主 論 文

Title:

Pattern of response to interstitial hyperthermia and brachytherapy for malignant intracranial tumor: A CT analysis

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Short running title

Pattern of response to interstitial hyperthermia and brachytherapy

Abstruct

Interstitial microwave hyperthermia in combination with iridium-192 brachytherapy has been administered to 23 cases of malignant brain tumors in a phase one clinical trial to assess the feasibility and safety of this treatment approach. In order to quantify the acute and long-term response of tumor and surrounding brain to this treatment, a morphometric CT scans analysis was performed in 18 evaluable patients.

Volumes defined by the outer margin of the contrast-enhancing rim, by the hypodense necrotic region within the enhancing rim, and by the surrounding hypodensity region were calculated from computer measurements. Hyperthermia equipment performance (HEP) was calculated for the evaluation of heating.

After the treatments, the volume of the inner hypodensity region decreased in seven patients, and the volume increased in 11 patients. In five patients, outer margin of the contrast enhancing lesion showed an initial increase in volume followed by a decrease, and in those patients higher HEP and longer survival were observed significantly. The volume of the surrounding hypodensity region varied following treatments, but in most instances, the region subsequently increased in the interal immediately prior to death.

Contribution of heat effect to those changes are discussed, and significance of aggressive heating which provides transient opening of blood brain barrier is shown.

Key words

Brain tumor, hyperthermia, computed tomography, blood brain barrier, interstitial

Text of papers

1. Introduction

Interstitial microwave (MW) hyperthermia in combination with iridium-192 brachytherapy has been administered to 23 patients with malignant brain tumors in a phase one clinical trial to assess the feasibility and safety of this treatment approach (Lyons et al. 1984). We have previously reported the technical description and clinical features (Roberts et al. 1986, 1987, 1988, 1990). In order to quantify the acute and long-term treatment response of tumor and surrounding brain, a morphometric CT scan analysis was performed in 18 evaluable patients, this morphometric analysis of the CT images is reported, and the relevant factors concerning the efficiency of the treatments are discussed. With the analysis of chronological CT changes, heat effects and hyperthermia treatment outcome for malignant brain tumors are reported. To evaluate CT change, the significance of the enhancing lesion, which consists not only of active tumor but also of heat-induced blood brain barrier (BBB) disruption, is discussed.

2. Materials and Methods

2.1. *Patient profile*

Twenty-three patients with intracranial malignant brain tumors were treated at Dartmouth-Hitchcock Medical Center between 1983 and 1990. There were 18 patients for whom CT scans were obtained at least twice including just prior to and after the hyperthermia (HT) treatment. Five patients were excluded from this study because two patients did not have follow up CT scans and three patients underwent surgery after the hyperthermia treatments and were not suitable for analysis. For 14 patients, at least three CT scans were obtained. The 18 patients consisted of 11 males and 7 females, and their ages ranged from 35 to 73 years (mean: 57.9 years). Histologically one case was diagnosed as an intracranial metastasis of malignant melanoma and the remainder were diagnosed as anaplastic astrocytoma or glioblastoma multiforme. All the patients were followed in our hospital and the mean follow-up period was 12.1 months (range: 1 to 47 months). The earliest postoperative CT scans were obtained 1 day to 4 months after the HT treatments (mean: 18.7 days), and the final scans were 1 week to 25 months (mean: 7.5 months).

2.2. *Hyperthermia treatments*

The interstitial MW antenna array HT system used in this study has been

described previously (Ryan et al. 1984, 1990, 1991 Strohbehn et al. 1979). A 915 MIIz microwave generator (Holaday III-915) was used in 30 treatments of 16 patients, 2000 MIIz was used in 4 treatments of 2 patients, and 2450 MIIz was used in 2 treatments of 2 patients. The nylon catheters, into which MW antennas and iridium seeds strands were afterloaded, were stereotactically inserted. Temperatures were monitored with fiber-optic thermometry. The fiber-optic thermosensors were controlled by a computer system and automatically moved within the lumen of the catheter for measuring the temperatures at different depths. With the thermal data, hyperthermia equipment performance (HEP), defined as percent volume of the tumor heated over 43°C, was used for the evaluation of heat performance. The MW power distributed to each antenna was controlled automatically to optimize heating(Qjn et al. 1990, Roberts et al. 1986).

