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CLINICAL ARTICLE

Characteristics of radiation-induced brain tumors: case series and systematic review

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OBJECTIVE Radiation therapy (RT) improves the outcome of patients with cancer but introduces the risk of radiation-induced neoplasms in cancer survivors. The most common radiation-induced brain tumors (RIBTs) are gliomas (RIGs), meningiomas (RIMs), and sarcomas (RISs). To investigate the characteristics of these RIBTs, the authors conducted a comprehensive review and analysis of their case series and relevant cases from the literature.

METHODS Sixteen patients in the case series and 941 patients from the literature who previously underwent cranial irradiation were included in this study. The age at irradiation for primary disease was recorded, and the latency period from irradiation to the development of RIBT and the median overall survival (OS) of patients with RIBTs were analyzed using the Kaplan-Meier method. Patients were stratified by age at the time of irradiation (pediatric vs nonpediatric) and the irradiation dose (higher vs lower dose), and latency and OS were compared using the log-rank test.

RESULTS Among patients with RIBTs, 23.4% underwent radiation at < 5 years of age, and 46.6% underwent RT in the 1st decade of life. The median ages at cranial irradiation were 8.4 (IQR 4.1–16) years in patients with RIMs, 9 (IQR 5–23) years in patients with RIGs, and 27.7 (IQR 13.8–40) years in patients with RISs. The median latency period from irradiation to the development of RIM was significantly longer than that to the development of RIG and RIS (RIM: 20 years, RIG: 9 years, RIS: 10 years; $p < 0.0001$). The latency period was shorter in the nonpediatric patient group with RIMs ($p = 0.047$). The OS was significantly longer in patients with RIMs than in those with RIGs and RISs (RIM: not reached, RIG: 11 months, RIS: 11 months; $p < 0.0001$). The OS of patients with RIMs and RIGs was significantly shorter in patients who received higher radiation doses ($p = 0.0095$ and $p = 0.0026$, respectively).

CONCLUSIONS The prognosis was poor and worse for patients with RIGs and RISs than for those with RIMs, and patients with RIBTs who underwent higher-dose irradiation for primary disease had poor prognoses. Because RIBTs develop more than a decade after cranial irradiation, long-term follow-up is crucial.

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KEYWORDS radiation-induced brain tumor; glioma; meningioma; sarcoma; oncology; tumor

Radiation therapy (RT) is a crucial component in the treatment of various cancers.[1] Although cranial RT improves the outcomes of patients with cancer and brain tumors,[2,3] related long-term adverse events, such as radiation-induced neoplasms (e.g., brain tumor,[4] skin neoplasms, or thyroid cancers[5]), vascular malformation (cavernous malformation,[6] vascular arteriopathy, or moyamoya disease[7]), leukoencephalopathy,[8] cystic malacia,[9] cognitive impairment,[10] and hypothalamic-pituitary dysfunction[11] need to be considered. The association between radiation exposure and the development of brain tumors has been demonstrated in epidemiological studies of atomic bomb survivors,[12–14] radiation exposure for tinea capitis,[15] and reports from cancer survivors.[16]

A previous systematic review showed that the risk of secondary brain tumors was higher in childhood cancer

ABBREVIATIONS COG = Children's Oncology Group; IDH = isocitrate dehydrogenase; OS = overall survival; RIBT = radiation-induced brain tumor; RIG = radiation-induced glioma; RIM = radiation-induced meningioma; RIS = radiation-induced sarcoma; RT = radiation therapy.

