CNS irradiation
A comparative study of the extent of cerebral microvascular injury following whole-brain irradiation versus reduced-field irradiation in long-term survivors of intracranial germ cell tumors
Li Li a,b, Shunji Mugikura a,d, Toshihiro Kumabe c, Takaki Murata a, Etsuro Mori d, Kei Takase a, Keiichi Jingub, Shoki Takahashia

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A B S T R A C T
Background and purpose: Radiation-induced cerebral cavernous malformation reflects post-irradiation impairment of cerebral microcirculation. Our purpose was to determine effects of radiation field size and dose on the extent of developing cavernous malformations in long-term survivors of intracranial germ cell tumors (GCTs).

Methods: The study involved 34 patients with a history of intracranial GCTs treated with either whole-brain or reduced-field irradiation and undergoing magnetic resonance (MR) imaging with a mean follow-up of 18.5 years. The number of cavernous malformations on T2*-weighted MR images between whole-brain and reduced-field irradiation groups as well as between high- (50.2 Gy) and low-dose (24.4 Gy) fields were compared.

Results: A total of 235 cavernous malformation lesions were observed in 32 of 34 patients (94.1%). The mean number of lesions was 2.3 times as high in the whole-brain group as in the reduced-field group (P=0.00296). The number of lesions in high-dose fields was significantly larger than in low-dose (P<0.000001) or untreated fields (P<0.001).

Conclusion: Radiation field size and dose were positively associated with the number of cavernous malformations developed. Cavernous malformations detected on MR imaging can be used as a surrogate marker for microvascular injury following intracranial irradiation in long-term cancer survivors.

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Intracranial germ cell tumors (GCTs) are a heterogeneous group of tumors and are subclassified into germinomas and nongerminomatous GCTs; most of them are radiosensitive and generally have an excellent prognosis and good long-term survival [1]. In western countries, intracranial GCTs represent 0.4–3.4% of all pediatric brain tumors [2]. Controversy remains regarding the optimal management of intracranial GCTs [2,3]. Whole-brain irradiation plus boost is still used as a primary treatment approach so as to maintain a high cure and low relapse rate [4–6], but there have been suggestions that reduced-field irradiation could be adequate for a cure [7,8]. There is concern about the late toxic effects that might arise from irradiation of a large volume in the young-age group [9].

Cognitive impairment has been reported to occur in 40–50% of long-term cancer survivors after treatment with whole-brain irradiation [10,11]. The specific etiology of these neurocognitive deficits has not been established. However, some evidence suggests that radiation-induced cognitive impairment is linked to vascular endothelial cell loss, capillary occlusion, proliferative and degenerative glial reactions and demyelination [12–14]. The vascular hypothesis, which posits radiation-induced vascular injury, is probably the most recognized and most long-standing premise as the primary cause of radiation-induced cognitive impairment [12].

Radiation-induced vascular injury is often classified into two types: large arterial injury and cryptic vascular malformation. Large arterial injury likely represents atherosclerotic changes in larger arteries [15], whereas cryptic vascular malformations of the brain may reflect post-irradiation impairment of cerebral microcirculation [16,17]. The latter appear as hypointense foci on...
magnetic resonance (MR) T2-weighted spin-echo or T2*-weighted gradient-echo images and have been called either telangiectasias [16] or cavernous malformations [18]. Because their clinical behavior and pathologic characteristics are often similar to those of spontaneous cavernous malformations [19–21], we call them radiation-induced cavernous malformations (RI-CMs). RI-CMs were first reported in 1994 [22]; since then, additional cases have appeared in the literature. However, whether there is any quantitative relationship between radiation field size and dose on the development of RI-CMs remains unclear [23].

The purpose of the present study was to determine effects of radiation field (whole-brain versus reduced-field irradiation) and radiation dose (high- versus low-dose fields) on the extent of developing cavernous malformations in long-term survivors of intracranial GCTs.

