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Impact of radiotherapy on normal brain tissue: Semi-automated quantification of decrease in perfusion

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Purpose: We attempted to ascertain the impact of Co-60 conventional external radiotherapy (cRT) on the perfusion of normal brain tissue in relation to the radiation doses delivered to the tumors in patients with primary brain tumors.
Materials and Methods: After surgery 18 patients (pts) were due to undergo cRT with a total dose of 5400–6400 cGy. All the patients had a Tc-99m-HMPAO SPECT study prior to cRT (basal), 15th and 30th days of cRT as well as 1 (in 6 pts), 3 (in 9 pts), and 6 (in 3 pts) months after cRT. For quantitative evaluation, the entire set of transverse slices were divided into 4 regions as frontal, parietal, occipital and temporal regions by means of a computer software program. Semi-automated quantification was performed on a total of 1392 regions in 87 studies to determine left to right ratios. An interregional difference of at least 10% was considered abnormal.
Results: After elimination of tumor sites, 80 normal brain regions showed decreased perfusion after cRT. The percent decrease in perfusion was (mean 22.5 ± 9.9) significantly higher in areas irradiated with doses > 3000 cGy ($p < 0.05$).
Conclusion: cRT has adverse effects on the perfusion of normal brain tissue for doses > 500 cGy. Our findings justify treating patients with small and limited lesions with stereotactic radiotherapy in order to minimize the adverse effects of cRT on normal tissues.

Key words: Tc-99m-HMPAO, radiotherapy, brain imaging, single photon emission computed tomography

INTRODUCTION

THE PURPOSE of conventional external radiotherapy (cRT) is to increase the patient's survival time and quality of life while decreasing residual tumor volume. Although early diagnosis and effective therapeutic approaches result in better survival rates, radiation-induced complications still constitute major limitations. In this regard, because avoidance of undue irradiation is pivotal, precise identification of the external radiotherapy (XRT) region and prevention of daily regional fluctuations become increasingly important.

Linear accelerators and cobalt-60 (Co-60) teletherapy machines have been in clinical use for implementation of cRT. A maximum tolerable dose to the brain tissue is rendered possible with dose fractionation techniques.[1] In general, a total of 5000–6000 cGy dose fractionated into daily 180–200 cGy doses is the choice in a radiotherapy plan for effective residual tumor irradiation. Unfortunately in most cases, normal tissues surrounding tumor regions are inadvertently included in the irradiation fields. Although this effect is desired when it occurs within a limited diameter and predicted distance, it may be responsible for the radiation damage to the normal brain parenchyma if not controlled.[2]

Radiation damage to the central nervous system is primarily the consequence of its effects on the vascular

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Table 1 Patient population

Pt. No.	Age	Sex	Tumor	Grade (n)	Localization	Follow-up
1	36	M	D.I.A	II	L frontal	7 months
2	10	M	G.M.	IV	L T.P.	7 months
3	44	F	A.A.	III	R T.P.	4 months
4	57	F	G.M.	IV	R T.P.	2 months
5	40	F	G.M.	IV	Mid frontal	2 months
6	29	M	G.M.	IV	R T.P.	7 months
7	43	M	O.D.G.	II	Frontal	2 months
8	35	M	O.D.G	II	R parietal	4 months
9	45	M	G.M.	IV	L frontal	4 months
10	55	F	G.M.	IV	L frontal	4 months
11	45	M	G.M.	IV	L F.P.	2 months
12	48	M	G.M.	IV	R T.P.	2 months
13	43	M	D.I.A.	II	R F.P.	4 months
14	14	M	O.D.G.	II	R temporal	4 months
15	40	M	O.D.G.	II	R F.P.	2 months
16	50	F	D.I.A.	II	R parietal	4 months
17	53	M	G.M.	IV	L T.P.	4 months
18	60	M	O.D.G.	II	R frontal	4 months

D.I.A: Diffuse infiltrative astrocytoma, G.M.: Glioblastoma Multiforme, A.A.: Anaplastic Astrocytoma, O.D.G.: Oligodendroglioma, T.P.: Temporoparietal lobe, F.P.: Frontoparietal lobe

structure.[1,3,4]