2.3. *Radiation therapy*

Iridium-192 seeds were inserted just after the first HT treatment and removed prior to the start of the second HT treatment. For the first 5 cases, the radiation dose at the treatment boundary ranged from 17.5 to 21.50 Gy (mean 15.84 Gy). For subsequent cases the dose was increased, resulting in delivery of 47.8 to 73.0 Gy (mean 60.7 Gy). Later whole brain cobalt irradiation was delivered in 10 patients with the dose ranging from 44 to 60 Gy (mean 58.3 Gy).

2.4. *Morphometric CT analysis*

Volumes defined by the hypodense necrotic region within the enhancing rim, by the outer margin of the contrast-enhancing tumor, and by the surrounding hypodensity presumably representing both edema and infiltrating tumor were calculated from computer measurements. The volume of the contrast-enhancing tumor was calculated, including the volume of the inner hypodensity. The volume of the surrounding hypodensity was calculated, including both contrast-enhancing tumor and the inner hypodensity. Measurements were made from scans beginning at the time of interstitial catheter implantation and continuing at subsequent two month intervals. The computer measurements were performed using an image digitizer which was controlled by a personal computer. The targeted area of each CT slice was measured by the digitizer, and these areas were summed for calculation of a volume.

3. Results

3.1. *Heat performance*

HEP was calculated in 12 of 18 and ranged from 19.5 to 100 % (mean : 69.0 %). In 14 treatments of 7 patients, HEP exceeded 70%. There was a good correlation between HEP of the first treatment and of the second one ($p< 0.001$; t-test), demonstrating the reproducibility of HEP in each patient. Many factors influenced HEP, including tumor size, location and number of antennas which remained similar between treatments.

3.2. *Summary of CT measurement*

For all patients, a CT scan was obtained immediately prior to the first hyperthermia treatment. The mean volumes of the margin of the inner hypodensity, outer margin of the contrast enhancing lesion and surrounding hypodensity were 6.54cm^3 (range 0-35.6cm^3), 27.43cm^3 (range 4.1-114.6cm^3) and 97.79cm^3 (range 9.0-229.2cm^3) respectively. In the second CT scan the mean volume of the margin of the inner hypodense was 6.54cm^3 (range 0-35.6cm^3), that of the outer margin of the contrast-enhancing lesion was 26.61cm^3 (range 2.0-101.8cm^3) and that of the surrounding hypodensity was 73.67cm^3 (range 5.5-213.9cm^3). In 14 of 18 patients more than two follow-up CT scans were obtained (Table 1).

3.3. *Inner hypodense region*

Most of the changes within the volume of the inner hypodensity were not dramatic compared with the changes in the enhancing lesion or surrounding hypodensity. A decrease in volume was seen in seven patients; a continuing decrease of the volume was observed in three patients and a subsequent increase was seen in two patients. A single CT scan was obtained in two patients who showed a decrease of the volume just after the treatment (Fig, 1). On the other hand, there were six patients who showed an initial increase in volume followed by a decrease, and three who showed an initial increase in volume followed by a further increase. Two patients with a single follow-up scan showed an increase in volume (Fig. 2). There was no correlation between HEP and volume change.

3.4. *Outer margin of the contrast-enhancing lesion*

Nine patients demonstrated a decrease in the volume of the contrast-enhancing lesion after treatment, and an equal number demonstrated an increase. In the group showing a decrease, more than two follow-up CT scans were obtained in eight patients. The second follow-up CT showed an increase in the volume in six patients (decrease-increase) and further decrease in two patients (decrease-decrease) (Fig. 3). In the group showing an increase, extended evaluation was done in six patients: increase in the volume was observed in one patient (increase-increase) and decrease was seen in five patients (increase-

decrease) (Fig. 4).

Patients belonging to the increase-decrease group showed several interesting tendencies which were not seen in other groups: 1) HEP of the increase-decrease group could be calculated for three cases out of six, and was significantly higher than that of other groups ($p < 0.05$; t-test), 2) the survival was significantly longer than other patients ($p < 0.05$; chi-square test), and 3) mean volume of the tumor was smaller than others (not significant).

3.5. *Surrounding hypodense region*

The volume of the surrounding hypodensity varied in response to treatments. Seven patients showed initial decrease in volume, followed by a further decrease in two patients and an increase in five patients (Fig. 5). There was an initial increase in 11 patients, followed by a decrease in three patients, and followed by an increase in four patients; for the remaining 4 patients, only two CT scans were obtained (Fig. 6). In 14 patients out of 18 this region subsequently increased immediately prior to death.

