grade 0 in four out of 24 patients (16.7%) at 6 months after therapy and in eight out of 16 patients (50%) at 12 months after therapy. The visual grade at 6 and 12 months after therapy was significantly lower compared with that before therapy (both p<0.0001). At 24 months after therapy the visual grade had almost no change compared with that 12 months after therapy (p=0.36) and the visual grade became Grade 0 or Grade 1 in 85.7% of patients. Only one case (Case 22) showed Grade 2 uptake even at 24 months after therapy.

Time course of TBR. Table II summarizes the time course of TBR for all patients. Figure 2B demonstrates the time course of mean TBR at each follow-up period. TBR before CIRT averaged 1.88±0.65 (range 0.63-3.17, n=24). There was no correlation between TBR and maximum tumor size (R^2=0.25, figures not shown). At one month after therapy,

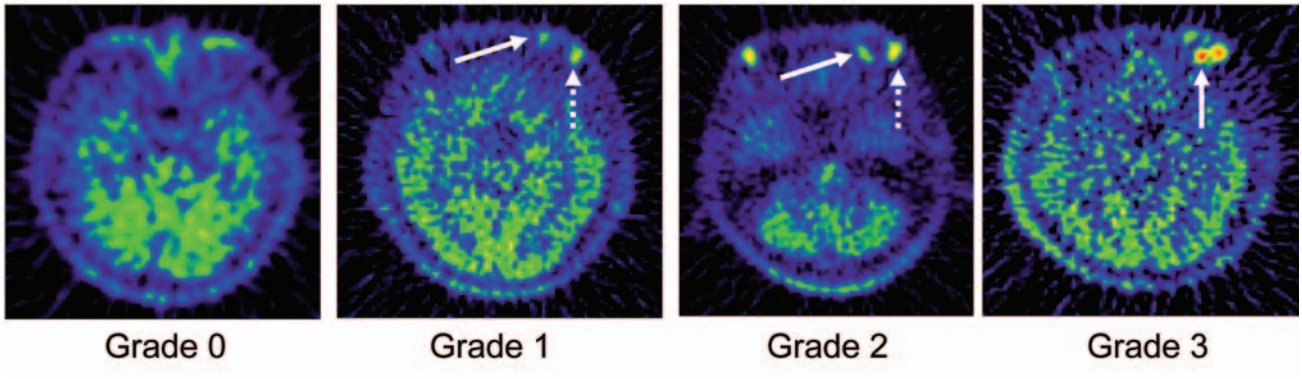

Figure 1. *Definition of four visual grades. Grade 0: no visible uptake; Grade 1: uptake in tumor lower than in the cerebellar or occipital cortex; Grade 2: similar to that in the cortex; Grade 3: higher than in the cortex. Arrow: melanoma lesion; dotted arrow: physiological uptake in the lachrymal gland.*

