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Secondary brain tumors after cranial radiation therapy: A single-institution study

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ABSTRACT

Aim: To study the probability of developing secondary brain tumors after cranial radiotherapy.

Background Patients treated with cranial radiotherapy are at risk for developing secondary brain tumors.

Patients and methods: We planned an institutional survey for secondary brain tumors in survivors after cranial irradiation and reviewed the 30-year duration data. Event analysis and cumulative proportion curves were performed to generally estimate the cumulative proportion of developing secondary brain tumors, cavernoma and meningioma at different periods of time.

Results: Secondary brain tumors occurred in 21% of cases: 10% were cavernomas, 6% were meningiomas, 3% were skull osteomas, and 1% were anaplastic astrocytoma. The cumulative proportion of developing secondary brain tumor was 6% at 10 years and 20% at 20 years, while the cumulative proportion for developing cavernomas and meningiomas was 16% and 7% at 20 years, respectively.

Conclusion: Our study shows that patients who received cranial irradiation were at risk of secondary brain tumors such as cavernomas and meningiomas. Thus, a meticulous follow-up of cancer survivors with history of cranial irradiation by an annual MRI scan is justifiable. This will help clinicians to detect secondary brain tumors early and make its management much easier.

1. Background

Radiotherapy is commonly used to treat various brain lesions. Patients treated with cranial radiotherapy are at risk for long-term neurological complications such as progressive leukoencephalopathy, arteritis, hypothalamic-pituitary axis insufficiency, optic neuritis, and other secondary malignancies. Since the prognosis for cancer patients is improving, the chance of developing secondary brain tumors is increased in long-term survivors who received cranial irradiation. We previously reported three patients with WHO grade 2 meningiomas after prophylactic cranial irradiation for acute lymphoblastic leukemia (ALL) in childhood.[1] Two of them received cranial irradiation in our institute. Accordingly, we planned an institutional survey of secondary brain tumors in cancer survivors after cranial irradiation. Although multi-institutional studies have demonstrated the risk of secondary brain tumors, single-institutional studies can help to outline the risks of secondary brain tumors to inform physicians, patients and their families.

2. Patients and methods

In 2013, we initiated an institutional survey of secondary brain tumors after cranial radiation therapy. To include the patients who received cranial radiation therapy with an existing follow-up of five years or more, we studied the clinical charts of cases with a history of cranial irradiation from 1980 to 2008. A total of 1112 patients received cranial radiation therapy in our institute. Deceased cases, patients with metastatic brain tumors or primary malignant brain tumors in terminal stages, and patients older than 70 years old at April 2013 were excluded. Consequently, clinical records of 143 patients were included and followed until April 2019.

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Event analysis and cumulative proportion curves were performed to estimate the cumulative proportion not only to develop secondary tumors in general but also for specific types of secondary tumors (cavernomas and meningiomas). Descriptive data analysis results are expressed in mean ± standard deviation (SD). The whole statistical analysis was done using SPSS (version 25.0). This study was approved by our local Institutional Review Board (#1614).

3. Results

In April 2019, 77 living patients with available follow-up head MRI data were included in the study: 39 (51%) females and 38 (49%) males. Their ages at the time when they received cranial radiation therapy ranged from 0 to 68 years old (19.9 ± 20.1). Of the patients, 28 (36%) received cranial irradiation for ALL and 49 (64%) for cranial tumors (13 gliomas, 8 germ cell tumors, 5 medulloblastomas, 5 malignant lymphomas, 5 craniopharyngiomas, 4 pituitary adenomas, 3 meningiomas, and 6 other types). The radiation dose ranged from 10 to 60 Gy (27.96 ± 12.38), excluding one case who received a total of 99 Gy due to repeated irradiation for a recurrent medulloblastoma. The time from the first dose of cranial radiation therapy until the date of the follow-up brain MRI scan that showed a secondary brain tumor ranged from 43 to 420 months (185 ± 81).