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survivors than in the general population and that most patients with secondary brain tumors had been exposed to cranial irradiation.[16] In the SEER (Surveillance, Epidemiology, and End Results)–based analysis, cancer survivors or patients with pediatric low-grade gliomas treated with RT showed a higher incidence of secondary neoplasms, including brain tumors, than those without RT.[17,18] Additionally, a large, long-term image surveillance study of pituitary adenoma or craniopharyngioma showed that RT increased the risk of secondary brain tumors.[19]

Secondary brain tumors after RT, so-called radiation-induced brain tumors (RIBTs), are important clinical issues for cancer survivors after RT. The most common RIBTs are gliomas (RIGs),[20] meningiomas (RIMs),[21] and sarcomas (RISs).[22] RIBTs require additional treatment, and some are life-threatening. The Children's Oncology Group (COG) long-term follow-up guideline recommends annual physical examinations for children, adolescents, and young adult cancer survivors who have received cranial irradiation and MRI screening for symptomatic patients.[23] However, there is no doubt that early detection is desirable because treatment of brain tumors may become more difficult once they become symptomatic. Unfortunately, an appropriate MRI follow-up program has not been established because of the cost and risk of unnecessary follow-up.[24] There have been no reports on integrated analyses of RIBTs. The aim of this study was to conduct a comprehensive analysis of a case series and cases of patients with cancer in the literature who developed RIBTs to clarify the integrated characteristics of RIBTs (RIMs, RIGs, and RISs) and assess the difference in survival of patients with cancer after the development of RIBTs, with the goal of providing better follow-up and treatment strategies for RIBTs.

Methods

Study Design

This retrospective study was approved by the Ethical Committee for Epidemiology of Hiroshima University. Because of the retrospective nature of the study, the committee waived the need to obtain informed consent. All methods were performed in accordance with the relevant guidelines and regulations.

Criteria for RIBTs

In this study, tumors identified as RIBTs had to meet the following criteria. 1) The tumor arose within an irradiated field. 2) The secondary tumor was histologically distinct from the primary tumor. 3) A sufficient latency period had passed between the irradiation time point and development of the second tumor. Although DNA damage caused by RT occurs soon after irradiation, the length of a sufficient latency period has not been established. In fact, there has been a wide range of variation in the latency period following high-dose irradiation, so it remains uncertain, including in this study, whether brain tumors are induced by RT or not. Therefore, we included RIBTs with > 10-month latency periods. 4) Patients with RIBTs were required to have no genetic history of cancer predisposition (e.g., Li-Fraumeni syndrome, Gorlin syndrome, or neurofibromatosis). In addition, patients with retinoblastoma were excluded because germline pathogenic variants of the RB1 gene were reported in approximately 40% of patients with retinoblastoma.[25]

Selection of the Case Series

Medical records for all patients with surgically confirmed gliomas, meningiomas, and sarcomas treated at our institution from 2008 to 2022 were reviewed, and patients with gliomas, meningiomas, and sarcomas who had undergone RT were identified. Patients without pathological confirmation and those with a genetic history of cancer predisposition were excluded from the study.

Selection of Articles and Literature Review

The systematic review was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria. Two authors (S.O. and F.Y.) conducted a systematic literature search for articles related to RIGs, RIMs, and RISs of the central nervous system or the cranium in the PubMed database until December 31, 2022, respectively. For RIM, the search terms included "radiation-induced meningioma," and any of the terms "meningioma," "secondary meningioma," were searched along with "radiation-induced," "radiotherapy-induced," and "after radiation." For RIG, the terms "glioma," "glioblastoma," and "gliosarcoma," were searched along with "radiation-induced," "radiotherapy-induced," and "after radiation." For RIS, the search terms included "sarcoma," "osteosarcoma," "fibrosarcoma," "malignant fibrous histiocytoma," "leiomyosarcoma," "chondrosarcoma," "radiation-induced," "radiotherapy-induced," "craniospinal," and "central nervous system."

We obtained all articles that were potentially eligible for inclusion in our review. The references listed in all potentially eligible articles were inspected to identify other eligible articles. Review articles that did not report original individual patient data were excluded; however, their references were checked for other eligible articles. The literature review and study selection process are summarized in Fig. 1.