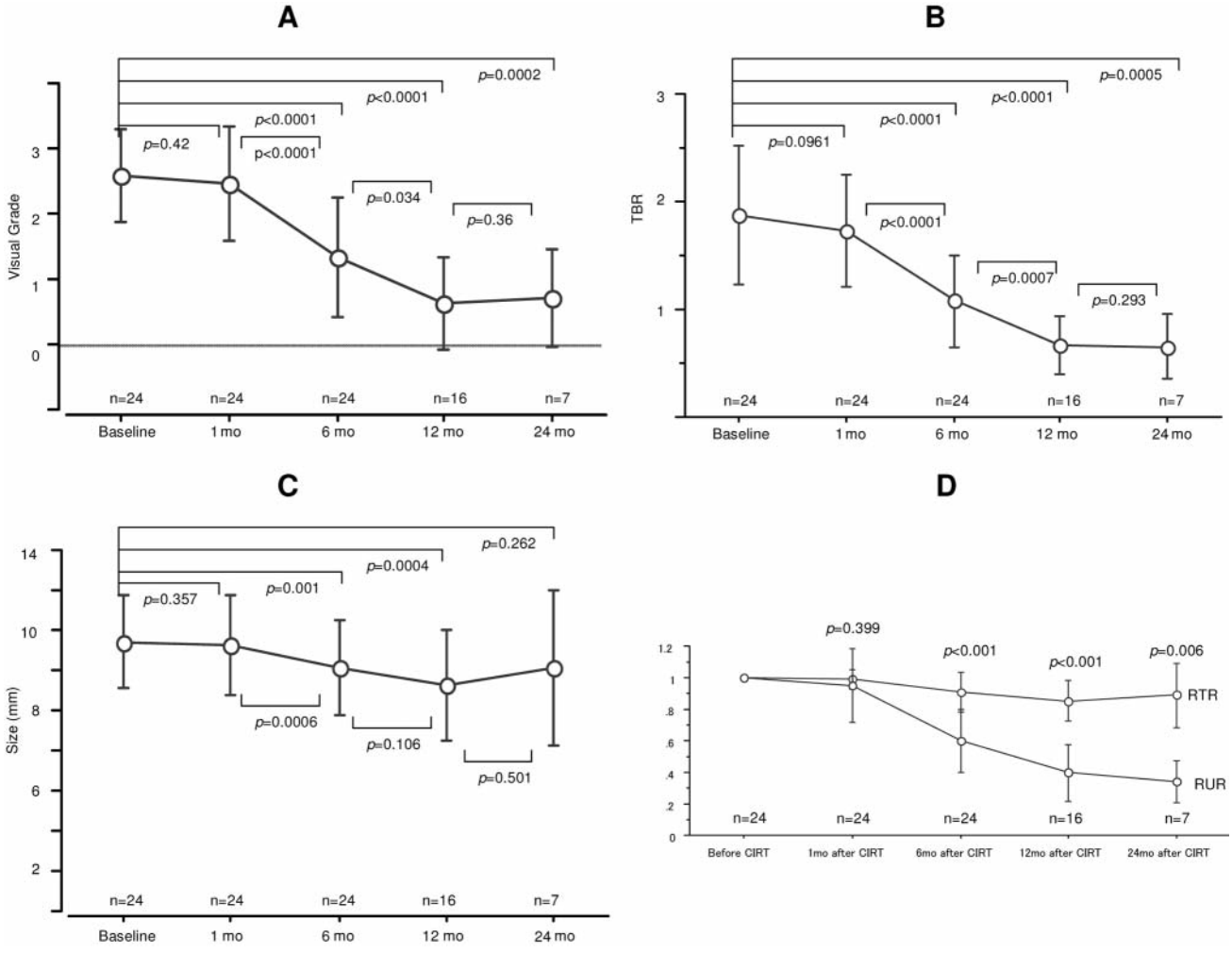

Figure 2. *(A) Time course of visual grade, (B) Time course of TBR, (C) Time course of tumor size, (D) Time course of RUR and RTR before and after CIRT. Error bars denote 1 standard deviation. mo, month. TBR, Tumor-to-Brain Ratio. RUR, Residual Uptake Ratio. RTR, Residual Tumor Ratio.*