Secondary brain tumors occurred in 16 (21%) patients out of 77 cases: 8 (10%) cavernomas (6 males and 2 females), 5 (6%) meningiomas (3 males and 2 females), 2 (3%) skull osteomas (2 females), and 1 (1%) anaplastic astrocytoma (1 male). Among eight patients with cavernomas, four had multiple cavernomas. Two of them required surgical resection: one received a single surgical resection and the other received repetitive s ones (Illustrative case 1). The remaining four patients had a single cavernoma, with one of them requiring surgical resection (Illustrative case 2). Additionally, six patients with cavernomas had microbleeds beside the existing cavernomas. Among five meningioma cases, two with WHO grade 2 (previously reported by our group) and one with WHO grade 1 required surgical excision.[1] The first case was a parasagittal atypical meningioma with maximal diameter of 43 mm, which was completely removed but required resection in two different stages due to recurrence. The second case was a cerebellopontine angle atypical meningioma with a maximal diameter of 35 mm and was partially removed. The remnant tumor was treated with a gamma-knife radiosurgery, but the recurrent tumor required repeated stereotactic radiosurgeries. The third case was a frontal convexity WHO grade 1 meningioma with maximal diameter of 40 mm and was totally excised. The remaining two cases were falx meningiomas with maximal diameters of 14 mm and 10 mm, and were observed and followed with serial MRI scans.

The cumulative proportion of developing secondary brain tumor was 6% at 10 years and 20% at 20 years (Fig. 1), while the cumulative proportion of developing cavernomas and meningiomas at 20 years was 16% and 7%, respectively (Figs. 2 and 3). At the start of radiation therapy, the average ages of cases that developed secondary brain cavernoma and meningioma tumors were 11.4 ± 9.6 years and 8.6 ± 4.8 years, respectively. The average time periods until the diagnosis of secondary brain cavernoma and meningioma tumors were 143 ± 84 months and 280 ± 108 months, respectively. The average radiation doses for patients that developed secondary brain cavernoma and meningioma tumors were 35.8 ± 29.6 Gy and 26.0 ± 9.3 Gy, respectively.

Among 16 patients with secondary brain tumors, 10 received cranial radiation therapy for ALL and six for primary brain tumors. The average age at radiation therapy of patients with secondary brain tumors was 9.6 ± 7.3 years old, which was significantly younger than the ages of patients without secondary brain tumors: 22.6 ± 21.5 years old ($p < 0.05$). The radiation doses of patients with and without secondary brain tumors were 31 ± 22 and 28 ± 12 Gy, respectively.

4. Illustrative cases

4.1. Case 1

A 16-year-old male was referred from the pediatric department due to headache for one week, while brain CT scans showed a right temporal stem hematoma. Follow-up CT after one week showed an increase in the size of the hematoma. An MRI revealed that the bleeding source was a cavernoma 25 mm in diameter; additionally, there was another one in the right frontal lobe (Fig. 4). He had received 18 Gy for whole brain irradiation for ALL when he was seven years old. The cavernoma in the temporal stem was surgically resected. Postoperatively, he had mild left hemiparesis. At the 10-year follow-up, no recurrence and no change regarding the size of the other cavernoma in the right frontal lobe were detected.

4.2. Case 2

A 36-year-old male was referred to us due to a growing left temporal multi-lobulated cavernoma 26 mm in maximal diameter (Fig. 5). He had received 24 Gy for whole brain and 24 Gy for local irradiation for pineal germinoma when he was 30 years old. Eighteen months earlier, MRI scan revealed a small cavernoma. The cavernoma was surgically resected. At the six-year follow-up, no recurrence and no other new cavernomas were detected.

5. Discussion

Since many cancer patients now achieve long-term survival, adverse effects, including secondary brain tumors, years later are seen more and more often. Regarding secondary brain tumors, cavernomas, meningiomas, gliomas, and sarcomas were reported after cranial irradiation for ALL or cranial tumors including malignant brain tumors or benign brain tumors such as pituitary adenomas.[2,3] In the Childhood Cancer Survivor Study, 66 meningiomas, 40 gliomas and 10 other CNS tumors were found within a cohort of 116 survivors of childhood cancers.[4] The most common dose range that might have caused post-radiation secondary brain tumors was found to be a moderate dose with a range of 20–36 Gy.[5] The relative risks of secondary meningiomas and gliomas after 25 Gy irradiation dose in childhood cancer survivors were about 30% and 10%, respectively.[6] In the British Childhood Cancer Survivor Study, a cohort study of 17,980 cases, 137 meningiomas, 73 gliomas, and 37 other CNS tumors were reported.[7] Galloway et al. reported that the actual incidences of secondary tumor in pediatric patients were 8% and 24% at 20 and 30 years, respectively, and most secondary tumors were meningiomas.[8] Vinchon et al. reported a cumulative incidence of 8.9% at 10 years representing 60 cavernomas, 26 meningiomas, 2 malignant gliomas, and other cranial lesions.[9] In the Tokyo Children's Cancer Study Group protocols, the cumulative incidence in patients who received cranial radiation therapy for ALL was 2.9% at 20 years.[10]