4. Discussion

The infiltrating nature of malignant glioma and the implications for any resective approach have limited the role of surgical treatment in this desease. To selectively treat tumor cells, radiation therapy, chemotherapy and hyperthermia have been utilized based on experimental results that the normal brain tissue is slightly more resistant than the tumor cells for such treatments (Coughlin et al. 1983, 1985, Salcman and Saramas 1981, Suit and Gerweck 1979, Tanaka et al. 1987). Due to improvements in the technology (Ryan et al. 1991), an interstitial MW system can produce adequate heating in brain tumors. Heat performance can be evaluated from the thermal mapping data obtained by fiber-optic thermometry. The ideal treatment volume with respect to tumor size remains to be determined.

In our clinical experiences reported previously, hyperthermia treatments were performed without any serious complication. CT scans demonstrated that changes in the enhancing lesion, in edema and in the necrotic region varied greatly. In this study, we analyzed chronological morphometric changes of CT images by analysis of the inner hypodense region, the outer margin of the contrast enhancing lesion and the surrounding hypodense region. The necrotic lesion was expected to enlarge after the HT treatment because of microvascular thrombosis caused by the heat effects, and as a result, shrinkage of the contrast enhancing lesion was also expected (Roberts et al. 1990). The edema had been thought to increase in volume initially because of acute heat and radiation effects, which was followed by a decrease in volume with the shrinkage of the enhancing lesion.

Change in the inner hypodense region, which is presumed to recrosis, was not significant. In the aggressively heated group (HEP> 75%), 5 cases out of 7 demonstrated an increase of the inner-hypodense region, but the volume changes did not correlate with HEP. The CT scans of the two cases who were heated aggressively but did not show increase of inner-hypodense region were obtained within three days after the treatment; others were obtained more than 5 days later. The necrosis may chiefly derive from microthrombosis and degeneration of the enhancing tumor caused by heat and radiation, and such changes may appear in CT images several days after the treatment. At the border of the necrotic lesion, local reactive gliosis and revasculalization followed by clearance by macrophages may have occurred, and this phenomenon may be the cause of the variability of the volume changes.

In order to evaluate the changes of the enhancing lesion, all the cases were categorized into four groups according to the volume changes of CT scans obtained just after the treatments and at the next follow up. There were five patients who showed initial increase of the enhancing lesion followed by decrease (increase-decrease group). HEPs of the increase-decrease group were significantly higher than those of other patients. This may imply that aggressively heated patients (HEP > 75%) demonstrated a temporary increase of the enhancing lesion after hyperthermia and brachytherapy. This may have been caused by a disruption of the BBB in the normal brain tissue which surrounds the enhancing brain tumor. Due to the aggressive treatments, the BBB of the surrounding brain tissue might have opened temporarily, and thus the enhancing tumor as well as the surrounding brain tissue might have been enhanced by contrast medium, appearing as increased volume of the enhancing lesion. No relationship was found between radiation dose and temporary increase of the enhancing lesion, so this effect was thought to derive mainly from thermal effects. On the other hand, there were seven patients who showed a decrease of the enhancing lesion after the treatments (decrease-decrease or decrease-increase group). The HEP values of those patients were lower than those of the increase-decrease group. As an explanation of this phenomenon, only the inside of the enhancing rim of the lesion may have been heated, and additionally, the volume of the lesion may have decreased because of the micro-thrombosis which was expected.

There are many previous reports discussing the MW effects to the brain tissue. Some groups have reported the existence of increased brain permeability (Albert and Kerns 1981, Goldman et al. 1984, Lyons et al 1986, Moriyama et al. 1991,Neubauer et al. 1990, Oscar et al. 1977); others have reported failure to such

an effect (Gruenau et al. 1982, Lin and Lin 1982, Merrit et al. 1978, Oscar et al. 1981, Preston and Prefontaine 1980, Ward et al. 1982, 1985, Williams et al. 1984) or a decrease in permeability (Preston 1982, Williams et al. 1984). Lin et al (1980) exposed rat brains to pulsed 2450 MHz MW, and examined histological tissue-permeability with an injection of Evans-Blue dye. They concluded that MW heating for 20 minutes at 44°C was a critical condition for the disruption of the BBB. In other reports which failed to detect MW induced BBB disruption, the brain tissue was heated at comparatively lower temperatures or temperatures were not monitored.