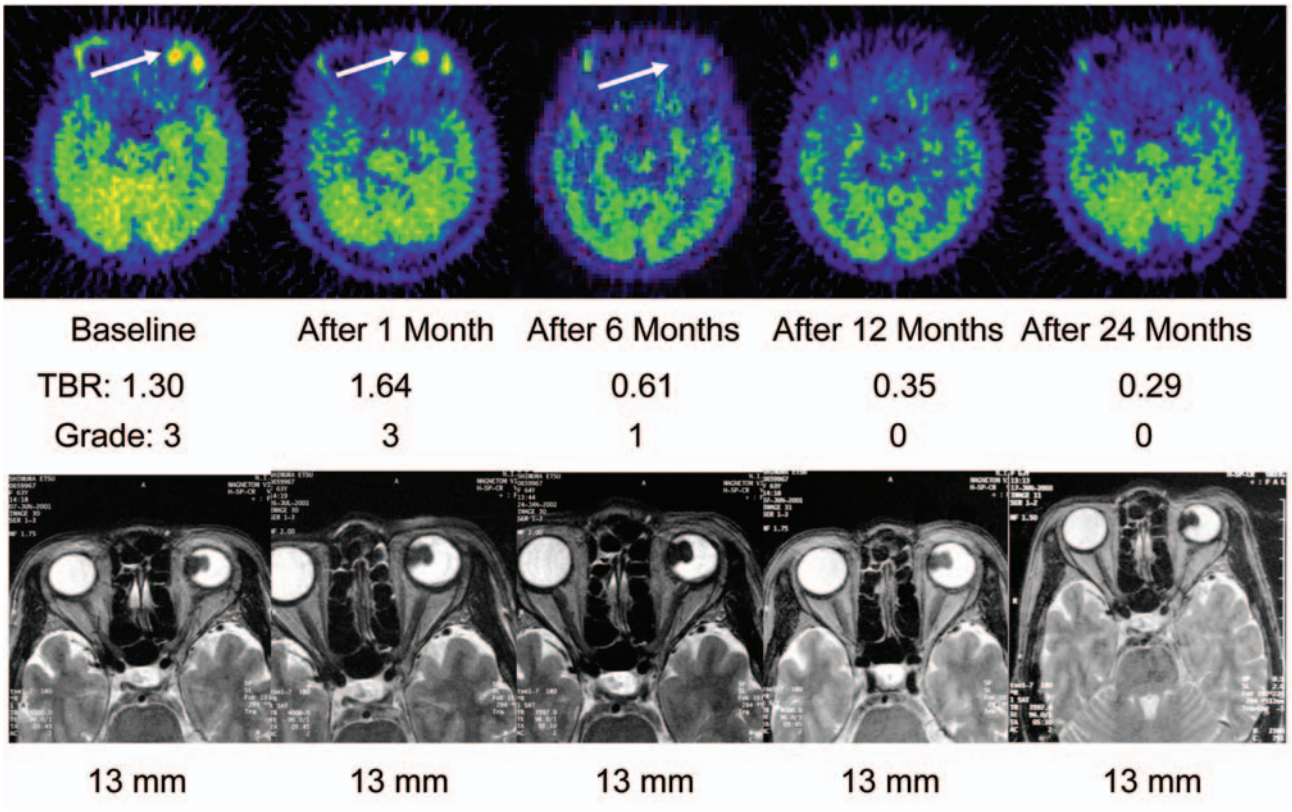

Figure 3. *MET-PET and MRI T2 weighted image of Case 14. Tumor size was almost unchanged throughout the follow-up term, but MET uptake disappeared after 12 months. This patient has shown no regrowth so far. Arrow: melanoma lesion.*

TBR averaged 1.73±0.52 (range 0.33-2.54, n=24). TBRs at one month after therapy varied from increased to decreased as compared with the TBRs before therapy. TBR at one month after therapy was not significantly different from that before therapy (p=0.0961).

TBR at 6 months after therapy averaged 1.08±0.42 (range 0.15-2.02, n=24). In 23 patients (95.8%), MET uptake was decreased compared with that before therapy. Only in one patient (Case 15), there was a slight increase from 0.33 to 0.44. But the visual grade in Case 15 was Grade 0 at both one month and six months after therapy. The reason for this slight increase of TBR is considered to be within the error range and due to placing the ROI to an invisible uptake in the primary lesion. TBR was significantly decreased compared with that before therapy (p<0.0001).

Sixteen patients were followed up for more than 12 months. TBR at 12 months after therapy averaged 0.67±0.27 (range 0.22-1.23, n=16). In 14 patients out of 16 (87.5%), there was an additional decrease of TBR compared with that at 6 months after therapy. Although TBR was slightly increased compared with that at 6 months after therapy in two patients out of 16 (Case 4: from 0.68 to 0.74, Case 11: from 0.15 to 0.22), the visual grade of these two cases was Grade 0 (no visible uptake) and both TBRs were very low. The reason for this slight increase of TBR is thus again attributed to the error range. TBR at 12 months after therapy was significantly decreased compared with that before therapy and at 6 months after therapy (p<0.0001, p=0.0007, respectively).

Seven patients were followed up for more than 24 months. The TBR at 24 months after therapy averaged 0.65±0.30 (range 0.29-1.05, n=7). In 6 patients (85.7%), TBR was further decreased than that of the previous MET-PET. In one patient (Case 22), TBR was increased compared with that at 12 months after therapy but it was not possible to measure the tumor size on the MRI image at 24 months after therapy because of severe retinal detachment. The tumor size measured by echograhy was not known because the patient did not undergo echography. TBR at 24 months after therapy was not significantly different from that at 12 months after therapy (p=0.293).