In our study, the cumulative incidence of secondary brain tumors was 20% at 20 years, and the most frequent tumor was cavernoma. Since many cavernomas grow to the size requiring surgical resection, we believe that it should be considered an intracranial tumor despite its vascular origin and, moreover, should be included in our secondary brain tumors after cranial radiation list. Cavernomas seem to appear earlier after radiation therapy compared to meningiomas.[9] Median latency from radiation to radiation-induced cavernoma was previously observed to be 8.9–12 years.[11,12] In accordance to our findings, the major-

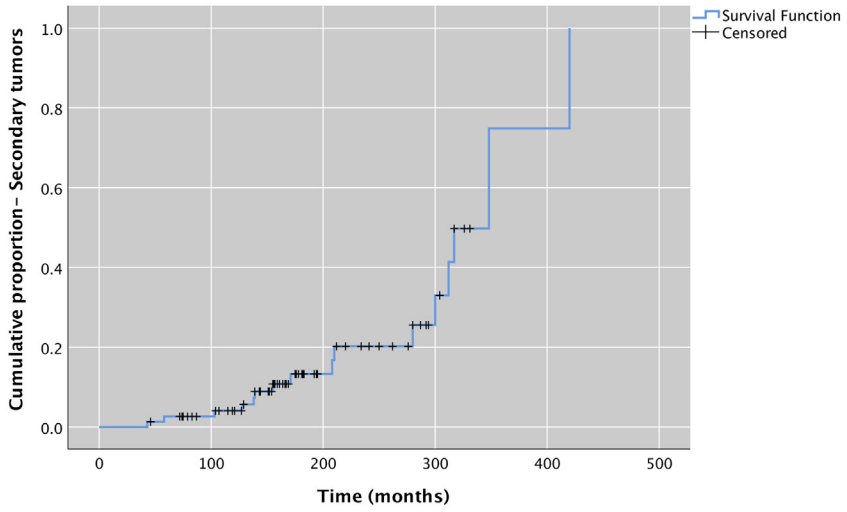

Fig. 1. Cumulative proportion curve for cranial-irradiated patients who developed secondary brain tumors.

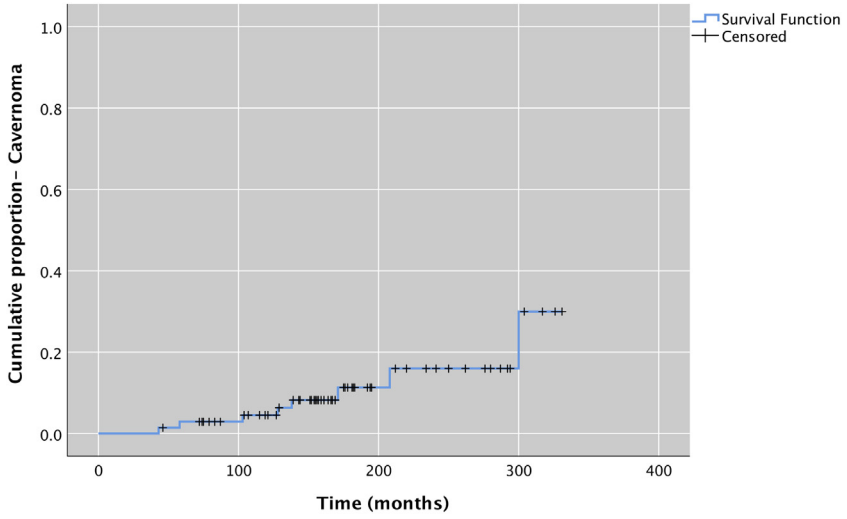

Fig. 2. Cumulative proportion curve for cranial-irradiated patients who developed secondary cavernomas.