Mechanisms of the BBB disruption induced by MW irradiation or heat have been proposed (Merrit 1978, Moriyama et al. 1991). Oscar et al. (1981) hypothesized that the alteration of brain activity may be a secondary effect caused by MW alteration of blood flow, blood pressure or blood vessel area. Dietrich et al. (1990) heated ischemic rat brains, and their results demonstrated that brain temperature was a critical factor for the determination of BBB function. Moriyama et al. (1991) exposed rat brain to temperature above 44.3°C for 30 min using 2450 MHz MW. They showed that extravasation of blood-borne peroxidase occurred at sites of maximum-temperature elevation, even when these did not coincide with the site of maximum power density. They concluded that the BBB disruption was related to the thermal effect of MW. In our series, the goal of treatment was to produce a treatment temperature equal or greater than 43°C throughout the treatment volume.

With moderate injury, BBB is supposed to open reversibly (Lin and Lin 1982, Qjn et al. 1990). Albert et al. (1981) reported reversible alternations of BBB with MW exposure to Chinese hamster. As explanations they proposed two hypotheses: 1) tight junction between endothelial cells and a paucity of a pinocytic vesicle openings, 2) the number of pinocytic vesicles in the endothelium of the microvasculature increases and it acts like as opening of alternative pathway. Neubauer et al. (1990) presumed that the mechanism originated in a " pinocytotic-like" uptake system which existed in microtubules. Reversible changes of BBB derived from radiation therapy have been also reported (Qjn et al. 1990).

In previous reports of animal experiments, total reversibility of BBB after cessation of MW irradiation was observed within a couple of hours (Albert et al. 1981, Lin and Lin 1980, Sutton and Carrol 1979). In our study, temporary enlargement of the enhancing lesion was observed for a much longer period (mean 16.2 days; range: 3 days to 34 days). The cause of this persistence is unclear. It is possible that a combination of brachytherapy late effects to the brain may have prolonged the temporary BBB opening, and may have played a role in enhancement. Groothuis et al. (1987) studied a constitution of the lesion which is caused by experimental brachy- therapy histologically and functionally. In their results, the lesion consisted of 1) a central zone of calcified necrosis, 2) a spongy, fluid-filled zone, and 3) a narrow rim of viable brain tissue with increased permeability. Similar changes were reported with experimental interstitial HT and brachytherapy (Hoopes et al 1991, Ostertag et al. 1983).

In our study CT images were used for the morphometric evaluation of BBB opening. Previous reports have shown that contrast enhancement primarily reflects disturbance in the BBB rather than increase in vascularity (Fike at al. 1982, 1985, 1988) . Even though the molecule size of the contrast medium may not be the most preferable one for the evaluation of the BBB opening area, enhanced CT scans are thought to be a useful modality for the evaluation of morphometric studies (Turowski et al. 1986). Some studies reported that Gd-DTPA enhanced MRI reflects BBB disruption more accurately (Greenwood 1991, Hayakawa et al. 1990, Larsson et al. 1990, Lo et al. 1990) , and is expected to play an important role for follow-up studies in the near future.

The volume of the surrounding hypodense region, which is thought to consist chiefly of edema, varied significantly. Even in those cases which showed decrease of the enhancing lesion, decrease of surrounding hypodense region was not clear. Steroids were administered for many of the patients, and would have had an effect on the edema. Some patients received external beam irradiation which may have produced degenerative low density areas, as early or late effects of radiation.

The mean survival of the aggressively heated group was significantly longer than others. There was no statistically significant difference between tumor volume and survival. In conclusion, aggressive heating with high HEP is preferable for the effective treatment of malignant brain tumors if the invading zone of the tumor is also treated by heat. The efficiency of the treatment can be evaluable by the temporary increase of the CT enhancing lesion, showing reversible change of BBB in brain-tissue having an infiltration of the tumor cells.