In general, TBR decreased markedly at 6 months and 12 months after therapy, and the downward trend became slight at 12 months and later (Figure 2B).

Table III. *Time course of RUR and RTR before and after CIRT.*

Pt. no.	RUR					RTR				
	Before CIRT	1mo after CIRT	6mo after CIRT	12mo after CIRT	24mo after CIRT	Before CIRT	1mo after CIRT	6mo after CIRT	12mo after CIRT	24mo after CIRT
1	100%	60.4%	41.4%	24.7%	22.5%	100%	83.3%	83.3%	83.3%	58.3%
2	100%	125%	73.7%	42.4%	38.1%	100%	100%	100%	100%	69.2%
3	100%	83.6%	69.2%	38.4%	-	100%	100%	76.9%	76.9%	-
4	100%	56.8%	26.3%	28.6%	16.2%	100%	100%	100%	100%	100%
5	100%	115%	80.7%	-	-	100%	100%	85.7%	-	-
6	100%	89.4%	80.5%	61.9%	-	100%	100%	66.7%	66.7%	-
7	100%	80.1%	32.8%	-	-	100%	115%	115%	-	-
8	100%	83.5%	63.6%	-	-	100%	86.7%	60.0%	-	-
9	100%	125%	81.8%	68.9%	-	100%	100%	100%	75.0%	-
10	100%	132%	94.7%	38.2%	-	100%	100%	100%	100%	-
11	100%	101%	8.9%	13.0%	-	100%	100%	100%	100%	-
12	100%	72.8%	62.6%	18.9%	-	100%	100%	86.7%	86.7%	-
13	100%	101%	76.6%	-	-	100%	92.9%	78.6%	-	-
14	100%	125%	46.6%	26.7%	22.1%	100%	92.3%	92.3%	92.3%	92.3%
15	100%	52.4%	69.8%	-	-	100%	100%	100%	-	-
16	100%	113%	70.8%	69.1%	47.2%	100%	100%	100%	100%	100%
17	100%	104%	54.7%	-	46.2%	100%	100%	100%	-	108%
18	100%	97.7%	67.6%	-	-	100%	100%	100%	-	-
19	100%	84.3%	38.0%	19.0%	-	100%	100%	81.3%	81.3%	-
20	100%	99.0%	61.2%	55.3%	-	100%	100%	100%	100%	-
21	100%	126%	71.8%	59.5%	-	100%	100%	100%	85.7%	-
22	100%	75.5%	70.0%	35.2%	45.1%	100%	100%	85.7%	57.1%	*
23	100%	79.1%	56.2%	-	-	100%	100%	100%	-	-
24	100%	100%	48.4%	34.3%	-	100%	100%	100%	81.8%	-
mean±SD		95.0% ±23%	60.3% ±20%	39.6% ±18%	33.9% ±13%		98.8% ±6%	90.8% ±12%	85.2% ±13%	
89.0% ±20%										

RUR: Residual uptake ratio; RTR: residual tumor ratio; CIRT: carbon ion beam radiotherapy; mo: month.

Time course of tumor size. Table II summarizes the time course of tumor size for all patients. Figure 2C demonstrates the time course of the mean tumor size at each follow-up period. At one month after therapy, the tumor size was almost the same as that before therapy and did not significantly differ from that before therapy (p=0.357). At 6 months and 12 months, tumor size was slightly decreased. Tumor size at 6 months after therapy was significantly decreased compared with that before therapy (p=0.001). Mean tumor size at 24 months after therapy was slightly increased. The reason for this increase is attributed to the difference in patient numbers.

Comparison between RUR and RTR. Table III summarizes the time course of RUR and RTR for all patients. Figure 2D compares the time courses of RUR and RTR. RUR was smaller than RTR at all follow-up periods. RUR was significantly smaller than RTR at 6 months after therapy (p<0.001), 12 months after therapy (p<0.001) and 24 months after therapy (p=0.006). It is particularly worth noting that the mean RTR at 24 months after therapy was only 89.0% and that the tumor size changed very little in 4/7 patients who were followed up for more than about 24 months (Figure 3).