Materials and methods

Patients and groups

The institutional ethics review board approved this retrospective cohort study and waived informed consent. A review of medical records from the radiation oncology department of a single institution between January 1983 and December 1996 identified 79 patients with newly diagnosed intracranial GCT. The study enrolled 34 consecutive subjects (29 males and five females aged 8–44 years; mean age, 15.2 years; median age, 14.0 years) who had received radiotherapy during the above period and underwent long-term follow-up with brain MR imaging at least 10 years after completion of irradiation. The 34 patients included 30 germinomas and four non-germinomatous GCTs: 13 were pathologically verified GCTs and 21 were not pathologically verified but were diagnosed as GCTs by clinical and neuroradiologic diagnostic signs. The diagnostic signs of GCT [24] included age within the typical range (8–32 years, with approximately 90% occurring before age 20 years), tumor site (usually located in suprasellar and/or pineal regions), characteristic CT and MR imaging findings, serum and/or cerebrospinal fluid levels of HCG, β-HCG and α-fetoprotein and response to radiotherapy. In 13 patients (38.2%), the primary site of the GCTs was the pineal region and in eight patients (23.5%), the primary site was the suprasellar region. Nine patients (26.5%) had multifocal tumors involving both pineal and suprasellar regions. Four patients (11.8%) had tumors in the basal ganglia.

All 34 patients underwent extended-local irradiation including the third and lateral ventricles as well as the suprasellar and the pineal regions [25]. Of them, twenty patients additionally underwent whole-brain irradiation. Therefore, our subjects were divided into two groups according to the radiotherapy received: (a) combined whole-brain and extended-local irradiation (whole-brain group; 50.2 ± 1.6 Gy; n = 20); and (b) extended-local irradiation alone (reduced-field group; total dose, 53.5 ± 2.3 Gy; n = 14). Between the whole-brain and reduced-field groups, there were no significant differences in the total dose of radiation received (P = 0.260), age at initial irradiation (P = 0.751) and administration of adjuvant chemotherapy (P = 0.409) or surgical intervention (P = 0.171). Patient characteristics are summarized in Table 1.

Details of radiation therapy

Radiation therapy was administered using a 10-MV linear accelerator. The treatment technique used for whole-brain irradiation was conventional two-dimensional (2D) helmet-field irradiation. The size of radiation fields ranged from 12 × 17 cm² to 19 × 20 cm² (mean field size, 17.0 × 18.2 cm²). The treatment technique used for extended-local irradiation was two parallel-opposed fields, with radiation fields ranging from 6 × 6 cm² to 10 × 13 cm² (mean field size, 7.8 ± 10.1 cm²). Daily fractions of 2.0 Gy were administered to the primary tumor, 5 days/week. Daily fractions of 2.4 or 2.6 Gy were administered in two patients.

MR imaging

Routine follow-up MR imaging surveillance to assess for tumor recurrence and complications of radiation therapy included axial T1-weighted spin-echo (T1WI), axial T2-weighted fast spin-echo (fast-SE T2WI) and axial gadolinium-enhanced (Magnevist, Schering AG, Berlin, Germany) T1-weighted spin-echo (post-contrast T1WI) sequences, which were performed in all patients every 1–2 years. From 2006 onward, an axial T2*-weighted gradient-echo sequence (T2*GRE) was added to the routine follow-up protocol. The T2*GRE images were available for all patients and were acquired 4.4 times on average per subject between 2006 and 2013. The most recent T2* GRE images (TR/TE = 600/26 ms, flip angle 30°, 6.0-mm sections, 1.0-mm intersection gap) acquired with a 1.5 T MR imaging system (Signa Horizon LX CV/I; GE Medical System, Milwaukee WI, USA) were analyzed for RI-CM. The mean follow-up period from completion of irradiation to RI-CM analysis was 18.5 years (range, 11.3–25.6 years) and there was no difference between the groups (P = 0.146). MR angiography (MRA) was acquired at least once in all the subjects.