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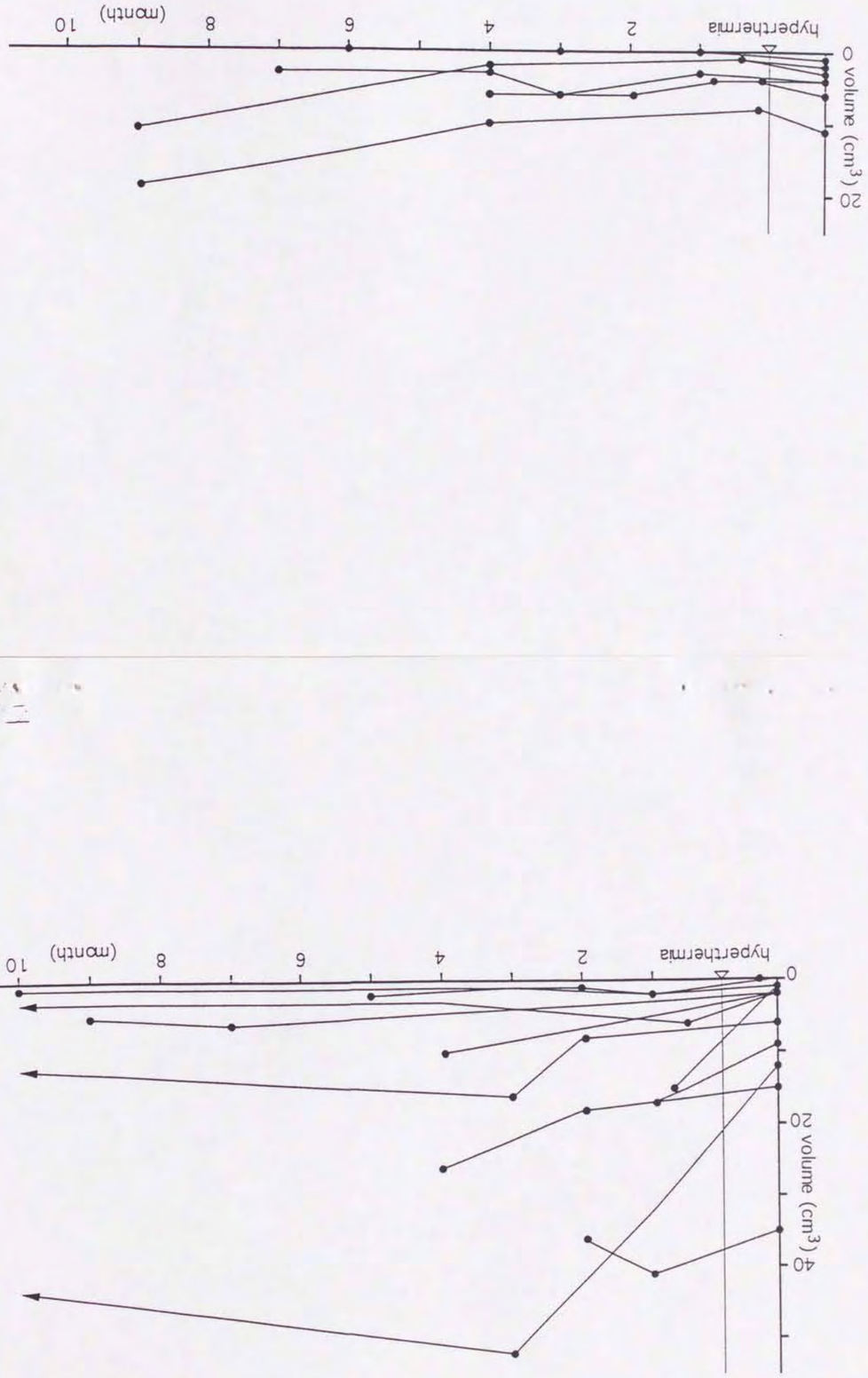
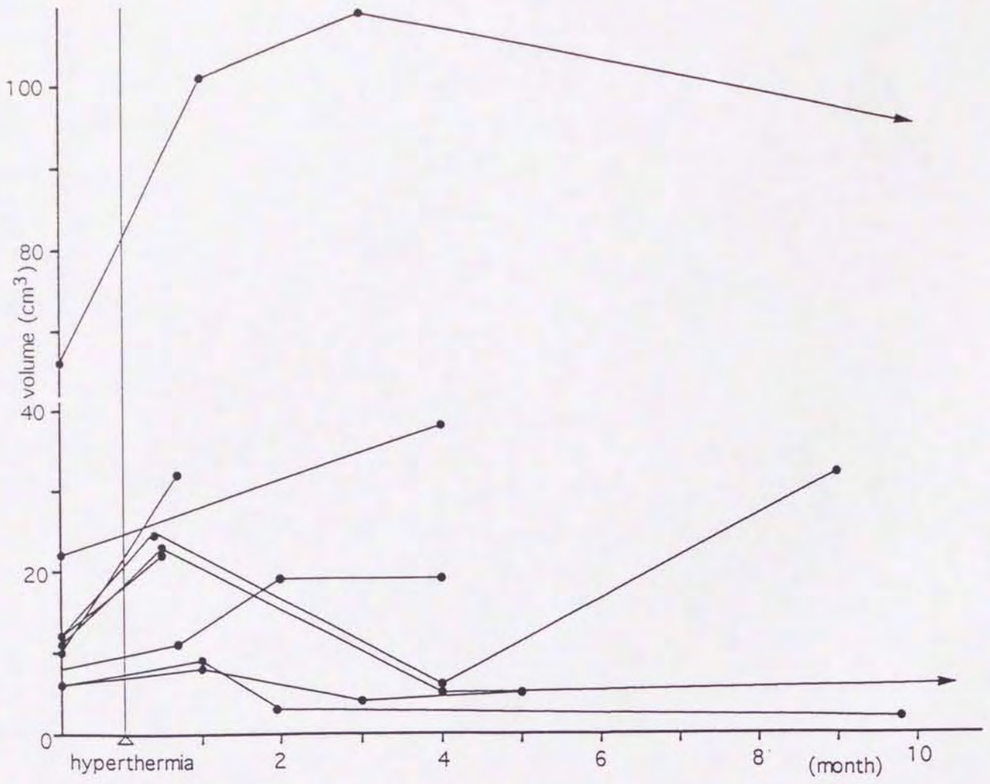
case #	Tx #	age	sex	*tumor location	# of an-tennas	RT: whole brain+ boost(Gy)	RT Ir-192 (Gy)	Follow-up (month)	**volumes of IH, ET, OH before treatments (cm3)	after treatment (cm3)	HEP (%)
1	1	53	M	Rt F-P	4	50+10	19.00	16	1827.0, 66.6, 12.1	213.9, 101.8, 52.3	NA
	2				4						NA
2	1	73	M	Lt P	4	44	21.20	3	132.6, 62.4, 8.7	140.9, 54.5, 15.4	NA
	2				4						NA
3	1	48	M	Lt F	6	0	21.50	13	229.2, 114.6, 35.6	95.7, 54.9, 41.0	NA
	2				6						NA
4	1	61	F	Rt F	5	50+10	20.10	5	48.8, 22.2, 2.4	21.2, 38.7, 9.9	NA
	2				5						NA
5	1	62	F	Rt F	5	50+10	17.50	12	103.4, 40.3, 5.8	40.2, 15.2, 7.7	NA
	2				5						NA
6	1	35	F	Lt T-P	5	0	65.80	13	9.0, 4.1, 0.4	5.5, 2.0, 0.0	NA
	2				5						NA
7	1	62	F	Lt P-O	5	50+10	66.00	13	47.6, 12.0, 3.32	95.5, 25.5, 0.6	72.7
	2				5						90.9