Statistical Analysis

We evaluated factors influencing differences in latency years from irradiation to the development of RIBTs by performing Kaplan-Meier analyses between groups based on the pathological type of RIBTs and age at irradiation. The overall survival (OS) of patients with RIBTs was also analyzed by Kaplan-Meier analysis between groups based on the pathological type of RIBTs and age at irradiation. The log-rank test was used to compare the latency period and OS between the groups. The level of statistical significance was set at $p < 0.05$. JMP Pro version 17.0 (SAS Institute) and GraphPad Prism version 7.00 for Mac (GraphPad Software) were used for statistical analyses.

Results

Case Series and Cases From the Literature Review

Our institutional case series included 16 cases (7 cases

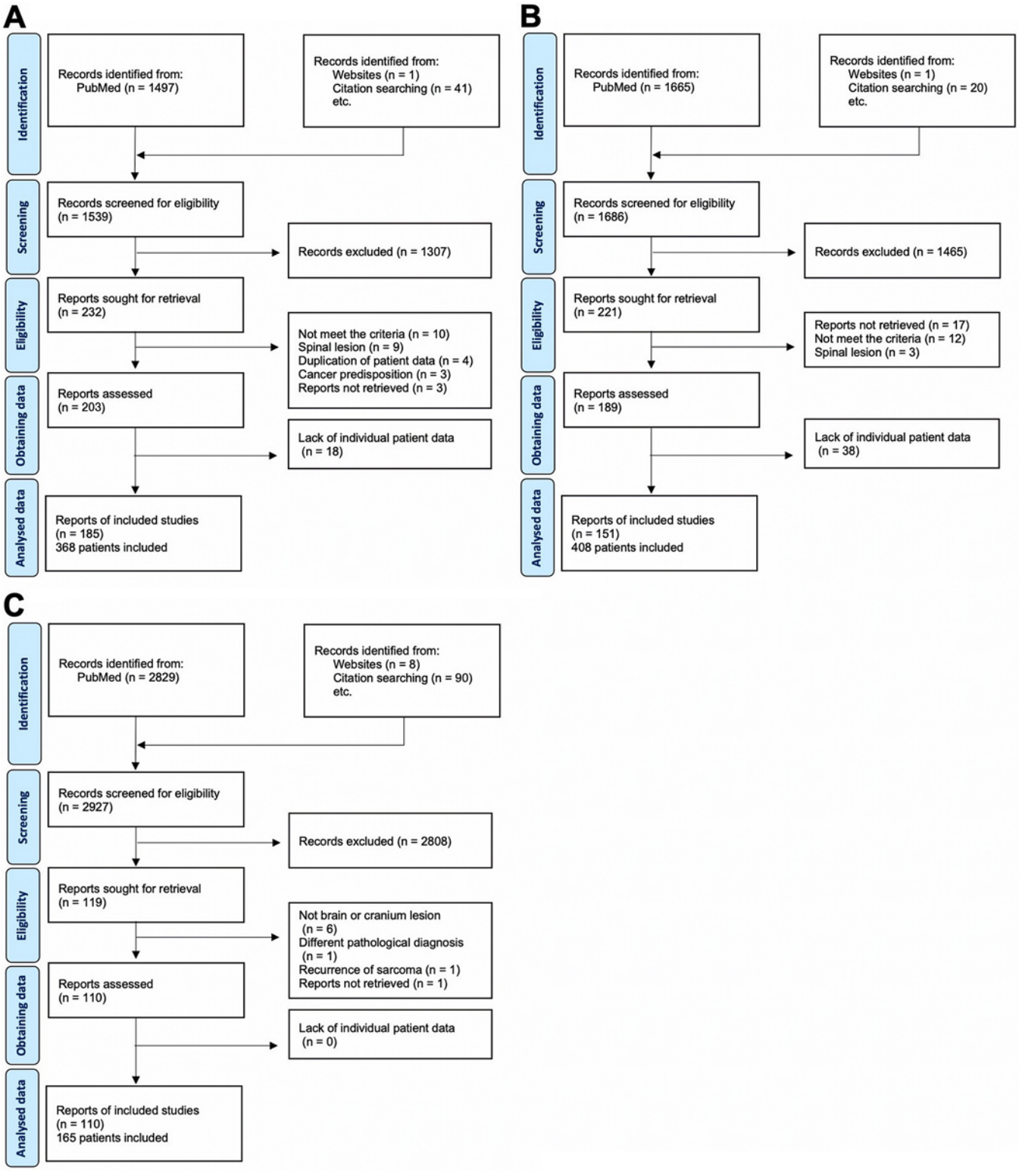

FIG. 1. Flow diagram showing the selection of studies in the systematic review of RIGs (**A**), RIMs (**B**), and RISs (**C**). Figure is available in color online only.

TABLE 1. Patients with different types of metachronous and simultaneous RIBTs

Authors & Year	Age at RT, yrs	Sex	Primary Disease	RT Dose, Gy	Type of RIBT	Pathology of RIBT	Latency, yrs	Age at Development of RIBT, yrs	Treatment for RIBT
Kumar et al., 1987[30]	1	F	Medulloblastoma	65	1st: RIM	Atypical meningioma	12	13	Surgery
					2nd: RIS	Polymorphous cell sarcoma	13	14	Surgery, ^{125}I seeds
Hope et al., 2006[27]	15	M	Medulloblastoma	54	1st: RIM	Atypical meningioma	18	33	Surgery
					2nd: RIG	Anaplastic astrocytoma	24	39	Surgery, chemo (TMZ, PCV)
Sasayama et al., 2008[28]	1	M	Medulloblastoma	30	1st: RIM	Meningotheliomatous meningioma	23	24	Surgery
					2nd: RIG	Anaplastic astrocytoma	28	29	Surgery, chemo (TMZ)
Kon et al., 2013[29]	16	F	Pituitary adenoma	50	1st: RIM	Fibrous meningioma	22	38	Surgery
					2nd: RIG	Glioblastoma	30	46	Surgery, chemo (ACNU, TMZ)