Although some physiological and biochemical changes have been shown to precede the damage to the vascular structures, these changes might not necessarily indicate parenchymal damage of these parameters could non-specifically increase, rendering monitorization difficult.[3]

There are several PET studies which report metabolic and hemodynamic changes in seemingly normal gray matter after radiotherapy for gliomas. They showed that while the oxygen extraction fraction, glucose consumption and glucose extraction fraction were all decreased in the early and the late stages of radiotherapy, regional cerebral blood flow and blood volume were decreased only in the late stage.[5,6]

Tc-99m-d,l HMPAO is a widely used brain perfusion tracer that could offer excellent sensitivity in revealing pathological cerebral perfusion changes. This lipophylic radiotracer readily crosses the intact blood brain barrier by passive diffusion and its distribution is proportional to blood flow.[7]

This study was designed to investigate the radiation effect on normal brain tissue perfusion including gray and white matter and to describe its relation, if any, to the dose of radiation given and its appearance time.

MATERIALS AND METHODS

Patient Population

Eighteen patients were included in the study (age range 10–60, mean: 41.5 ± 13.4, 13 males, 5 females) (Table 1). Informed consent was obtained from each patient. All patients had total or subtotal tumor excision of their primary tumor and none had any prior history of cRT.

Table 2 Patients who received chemotherapy before cRT

Pt. No.	Agents	Amount
2	NM + VCR + Procarbazin	2
9	VCR + Procarbazin + CCNU	1
10	VCR + Procarbazin + CCNU	1
14	NM + VCR + Procarbazin	4
17	VCR + Procarbazin + CCNU	1

NM: Nitrogen Mustard, VCR: Vincristin

Histopathologically, all tumors were primary glial tumors in origin and they were consisted of 13 astrocytic [(3 diffuse infiltrative astrocytoma (WHO grade II), 1 anaplastic astrocytoma (WHO grade III), 9 glioblastoma multiforme (WHO grade IV)] and 5 oligodendroglioma (WHO grade II) type. The tumors were located in the frontal lobe in 6, parietal lobe in 2, temporal lobe in 1, temporo-parietal region in 6 and fronto-parietal region in 3 subjects. Five patients received chemotherapy in addition to cRT (Table 2).

A total of 5400–6400 cGy in daily 200 cGy dose fractions was delivered with a cobalt-60 teletherapy unit 7–20 days (mean 15 days) after surgery. Magnetic resonance imaging (MRI) was used to delineate the safety margins of cRT regions. A safety margin of 3 cm to the tumor and surrounding edematous tissue was left for wide parallel irradiation up to the 3000 cGy and a 2 cm margin was kept for localized irradiation up to the planned maximum total dose level. Patients were clinically followed-up for 4–15 months.

Acquisition of SPECT Data

A basal brain perfusion SPECT study was performed 1–

3 days prior to cRT with 555 MBq Tc-99m HMPAO (Rotop, Mallincrodt, Germany). Tc-99m HMPAO was prepared according to the manufacturer's instruction and dose amount given was adjusted to the body weight in children. Tracer injection was performed in a quiet room with the patient's eyes closed. Images were acquired within 30–45 minutes after injection of the tracer by a step and shoot technique in 128 steps with an acquisition time of 30 sec/frame, a zoom factor of 1.85 and a matrix size of 64 × 64 on a dual-head gamma camera (ADAC Genesys camera, Pegasys SP10, IP8 computer system, CA, USA). An elliptic orbit was preferred for obtaining the best camera resolution and count rate. After doing the basal study, the Tc-99m HMPAO SPECT study was repeated at 15 days, 30 days, 1 month (in 6 pts), 3 months (in 9 pts), and 6 months (in 3 pts) after cRT. Scintigraphic raw data were reconstructed by the filtered backprojection method with a Gaussian filter (cut-off frequency: 0.5 cycles/cm, order: 20). Attenuation correction according to Chang's method was applied to transverse sections. Reorientation was performed with reference to the orbito-meatal line. We decided to use the reoriented transaxial slices to make more reliable comparison between and within the subjects.