Assessment of three anatomical zones on MR images and their presumed relationship to high- and low-dose radiation fields

All axial MR images were divided into three zones (zones 1, 2 and 3) in an axial plane nearly parallel to the AC–PC line from vertex to base (Fig. 1). The superior border of the corpus callosum and the superior aspect of the middle cerebellar peduncle were used as anatomic landmarks for the superior and inferior borders of zone 2. Zone 2 was roughly equivalent to the ventricular level. Zone 1 included supraventricular structures (including a transverse section through the superior border of the corpus callosum) and zone 3 contained most of the infraventricular structures (including a transverse section through the middle cerebellar peduncle). The field of extended-local irradiation was encompassed by zone 2, whereas the field of whole-brain irradiation included zones 1, 2

Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Radiation field</th>
<th>Total radiation dose (Gy)</th>
<th>Age at irradiation</th>
<th>Underwent chemotherapy</th>
<th>Underwent surgery</th>
<th>Follow-up period (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole-brain group (n = 20)</td>
<td>WB, Ex-L</td>
<td>50.2 ± 1.6</td>
<td>14.1 ± 0.7</td>
<td>10</td>
<td>7</td>
<td>19.3 ± 0.9</td>
</tr>
<tr>
<td>Reduced-field group (n = 14)</td>
<td>Ex-L</td>
<td>53.5 ± 2.3</td>
<td>16.2 ± 2.6</td>
<td>5</td>
<td>2</td>
<td>17.4 ± 1.1</td>
</tr>
</tbody>
</table>

Note: Thirty-four patients were divided into two groups based on radiation field: a combination of whole-brain and extended-local irradiation (whole-brain group) vs. extended-local irradiation alone (reduced-field group). Differences in patient characteristics between the two groups were assessed by using the Fisher’s exact test or the Mann–Whitney U test.

WB = whole-brain irradiation; Ex-L = extended-local irradiation.
The whole-brain group received whole-brain irradiation in combination with extended-local irradiation, with zone 2 consequently receiving a higher dose (50.2 ± 1.6 Gy) as compared with zones 1 and 3 (24.4 ± 1.1 Gy).

**MR image evaluation**

MR image evaluation was conducted by two neuroradiologists (L.L. and S. M., with 9 and 23 years of experience, respectively), who were each blind to the subjects’ identities. The most recent MR images including T2*GRE obtained on the 1.5 T GE MR imaging system were used for analysis. MR imaging inclusion criteria for RI-CMs was very-low-signal-intensity foci (>2 mm in diameter), indicating hemosiderin deposits, on T2*GRE images. The number of RI-CMs in each anatomic zone was counted independently by the two neuroradiologists. Any initial disagreements in interpretation were resolved by consensus. We ignored the possibility of microbleeds resulting from hypertension or cerebral amyloid angiopathy because all cases were in young adult patients. To exclude sites of treatment-related hemorrhage or post-radiation mineralization foci that could mimic RI-CMs, we excluded regions around the primary tumor bed and areas of surgical intervention, the basal ganglia and the dentate nuclei from the evaluation.

Other radiologic sequelae, including cerebral infarction, occlusion of major artery, white matter T2 hyperintensities, atrophy and meningioma, were also evaluated.

**Analysis and statistics**

To determine effects of radiation field size on the extent of RI-CMs, we compared differences in the number of RI-CMs between whole-brain and reduced-field groups using the Mann–Whitney U test. To determine effects of radiation dose, differences in the number of RI-CMs among zones in each group were examined using Tukey’s Honest Significant Difference (HSD) test. The Poisson regression model was applied because the number of RI-CMs is a non-negative integer. To account for baseline differences in individual patients, the random effect was introduced to the Poisson regression model. Combining the random effect with the Poisson regression, the generalized linear mixed effect model (GLMM) with Poisson family was used for the analysis. The statistical analyses were performed using R 3.1.1 with MASS, lme4, and glht packages. The statistical significance was defined as a two-sided P-value less than 0.05. All measurements were presented as mean ± standard error of the mean (SEM) values and median values.

**Results**

Thirty-two (94.1%) of the 34 patients developed a total of 235 RI-CM lesions. Of the 235 lesions, 50 were detectable on both T2*GRE and fast-SE T2WI sequences, while the other 185 were detectable only on the T2*GRE sequence (Fig. 2). The data acquired with T2*GRE were used for statistical analysis.