Takase et al., 2021[31]	8	M	Anaplastic ependymoma	51	1st: RIM	Fibrous meningioma	41	49	Surgery
					2nd: RIG	Glioblastoma, IDH-wildtype	41	49	Surgery, chemo (TMZ), RT
Current case	15	M	Acute lymphocytic leukemia	24	1st: RIM	Meningioma	41	56	Surgery
					2nd: RIG	Glioblastoma, IDH-wildtype	45	60	Surgery, chemo (TMZ), RT

ACNU = nimustine hydrochloride; chemo = chemotherapy; PCV = procarbazine, lomustine, and vincristine; TMZ = temozolomide.

of RIGs, 8 cases of RIMs, and 1 case of an RIS). Some of our cases have been published previously.[20–22] From the comprehensive literature review, we identified 185 articles on RIGs, 151 articles on RIMs, and 110 articles on RISs that met the inclusion criteria. A patient with a secondary brain tumor diagnosed as a pilocytic astrocytoma 6 months after radiotherapy for craniopharyngioma was excluded from the study because of the short latency period.[26] The details of the RIBT cases from the literature review and of our case series are shown in Supplemental Table 1. The information from the published cases and from our case series at our institution was analyzed. Finally, 957 patients were included in this study.

Demographics of Patients With RIBTs

The patient age at irradiation for primary disease was available in 927 cases. Among these patients with RIBTs, 23.4% had undergone RT before the age of 5 years and 46.6% had undergone RT before the age of 10 years. The demographics of the age at irradiation are shown in Fig. 2. The median ages at irradiation were 8.4 (IQR 4.1–16) years in patients with RIMs, 9 (IQR 5–23) years in patients with RIGs, and 27.7 (IQR 13.8–40) years in patients with RISs. The age at irradiation for primary disease was significantly older in patients with RISs than in those with RIMs and RIGs ($p < 0.0001$ and $p < 0.0001$, respectively).