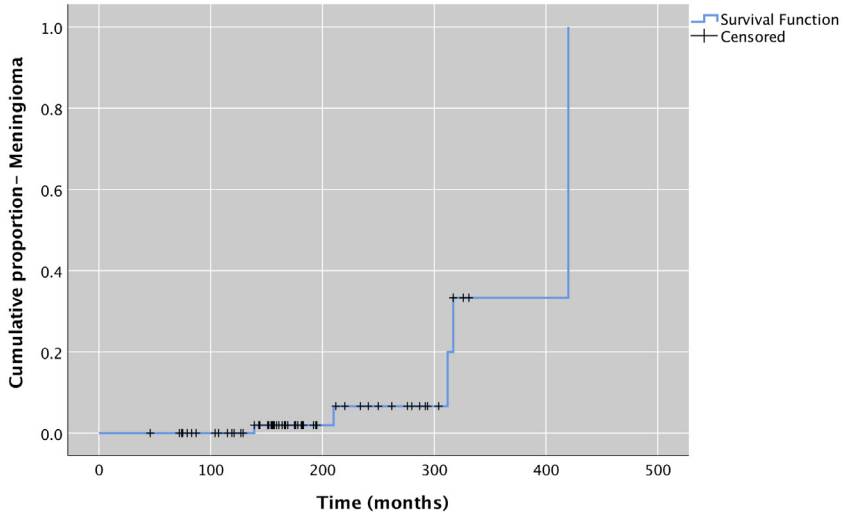

Fig. 3. Cumulative proportion curve for cranial-irradiated patients who developed secondary meningiomas.

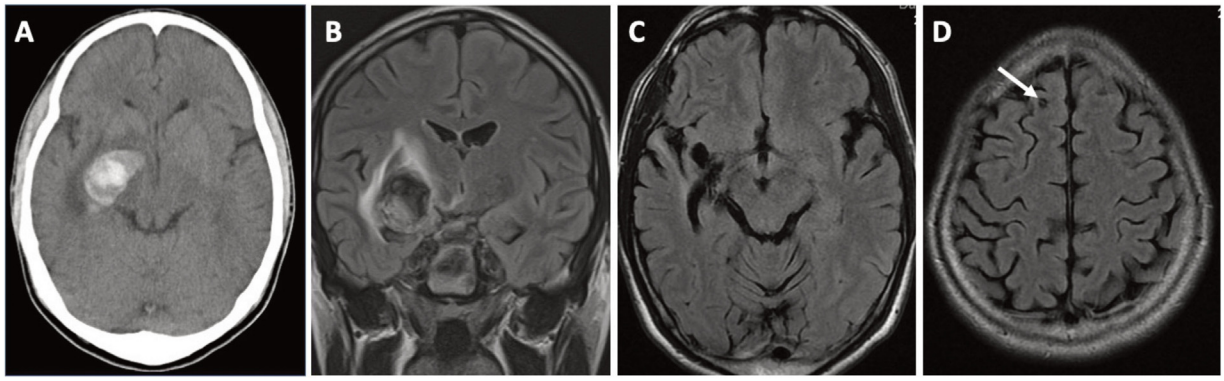

Fig. 4. Case 1. Axial plain CT scan (A) and coronal MRI FLAIR (B) images show a cavernoma in the right temporal stem. Postoperative follow up MRI FLAIR images show removal of the right temporal cavernoma (C) and the remaining small right frontal cavernoma (D, arrow).

