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Original article

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

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ABSTRACT

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, while studies from Japan have reported that GCTs account for up to 11% of 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

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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 $12 \times 17\ cm^2$ to $19 \times 20\ cm^2$ (mean field size, $17.0 \times 18.2\ cm^2$). The treatment technique used for extended-local irradiation was two parallel-opposed fields, with radiation fields ranging from $6 \times 6\ cm^2$ to $10 \times 13\ cm^2$ (mean field size, $7.8 \times 10.1\ cm^2$). 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 and 3. 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).

Table 1
Patient characteristics.

Patient	Radiation field*	Total radiation dose (Gy)	Age at irradiation	Underwent chemotherapy	Underwent surgery	Follow-up period (y)
Whole-brain group ($n = 20$)	WB, Ex-L	50.2 ± 1.6	14.1 ± 0.7	10	7	19.3 ± 0.9
Reduced-field group ($n = 14$)	Ex-L	53.5 ± 2.3	16.2 ± 2.6	5	2	17.4 ± 1.1
		$P = 0.260$	$P = 0.751$	$P = 0.409$	$P = 0.171$	$P = 0.146$

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.

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