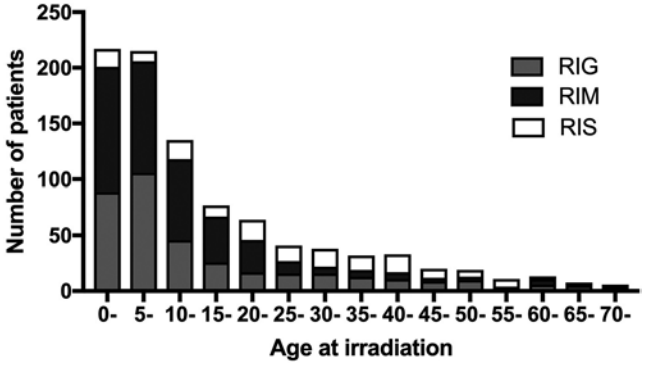

FIG. 2. Age distribution at the time of irradiation and age at RIBT development.

The median ages at the time of RIBT development were 33 (range 6.7–79) years in patients with RIMs, 21 (range 4–87) years in patients with RIGs, and 39.7 (range 7.6–85) years in patients with RISs. The age at the development of RIBTs was significantly younger for patients with RIGs than for those with RIMs and RISs ($p < 0.0001$ and $p < 0.0001$, respectively).

Patients With Different Types of Metachronous and Simultaneous RIBTs

Six patients presented with different types of RIBT (Table 1). The mean age (± SD) at irradiation for primary disease was 9.3 ± 7.1 years in patients with metachronous and simultaneous RIBT. RIG developed followed by RIM in 4 patients.[27–29] RIS subsequently developed into RIM in 1 patient.[30] Simultaneous RIM and RIG were found in 1 patient.[31] The mean radiation dose for the primary disease was 45.7 ± 15.5 Gy.

Latency Period From Irradiation to the Development of RIBTs

The latency periods from irradiation to the development of RIBTs were 22.2 ± 11.9 years in patients with RIMs, 12.0 ± 9.4 years in patients with RIGs, and 11.8 ± 8.1 years in patients with RISs. The latency period from irradiation to the development of RIBTs was statistically longer in patients with RIMs than in those with RIGs and RISs ($p < 0.0001$ and $p < 0.0001$, respectively) (Fig. 3A).

Thereafter, the patients were divided into pediatric (age at RT < 15 years) and nonpediatric patients (age at RT ≥ 15 years). There was no significant difference between the