MRI was performed prior to the start of cRT in the 3rd and 6th months of cRT. Both T1- and T2-weighted pulse sequences were generated with a slice thickness of 3–5 mm with i.v. gadolinium-DTPA as a contrast agent.

Clinical assessment was available in all patients for the corresponding time periods of the imaging studies.

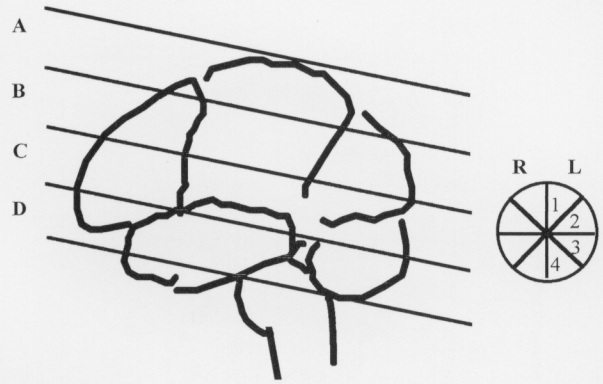

Fig. 1 Schematic representation of quantification procedure.

Quantification of SPECT Data

Semi-automated quantification was applied by means of a regional analysis program in order to reveal any asymmetric changes during and after cRT. Left to right ratios were obtained on attenuation corrected and reoriented transverse slices. All transverse slices were examined visually along with quantification and no increase in perfusion was found in any location after cRT. Although we obtained ratios throughout the entire brain volume, in order to avoid statistical fluctuations that could stem from an extraneous number of slices resulting in scattered data, we combined the 1 cm-thick slices to make 3 cm-thick slices. Hence the entire set of images was divided into 4 pie regions, namely the 1st, 2nd, 3rd and 4th regions from the anterior to the posterior, and composite into 4 levels namely A, B, C and D levels from the superior to the

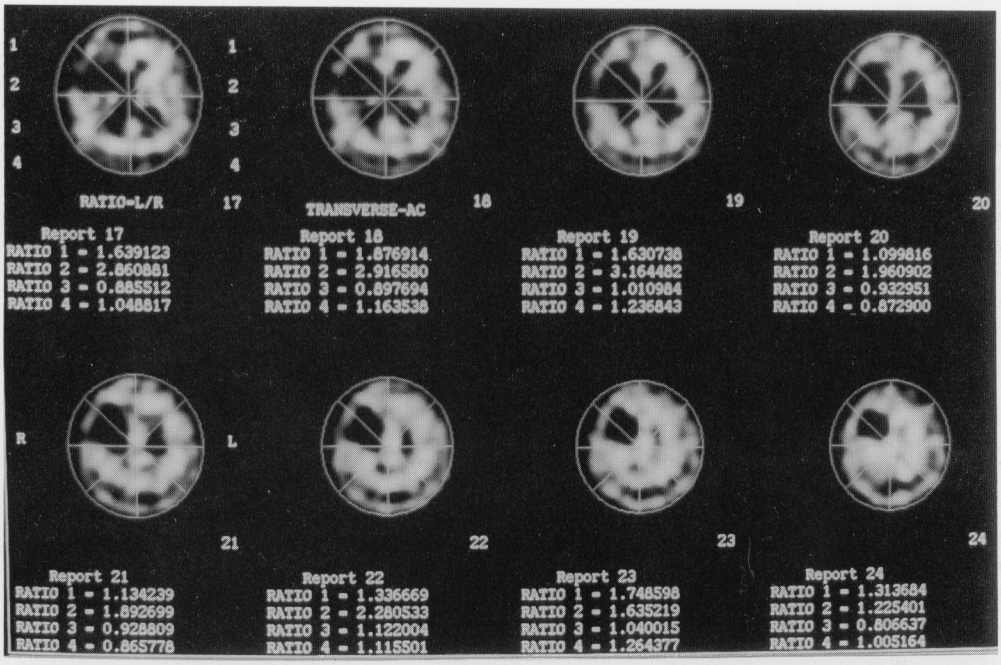

Fig. 2 Quantification procedure in a patient with operated right frontoparietal oligodendrioma (Patient No. 8).