8	1	58	F	Lt P	5	0	47.80	3	42.8, 12.6, 2.0	58.6, 22.8, 1.1	50
	2				5						57.1
9	1	61	M	Rt P	5	50+10	60.00	8	103.4, 40.2, 15.1	73.4, 34.2, 18.5	95.2
	2				5						91
10	1	66	M	Pt P	5	50+10	73.00	12	47.5, 39.0, 11.2	28.2, 19.9, 7.7	73.3
	2				5						94.6
11	1	67	M	Lt T	5	0	59.70	9	18.6, 11.6, 4.6	18.6, 9.8, 3.8	21.8
	2				5						60.8
12	1	64	M	Lt T	4	50+10	60.00	12	36.5, 10.7, 2.9	52.0, 7.6, 3.0	19.5
	2				4						37.8
13	1	49	M	Lt P	5	0	60.00	4	33.4, 14.3, 5.3	64.5, 7.9, 3.9	57.2
	2				5						33.7
14	1	64	M	Rt P	5	59	57.50	45	43.3, 11.4, 1.6	91.6, 23.7, 5.9	95.8
	2				5						91.4
15	1	51	M	Lt F-P	5	0	67.00	19	185.7, 6.5, 0.5	91.5, 8.0, 2.6	78.9
	2				5						88.8
16	1	38	F	Lt F-P	1	0	60.00	12	73.4, 6.8, 0.0	82.0, 9.8, 1.5	100
	2				1						90.9
17	1	59	F	Rt P	4	0	58.50	7	21.3, 8.1, 4.5	22.1, 10.5, 3.9	21.4
	2				5						47.4
18	1	73	M	Rt F-P	5	40+20	54.10	15	41.1, 10.3, 1.7	130.6, 32.1, 16.1	86.5
	2				4						100