Though there was no significant difference in the prevalence (presence or not) of RI-CMs between the whole-brain and reduced-field groups (20 of 20 cases in the whole-brain group versus 12 of 14 cases in the reduced-field group, P = 0.162), the mean number of RI-CMs per patient was 2.3 times as high in the whole-brain group as in the reduced-field group (mean, 9.0 ± 1.3 versus 3.9 ± 1.0; median, 7.5 versus 2.5, P = 0.00296), as shown in Fig. 3.

We further evaluated whether there was a difference in the number of RI-CMs among zones in each group (Fig. 4). In the whole-brain group, in which zone 2 received high-dose exposure (50.2 ± 1.6 Gy) and both zones 1 and 3 received low-dose exposure (24.4 ± 1.1 Gy), the observed mean numbers of RI-CMs were 6.6 ± 1.1 (median, 5.0) in zone 2, 1.3 ± 0.3 (median, 1.0) in zone 1 and 1.2 ± 0.3 (median, 1.0) in zone 3 (P < 0.00001), revealing a difference between irradiated and unirradiated areas. In addition, comparing zone 2 of the whole-brain group with that of the reduced-field group, there was a trend toward a higher number of RI-CMs in the whole-brain group (mean, 6.6 versus 3.7; median, 5.0 versus 2.5), though this difference did not reach statistical significance (P = 0.082).

During the observation period between 2006 and 2013, we observed increases in the number of RI-CMs in some cases and acute/subacute hemorrhage showing hyperintensities on T1WI in three cases. One patient reported a severe headache with vomiting 12 h prior to undergoing MR imaging, which revealed an acute hemorrhagic lesion in the splenium of the corpus callosum with intraventricular rupture and subarachnoid hemorrhage (Supplementary Fig. S1). As this lesion appeared in a location different from the sites of preexisting RI-CMs, it was interpreted as an interval appearance of a new RI-CM, followed by hemorrhage. In the other two patients, MR images revealed asymptomatic subacute hemorrhage (not shown).

Besides RI-CM, other radiological sequelae were also observed in long-term survivors (Table 2). There were no significant differences between the whole-brain and reduced-field groups in terms of the presence of cerebral infarction (P = 0.449), major artery occlusion (P = 0.672), white matter T2 hyperintensities (P = 0.378), brain atrophy (P = 0.080) or meningioma (P = 0.449).

**Discussion**

We investigated radiation-induced cavernous malformations (RI-CMs) in patients with intracranial GCT for a mean follow-up period of 18.5 years after radiation treatment and compared effects of whole-brain irradiation versus reduced-field irradiation based on the number of developing lesions. The mean number of RI-CMs per patient was 2.3 times as high in the whole-brain irradiation group as in the reduced-field irradiation group (P = 0.00296).
though the total radiation dose received was not significantly different between these groups (50.2 ± 1.6 Gy versus 53.5 ± 2.3 Gy; \(P = 0.260\)). This indicates that a larger radiation field is associated with a larger number of RI-CMs. It has been suggested that RI-CMs reflect post-irradiation impairment of cerebral microcirculation with preferential involvement of the venous endothelium, with resultant veno-occlusive changes and induction of vascular malformation [16,17,26]. Given that RI-CM is one indicator of post-irradiation impairment of cerebral microcirculation, larger radiation fields would be associated with a more extensive area of impairment in cerebral microcirculation, possibly related to cognitive decline reported in children undergoing whole-brain irradiation.

Comparing zone 2 of the whole-brain group to that of the reduced-field group, there was a trend toward a higher number of RI-CMs in the whole-brain group. This trend might be related to a difference in radiation fields between the zone 2 regions in the two groups; the areas in front of and behind the ventricle in zone 2 were included within the radiation field in the whole-brain group, but not in the reduced-field group.