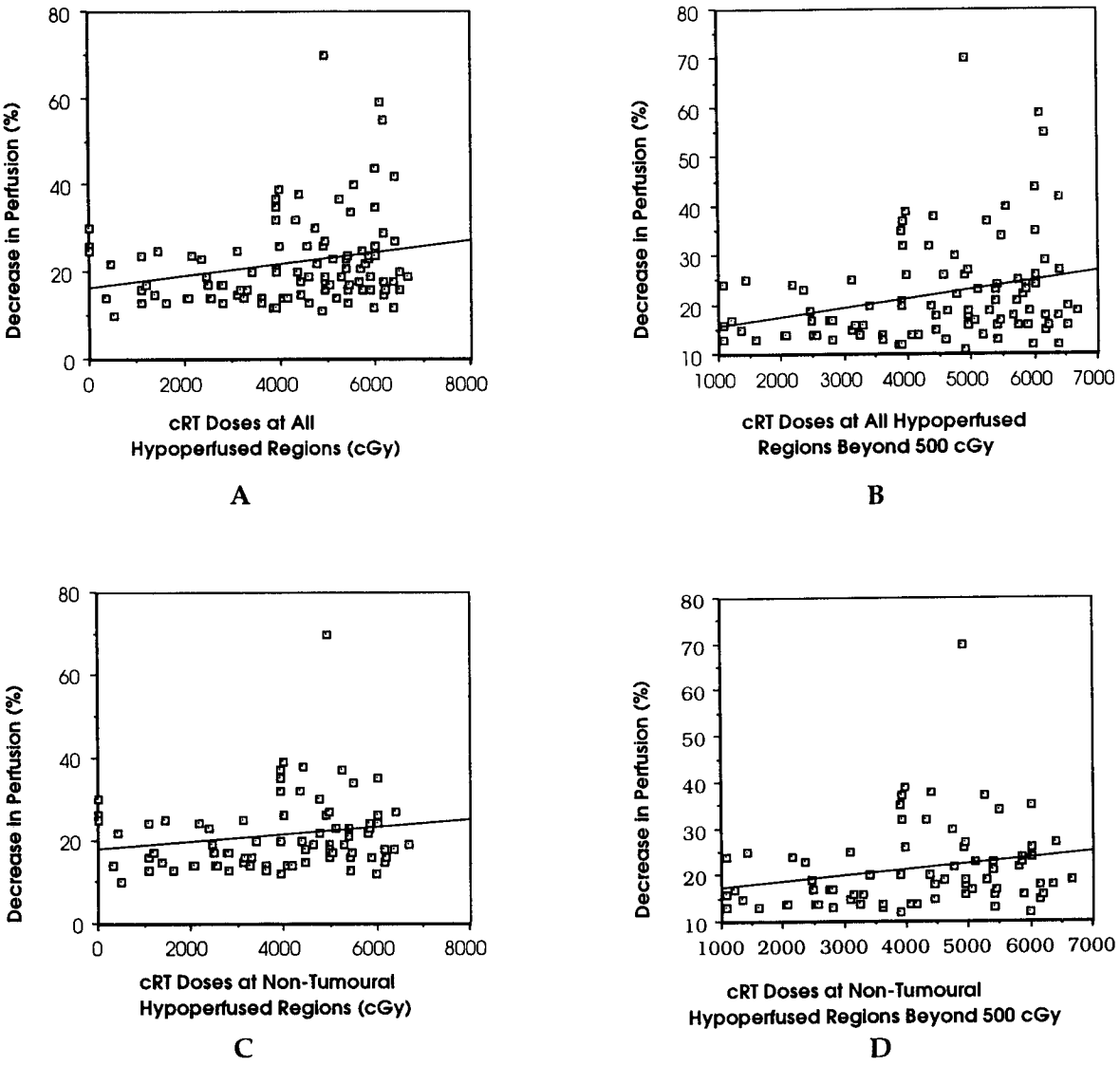

Fig. 3 Dose-perfusion relationships for each subgroup.
A: Relationship between cRT doses (cGy) at all hypoperfused regions including tumor regions and percent of decrease in perfusion ($r = 0.228$, $\mu = 103$, $p = 0.021$).
B: Relationship between cRT doses (cGy) at all hypoperfused regions including tumor regions irradiated beyond 500 cGy and percent of decrease in perfusion ($r = 0.290$, $\mu = 97$, $p = 0.004$).
C: Relationship between cRT doses (cGy) at hypoperfused regions without tumor regions and percent of decrease in perfusion ($r = 0.179$, $\mu = 80$, $p = 0.113$).
D: Relationship between cRT doses (cGy) at hypoperfused regions without tumor regions irradiated beyond 500 cGy and percent of decrease in perfusion ($r = 0.263$, $\mu = 74$, $p = 0.024$).

inferior in order to facilitate comparison of SPECT data with MR findings and avoid statistical variation (Fig. 1). Since we used 4 regions with a mean estimated thickness of 3 cm to calculate interregional difference, it was not necessary to delineate tumoral limits exactly. These ratios were converted to percentage values with respect to tumor locations and cRT regions. Therefore asymmetry values over the ratio of 1 were determined as relative percent value between the studies. All patients had their operation site less than the one specific region to take into account for quantification. Basal scintigraphies and subsequent studies were compared with one another to determine whether or not there were any changes more than a 10% decrease in the corresponding regions. There are several studies which imply that less than a 10% difference in the asymmetry index is a result of a normal anatomical variation between the regions. Hence we use this threshold level to interpret the blood flow change as significant (Fig. 2).[8–10] Semi-automated quantification was done on a total of 1392 region in 87 studies (in 18 patients) to

determine the left to right ratios. Tumor locations and operation regions were taken into account separately to minimize the effects of parenchymal loss, tumor recurrence and tumors crossing the mid-line.