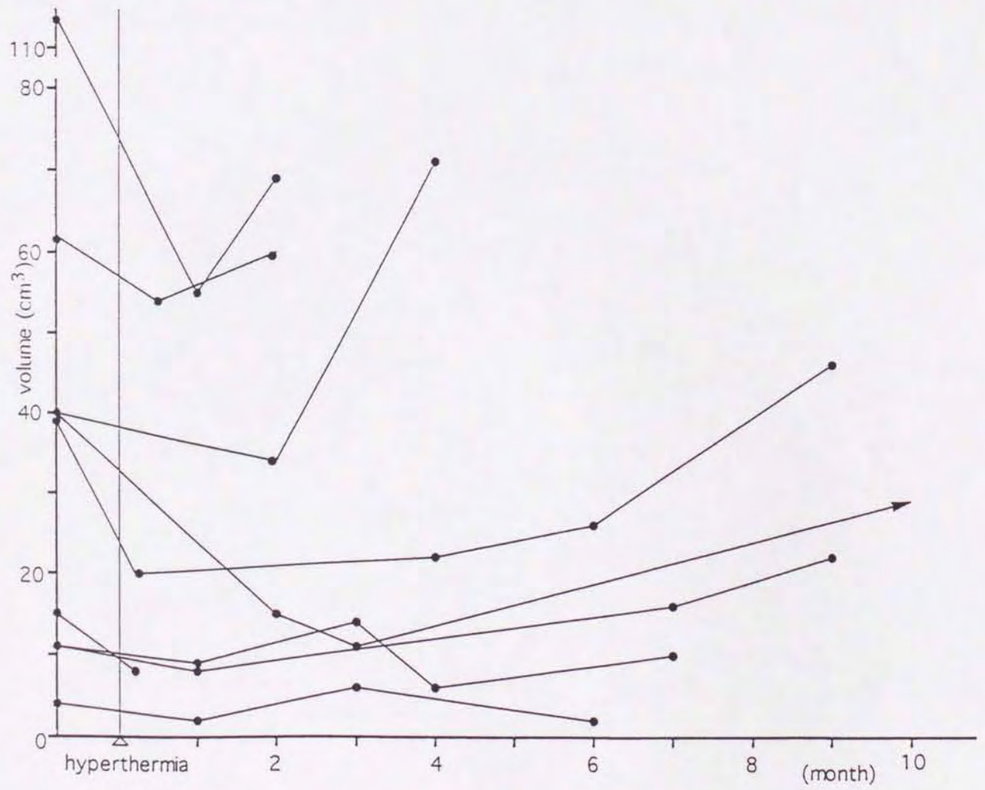
*: Rt= right, Lt= left, F= frontal, T= temporal, P= parietal, O= occipital