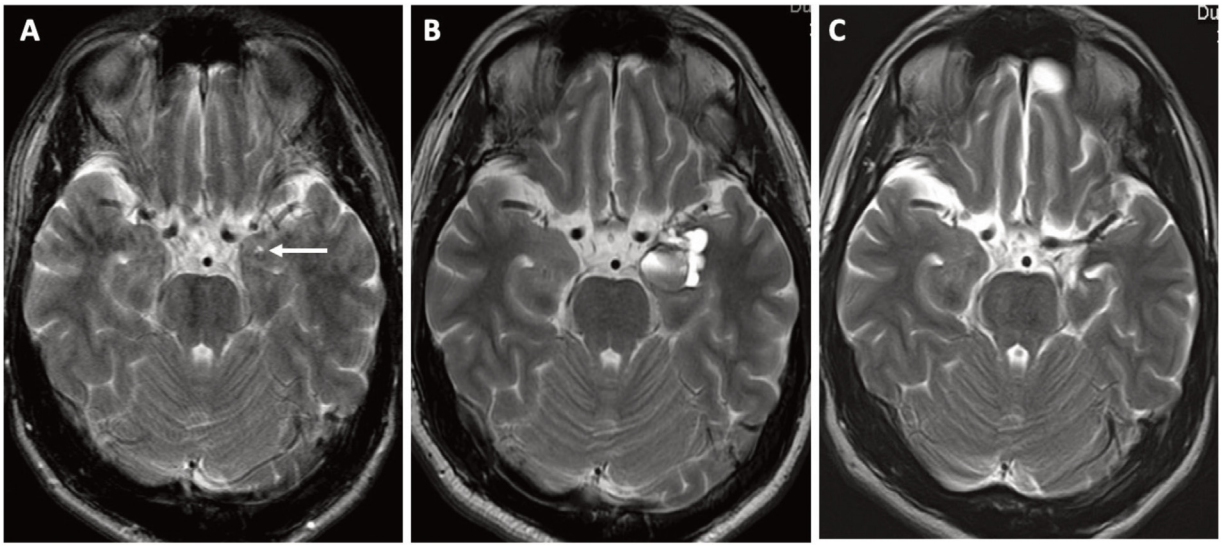

Fig. 5. Case 2. T2-weighted MRI images. Images taken 18 months before surgery (A) and before surgery (B) show an increase in the size of a left temporal cavernoma. Postoperative follow-up image shows removal of the cavernoma (C).

ity of cavernomas have occurred in males.[9,12] Radiation-induced cavernomas were more likely to be multiple and were associated with symptomatic intracranial hemorrhage at any time in 43.8% of cases. The risk of symptomatic hemorrhage was 4.2% per person-year, higher than 2.3% for non-radiation cavernomas.[11] In another report, 37% of radiation-induced cavernomas showed evidence of hemorrhage, and 54% of these required surgical intervention.[12] The incidence of radiation-induced microbleeds was even higher, as it was found in 16 (47%) of 34 patients by phase-sensitive 3.0 Tesla MRI.[13] The percentage of cerebral microbleeds in pediatric patients with brain tumors treated with proton beam radiation therapy was 83% at five years.[14]

We found five meningiomas after cranial radiation, including two atypical meningiomas. Upon reviewing the radiation-induced meningiomas, the average age at onset of the primary lesion was 13 years and the average radiation dose was 38.8 Gy. The risk of meningioma increased rapidly with increased dose of radiation.[7] The average latency from radiotherapy to developing a radiation-induced meningioma was around 20 years.[15–17] The estimated cumulative incidence in childhood cancer survivors was 10–30%.[6,17,18] Radiation-induced meningiomas are often aggressive, either atypical or anaplastic types.[1,19] Additionally, the mutational landscape of radiation-induced meningiomas was found to be distinct from sporadic meningiomas.[20]

We only had one malignant glioma in our sample, which occurred in a 23-year-old patient after irradiation for ALL. Incidence of radiation-induced gliomas is estimated to be at 0.5–2.7% with a latent period of approximately 15 years.[21] Additionally, glioma develops earlier than meningiomas.[4] In a review of radiation-induced gliomas, the median latency was about 9 years.[22,23] Characteristic glioma-associated molecular mutations may be rare events in radiation-induced gliomas.[24]

A drawback of this survey is that we could not import the dosimetry plan from the old clinical records, and we cannot define precisely the radiation dose delivered to the sites of the secondary tumors. Our survey revealed that patients who had received cranial irradiation were at risk of secondary brain tumors such as cavernomas and meningiomas, particularly if they received irradiation at a younger age. The risk of chemotherapy with irradiation has been controversial. In addition, a previous study showed that the risk of meningioma increased rapidly both with increased dose of radiation and with increased dose of intrathecal methotrexate.[7] After adjustment for radiation dose, neither original cancer diagnosis nor chemotherapy were found to be associated with the risk of post-radiation second tumor.[4]

We recommend an annual MRI follow-up scan of the head post radiation therapy to promote early detection of potential secondary brain tumors, since lesions like meningiomas and gliomas are better treated in early stages than later ones which are difficult to manage.

6. Conclusion

We conducted an institutional survey for secondary brain tumors in survivors after cranial irradiation and reviewed the 30-year duration data. Secondary brain tumors occurred in 21% of cases, and the majority of them were cavernomas. The cumulative proportion of developing secondary brain tumor was 20% at 20 years. Our study shows that patients who received cranial irradiation were at risk of secondary brain tumor. Thus, a thorough follow-up of cancer survivors with history of head irradiation with annual MRI scan is justifiable. This will help clinicians to detect secondary brain tumors early and make its management much easier.

Conflict of interest

None declared.

Financial disclosure

None declared.

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