Radiotherapy-induced perfusion decreases of more than 10% in basal scintigraphies were not taken into account when these locations did not show any decrease beyond 10% on subsequent scintigraphies. Moreover, sectors that involve the cerebellum (D4 level) were not taken into account because of the heterogeneity of cerebellar region of interest and inherent unequal blood flow distribution in the cerebellar hemispheres that may lead to incorrect calculations.

cRT Treatment Planning

For verification purposes, treatment fields were designated on simulation radiographs. Isodose distributions in 1 cm thick slices were obtained with a treatment planning system (Nucletron-Plato, Holland) for whole brain tissue in the transverse plane to reveal the percentage of the radiation dose delivered to each region. Cumulative doses to each region were calculated by using corresponding isodose distributions on simulation graphs and taking scintigraphic data planes and sectors as guides. Treatment planning and cumulative dose calculations involved two steps: One for wide field irradiation during the first half of the cRT course (phase I) and another for the localized boost region during the second half of cRT (phase II).

If one sector in any level encompasses more than one isodose value, the percentages were summed in relation to the magnitude of a region they represent. The resultant percentage values were converted to the received dose in cGy by using given dose amount.

Statistical Analysis

Spearman's correlation test was used for the evaluation of the significance of change in perfusion in the sequential studies. Mann-Whitney U test was performed to analyze the relationship between the radiation dose and the decrease in perfusion. The relationship between the time of perfusion decrease and the delivered dose was also analyzed by Spearman's correlation test.

RESULTS

Correlation between Delivered Doses and Percent Decrease in Perfusion

There were a total of 103 regions including tumoral areas ($r = 0.228$, $p = 0.021$) and 80 normal brain regions excluding regions involved by the tumor ($r = 0.179$, $p = 0.113$) that showed decreased perfusion after cRT and, of these, 97 ($r = 0.290$, $p = 0.004$) and 74 ($r = 0.263$, $p = 0.024$) regions each received more than 500 cGy. The scattered pictograms of each subgroup are shown in Figs. 3A–D.