In some studies of radiation dose as a risk factor, investigators found that patients that had received a higher dose of radiation showed a shorter latency period for cavernous malformation development in the treatment field [27]. Koike and colleagues studied the relationship between radiation dose and prevalence (presence or absence) of RI-CMs and found that the prevalence of RI-CMs did not differ significantly between the high- and low-dose radiation fields, despite a tendency to be higher in the field of high-dose radiation [17]. We focused on the relationship between radiation dose and extent (number) of RI-CMs and confirmed a positive relationship between these parameters; the number of RI-CMs in the high-dose field was significantly higher than in the low-dose fields, which had never before been documented. The increased number of cavernous malformations in high-dose fields may argue for low-dose irradiation for germ cell tumors whenever feasible.

Our results suggest that the risk of cerebral microvascular injury associated with radiotherapy needs to be considered when treatment is planned. This is especially true in cases of low-grade tumors because the adverse effects of irradiation, especially late sequelae, are of major concern considering the expected long survival of the patients. For treatment of intracranial GCTs, optimal management of radiotherapy remains an important topic [3,28]. A radiation field encompassing the whole brain is still widely used.
[4–6,29] because local irradiation alone to the tumor has been associated with an unacceptable relapse rate of about 15–40% [6,8,30]; most of these reported relapses developed in periventricular areas outside the radiation field [8]. To balance the trade-off between optimal treatment outcome and long-term adverse effects, chemotherapy followed by reduced-dose (24-Gy) reduced-field (whole-ventricle) irradiation was proposed by the Japanese Pediatric Brain Tumor Study Group [25,31]. With this approach, most relapses were avoided [7,8] and no difference was found in the 10-year overall survival rate following whole-ventricle irradiation as compared with whole-brain irradiation [7]. This guideline has been followed at our institution since 1997 [7] and patients who received whole-brain irradiation before 1997 were enrolled in the present study. To our knowledge, ours is the first comparative radiological study based on the extent of cerebral microvascular injury following whole-brain irradiation versus reduced-field irradiation.

Our study showed a very high prevalence of RI-CMs (94.1%). Most previous studies estimated the prevalence of RI-CMs as between 1.2% and 56% [32]. The wide variation probably derives from differences in MR imaging sequences, age at initial irradiation, radiation dose received, length of follow-up interval and presence or absence of chemotherapy. In the study of Koike et al., in which the prevalence of very-low-signal-intensity foci was 20% in pediatric patients with various brain tumors at 4.2 years after radiotherapy, the sequence employed was spin-echo or fast spin-echo T2WI. In contrast, we used a T2*GRE sequence and a much longer follow-up interval (18.5 years) in pediatric or young adult cases of intracranial GCTs. This may explain the higher prevalence that we observed.

A limitation of our study is that spontaneous cavernous malformations (not RI-CMs) might have been included in our RI-CMs counts; these are indistinguishable on T2*GRE imaging. The exact incidence of spontaneous cavernous malformations (not RI-CMs) is not known, though it was reported to be only 0.5–0.7% by Zabramski et al., in a study using T2WI instead of T2*GRE imaging [20,33]. This may have caused miscounting of RI-CMs because baseline T2*GRE imaging before radiotherapy was not obtained. In addition, though very-low-signal-intensity foci in the basal ganglia (especially symmetric ones in the Globus pallidus) and dentate nuclei were eliminated from the counting, those in cortical/subcortical regions were counted as RI-CMs. Some of these might have been mineralization foci instead of RI-CMs, indicating another potential limitation of our study.

In conclusion, radiation-induced cerebral cavernous malformations occur with extraordinary frequency in long-term survivors of cancer. We first demonstrated that the radiation field (whole-brain versus reduced-field irradiation) and radiation dose (high- versus low-dose) were associated with the number of cerebral cavernous malformations detected, which reflects the extent of cerebral microcirculatory impairment and might influence neurocognitive status in long-term survivors of these neoplasms. Our results help to inform the balance between risks and benefits that guide treatment decisions. T2-weighted gradient-echo sequence should be included in routine MRI follow-ups to detect and evaluate cerebral cavernous malformation, which can be used as a surrogate marker for microvascular injury post-irradiation in cancer survivors.

Conflict of interest statement
None declared.

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Appendix A. Supplementary data
Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2015.09.017.

References