**: IH= inner hypodensity, ET= enhancing tumor, OH= outer hypodensity

Table 1: clinical summary and CT measurements


hyperthermia
2
4
6
8
10
(month)
O2 volume (cm3)
0


100
80
40
20
0
volume (cm^3)
hyperthermia
2
4
6
8
(month)
10


110
80
60
40
20
0
volume (cm^3)
hyperthermia
2
4
6
8
(month)
10

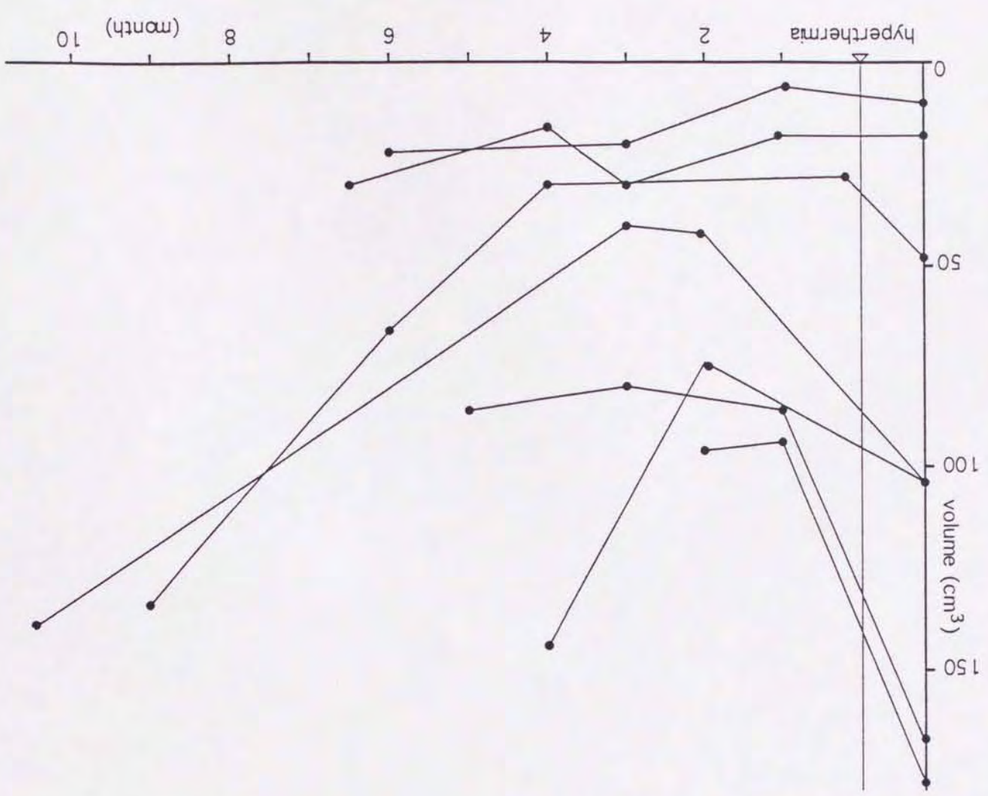

hypertherma
0
2
4
6
8
10
(month)
0
50
100
150
volume (cm3)

Fig. 5

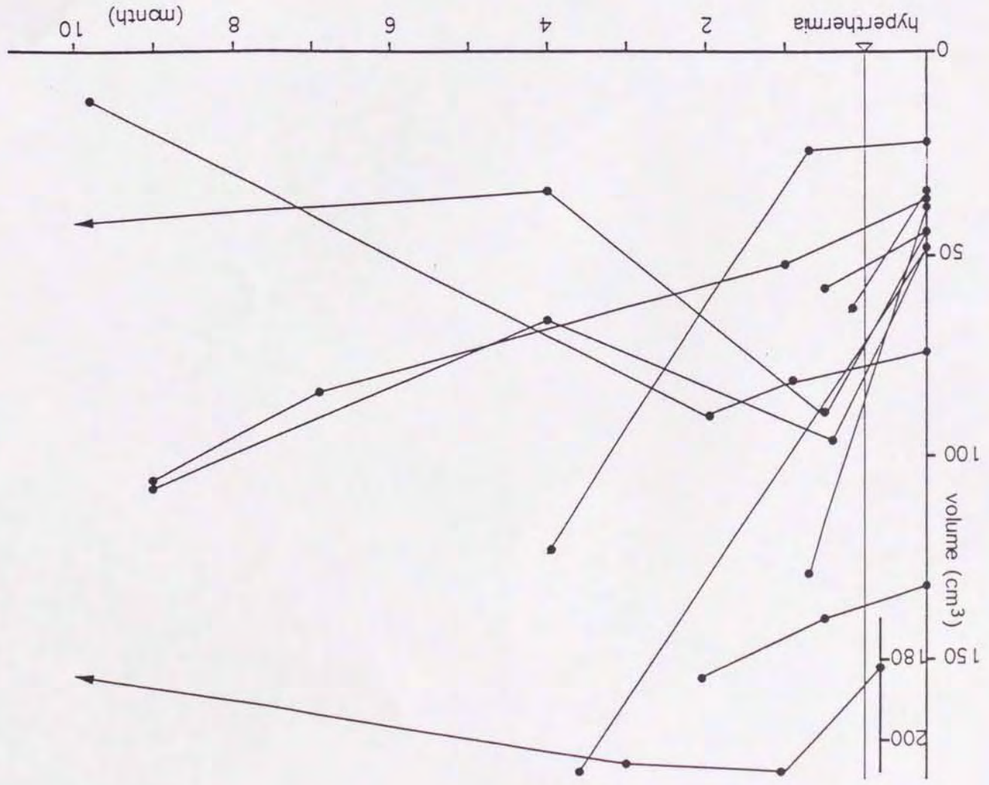

hypertherma
0
2
4
6
8
10
(month)
0
50
100
150
180
200
volume (cm3)

Fig. 6