There was good correlation between the magnitude of decrease in perfusion and the total amount of radiation delivered to these regions. The percentage of decrease in perfusion was significantly higher (mean 22.5 ± 9.9) in areas irradiated with doses higher than 3000 cGy ($p < 0.05$). Correlation values for subgroups with a threshold dose level of 3000 cGy are given in Tables 3–6. After elimination of regions exposed to less than 500 cGy, the percentage decrease in perfusion in all regions and normal tissues was significantly higher for doses higher than 3000 cGy with respect to regions exposed to 500–3000 cGy ($p < 0.05$) (Tables 4 and 6). When all the calculations were reperformed by including the regions exposed to doses less than 500 cGy, there was no significant statistical correlation, but the tendency towards a decrease in perfusion with higher doses was maintained (Tables 3 and 5).

Table 3 Dose-perfusion relationship for all hypoperfused regions

Dose	Mean	S.D.	No.	Median	IQR
< 3000	18.46	5.06	24	17	9.75 (14–23.75)
> 3000	23.27	11.12	79	20	10 (16–26)
p = 0.0669			103		

Table 4 All hypoperfused regions beyond 500 cGy

Dose	Mean	S.D.	No.	Median	IQR
< 3000	17.17	4.13	18	16.5	6 (14–20)
> 3000	23.27	11.12	79	20	10 (16–26)
p = 0.0169			97		

Table 5 Non-tumoral hypoperfused regions

Dose	Mean	S.D.	No.	Median	IQR
< 3000	18.46	5.06	24	17	9.75 (14–23.75)
> 3000	22.54	9.85	56	19.5	10 (16–26)
p = 0.0633			80		

Table 6 Relationship between the dose given and the percent decrease in perfusion at non-tumoral hypoperfused regions that were exposed beyond 500 cGy dose level

Dose	Mean	S.D.	No.	Median	IQR
500–3000	17.17	4.13	18	16.5	6 (14–20)
> 3000	22.54	9.85	56	19.5	10 (16–26)
p = 0.0148			74		

Correlation between the Magnitude of Perfusion Decrease and the Time of Its Appearance

There was no significant correlation between the time interval up to the first appearance of a perfusion decrease and its percentage during a 6 month period (Table 7).

Table 7 Correlation values calculated between the percentage of perfusion decrease and its time of first appearance for each subgroups

n	r value	p value
103	− 0.1429	0.150
97	− 0.08	0.436
80	− 0.094	0.406
74	− 0.011	0.92

Table 8 Clinical findings and amount of perfusion decreases

Patient No.	Findings	% decrease	No. of regions with decrease of perfusion
1	neurologic def. ϕ	13–21	(3)
2	neurologic def. ϕ	14–38	(6)
3	weight loss, fatigue	14–35	(7)
4	focal convulsion left facial paralysis	12–39	(7)
5	neurologic def. ϕ	13–40	(11)
6	neurologic def. ϕ	12–22	(7)
7	neurologic def. ϕ	13–14	(2)
8	neurologic def. ϕ	13–17	(4)
9	fatigue, difficulty in co-operation, weakness of upper and lower extr.	15–25	(4)
10	seizure, headache	15–19	(4)
11	headache, seizure fever, right hemiplegy	11–26	(6)
12	seizure during physical examination	15–27	(6)
13	fatigue, tinnitus forgetfulness	13	(2)
14	uveitis on left eye	14–32	(8)
15	noise, vomiting epileptic attach	12–70	(9)
16	weakness on left hand finger	13–55	(5)
17	orientation difficulties headache	14–59	(8)
18	headache	14–37	(4)

Correlation between Clinical Assessment and Percent Decrease in Perfusion

Symptoms and findings during a 4–12 month follow-up period after cRT are given in Table 8.

DISCUSSION

The primary effect of radiation on CNS is due to the vascular damage. The proliferation stimulus from damaged cells further sensitizes living cells to irradiation. Eventually this proliferation pattern would contribute to tissue ischemia via vascular occlusion and constriction.[2] Animal studies have shown that 2000–3000 cGy single dose exposure manifests itself in vascular damage, and thereafter glial cell dysfunction becomes apparent after single doses of 3000–4000 cGy.[4] When a fractionated dose regimen was used, it was found that a threshold dose which induces a morphologically detectable hazardous effect of irradiation on vascular structures increases up to 4000 cGy. In this study, apparently a threshold dose level of 3000 cGy determined the degree of perfusion decrease. Therefore, cRT field localization after a 3000 cGy dose should be carefully designed and maintained by taking the tumor volume into account.