Discussion

In this series of patients, MET accumulated in all choroidal melanoma lesions before therapy. The uptake was more intense than in the cerebellar cortex or occipital cortex in 87.5% of patients. From this it can therefore be concluded that MET-PET is effective in detecting choroidal melanoma. Garreston BR *et al*. reported an average reduction in tumor thickness of 44% after a mean follow-up period of 45 months in patients with choroidal melanomas treated with 125I brachytherapy (25). In the present series of patients, most of the tumor sizes measured by MRI were slowly decreased or did not change. In as many as 4/7 patients who were followed up for more than 24 months, no changes in tumor size were detected throughout the follow-up term. Hence, evaluation methods other than tumor size measurement are desirable.

In an experimental tumor model, MET uptake showed a rapid decrease after irradiation and was followed by necrosis

and progressive tumor shrinkage (26). Kubota *et al*. investigated the feasibility of the use of tracers for monitoring tumors after radiotherapy using five tracers and reported that MET was decreased more rapidly than FDG (24). Paula *et al*. studied the evaluation of response to radiotherapy in head and neck cancer using MET-PET, and reported that tumors with a ratio of the post irradiation tumor standard uptake value (SUV) to pre-irradiation tumor SUV smaller than 0.5 had a complete histological response more often than those with a ratio larger than 0.5 (27). In their report, MET-PET scans after radiotherapy were performed at 21 days on average after therapy. Huvinen *et al*. also studied the use of MET-PET for the evaluation of response to radiotherapy, hormonal therapy, or chemotherapy response in breast cancer metastasis and reported that MET uptake into the metastases decreased when the clinical target stability or regression of metastasis was later achieved, and increased in cases where progressive disease was seen during treatment (28). MET-PET scans after therapy were performed at 7 weeks on average after therapy.

In the presented study, MET-PET was found to reflect the therapeutic response more sharply than MRI because RUR was smaller than RTR in all follow-up periods. In the evaluation of response after radiotherapy, MET-PET scans performed at one month after therapy were considered of limited use in evaluating therapeutic response, because MET uptake in both the semi-quantitative and visual analyses changed from a decrease to an increase as compared with that before therapy despite good local control in the follow-up period. This finding is different from the study reported by Paula *et al*. (27) who reported that SUVs were decreased after therapy in 23 of 24 lesions. However, Maria *et al*. investigated the histopathologic findings of enucleated eyes after proton beam radiotherapy and enucleated eyes at primary treatment and reported that inflammatory cell infiltration of the tumor was more common in irradiated eyes (29). MET accumulates in active inflammation (30) and therefore it is concluded that MET accumulation in the melanoma lesions is largely affected by the inflammatory reaction at one month after CIRT. With regards to the early evaluation of radiation therapy using MET-PET, both the decrease of accumulation due to a decline in metabolism and the increase of accumulation associated with inflammation should be taken into consideration. On the other hand, MET-PET scans performed at 6 months and 12 months after therapy showed a remarkable reduction of uptake in general. It was reported that inflammatory infiltration was more common early after irradiation than in the later intervals whereas fibrotic change was a later finding (6). It can therefore be assumed that the influence of inflammation will subside at 6 months and later. In the three cases that showed a slight increase in TBR at 6 months or 12 months compared with the previous TBR, the visual grade was Grade 0 and TBR was low. This slight increase in TBR is considered to be within the error range. Therefore, visual analysis is considered essential, in addition to semi-quantitative analysis. Evangelos *et al*. evaluated the histopathologic changes in uveal melanoma enucleated at various intervals after proton irradiation or at autopsy (6), and reported that 8 of 70 tumors that showed no evidence of growth after proton beam irradiation had some mitotic figures. However, mitotic figures became progressively less common as the interval between irradiation and enucleation increased. Therefore, the fact that TBRs had continued to decrease in the follow-up term in controlled cases is considered to be consistent with the pathological findings and local tumor response. TBRs at 24 months after therapy were also decreased but the degree of decrease was generally slight in all but one case. In one case, TBR at 24 months after therapy was increased. But there was no evidence of recurrence because tumor size unfortunately could not be measured on the MRI due to severe retinal detachment. This patient died of metastatic disease.

Longer follow-up periods and additional patients will be required to improve evaluation accuracy and ultimate tumor control.

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