No significant correlation was found between the time interval from the start of a decrease in perfusion of more than 10% and percentage values in tumoral and non-tumoral regions. The time of perfusion decrease was therefore not predictable in the first 6 months. This might be due to the difference in age and tumor localization among patients.

We believe that wide variation in the clinical findings during and after cRT resulted from the tumor pressing on the surrounding tissue and brain edema caused by cRT, but the location and magnitude of the perfusion decrease may contribute to future clinical findings and neurologic deterioration. In addition, various tolerance differences in perfusion decreases among subjects may complicate existing clinical findings.

In addition to the advances in instrumentation, significant developments have occurred pertaining to the quantification methods for SPECT data. The best method is expected to be independent of a given dose amount, to be reproducible and compare favorably with other imaging methods.

Absolute quantification of regional blood flow can be done with arterial blood sampling, but this method is quite invasive and impractical in routine clinical practice, especially when it is used for monitoring the effects of a given therapy by serial studies.[11]

In general, quantification of brain perfusion SPECT data is based on the calculation of the ratios of counts per pixel in regions of interest and the cerebellum.[12–14] This ratio yields better results in localized diseases because of the minimal variation in mean cerebellar counts. We could not use the cerebellum as a reference region in all subjects, because of the possibility of a decrease in perfusion in the cerebellar region after radiotherapy.

An asymmetry index can be regarded as a reliable in measuring perfusion disturbances and tracing perfusion patterns during a disease process, owing to little variation in each contralateral region in a given transverse section. The main limiting factor in asymmetry index calculation with a manual ROI drawn in a small area is the partial volume effect due to the camera resolution.[5] We used ROIs as a pie alignment in four regions on each transverse section to calculate the left to right ratio considering that this wide arrangement of the ROI avoided the partial volume effect to some extent. Many investigators used cortically drawn ROIs for calculating the ratios of the disease site to the contralateral hemisphere to monitor the

response to therapy. Although these studies regarded the changes in ratios of more than 10% as pathologic, Suess et al. used 12% as a threshold value.[9] In line with previous studies, we considered changes of more than 10% as pathologic perfusion changes in our study.

Because we could not find any area that showed increased perfusion, the results were converted into percentage values to represent areas showing perfusion decreases of more than 10% without a plus or minus sign. The results were compared with sequential studies of the same patient so that variation that could stem from several factors such as age and dosage was prevented.

Percent decreases in perfusion in non-tumoral regions that fall into radiation dose distribution beyond 500 cGy had a statistically significant correlation with increasing dose levels, but by including the regions that received less than 500 cGy, this correlation was lost. Among 6 regions which received less than 500 cGy and had a 14–30% decrease in perfusion, 4 regions belonged to a patient who underwent a CCNU (lomustin) and procarbazin chemotherapy regimen before cRT. This might have contributed to the perfusion decrease in these regions, as alkylating agents bind to nucleoproteins of cells including the endothelium and this could lead to vascular damage at the molecular level. In particular, patient No. 14 had a 25–30% perfusion decrease in 3 regions, none of which was expected to suffer any radiation damage at the dose distributions involved.

Although cRT is more suitable for tumors of more than 3 cm in diameter which are located near neurologically significant centers, preference for stereotactic radiotherapy in the cases of small and limited lesions in proper locations will reduce irradiation of normal tissues.[15] Furthermore, the penumbra effect is visualized in isodose distribution curve with cRT and it was 1.3 cm in isodose regions between the 20% and the 90% distribution curves in our Co-60 teletherapy device.

In conclusion, cRT has adverse effects on the perfusion of normal brain tissue for doses above 500 cGy. Linear accelerators which are regarded as the point source are to be preferred instead of the Co-60 teletherapy device to prevent the penumbra effect and localize the irradiation field more efficiently. Moreover, portal X-ray imaging should be performed as frequently as possible in order to reduce daily cRT field displacements, but patients with small and limited lesions should be treated with the stereotactic technique to minimize the adverse effects of cRT on normal tissues.

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