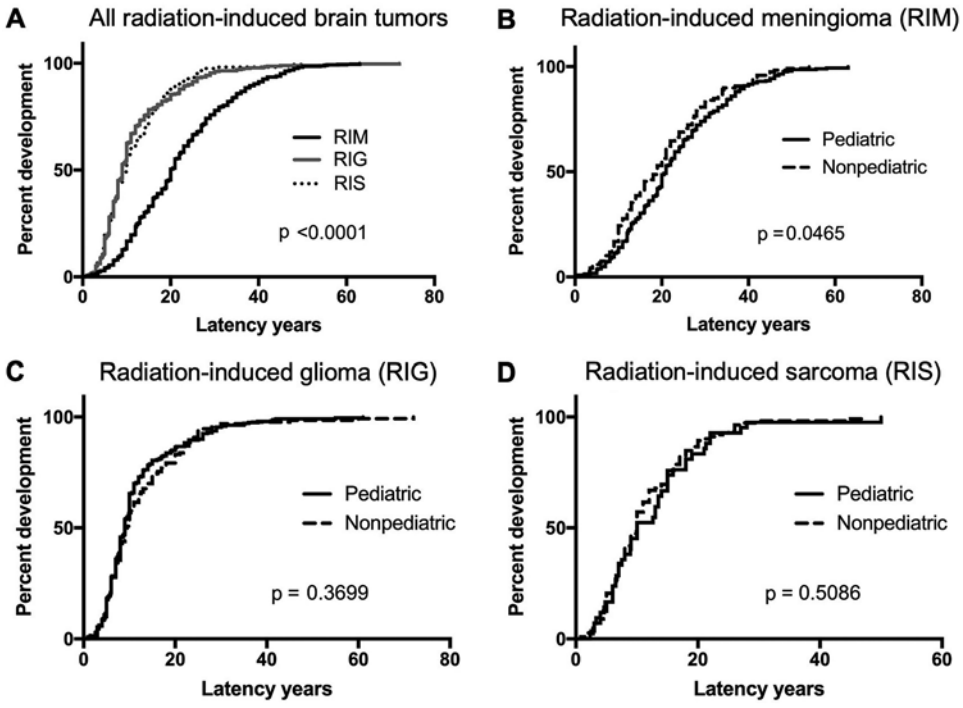

FIG. 3. Kaplan-Meier analysis of the latency period from irradiation to the development of RIBTs. Patients were classified on the basis of the type of RIBT (**A**). The patients were divided into the pediatric group (age at RT < 15 years) and nonpediatric group (age at RT ≥ 15 years) among patients with RIMs (**B**), RIGs (**C**), and RISs (**D**).

pediatric and nonpediatric group latencies in patients with RIGs and RISs (p = 0.32 and p = 0.51) (Fig. 3C and D). Among patients with RIMs, the latency was statistically shorter for nonpediatric patients with RIMs than for pediatric patients with RIMs (p = 0.047) (Fig. 3B).

Type of Primary Disease in Patients With RIBTs

The type of primary disease is shown in Fig. 4. Among all patients with RIBTs, brain tumor was the most common primary disease before the development of RIBTs. The second most common primary disease was hematological malignancy in patients with RIGs and RIMs and head and neck tumors in patients with RISs. The third most common primary disease in patients with RIMs was scalp disease, which was more common than in patients with RIGs and RISs (p < 0.0001 and p < 0.0001, respectively).

Comparison of the Prognoses of Patients With RIBTs

The median OS of patients with RIGs or RISs in this study was 11 months. The median OS of patients with RIMs was not reached. The median OS was significantly longer in patients with RIMs than in those with RIGs and RISs (p < 0.0001) (Fig. 5A).

Next, the patients were divided into a pediatric group (age at RT < 15 years) and a nonpediatric group (age at RT ≥ 15 years). The OS of patients with RIGs and RISs was not statistically significant between the pediatric and nonpediatric groups (p = 0.37 and p = 0.30, respectively) (Figs. 5C and D). Among the patients with RIMs, the OS was significantly shorter for the nonpediatric group with RIMs than in the pediatric group with RIMs (p = 0.023) (Fig. 5B).

Finally, we subclassified the patients into two groups on the basis of the radiation dose: the higher-dose group (≥ 30 Gy) and the lower-dose group (< 30 Gy). The OS of the patients with RIMs (not reached vs not reached, p = 0.0095) and RIG (13 months vs 9 months, p = 0.0026) was statistically shorter in the higher-dose group than in the lower-dose group (Fig. 5E and F). Among the patients with RISs, the radiation dose did not affect OS (11 months vs 10 months, p = 0.90) (Fig. 5G).

Discussion

The development of RIBTs is a challenging, late adverse effect of cranial irradiation. This study assessed the characteristics of different types of common RIBTs. The results showed that older age at irradiation correlated with a significantly shorter latency period in patients with RIMs than in those with RIGs and RISs. The results also showed that the prognosis was worse for patients with RIGs and RISs than for patients with RIMs.

Cancer survivors treated with RT have previously been shown to have a higher incidence of secondary neoplasms, including brain tumors, than those without RT.[16] In previous studies that included patients with childhood cancer exposed to cranial RT, 0.77%–3.39% and 5.6% of patients developed RIG and RIM, respectively.[32,33] Increased radiation dose increased the risk of subsequent meningioma and glioma among childhood cancer survivors.[34] In addition, the dose-dependent risk was significant in younger patients, especially those < 5 years of age.[35] Previous case

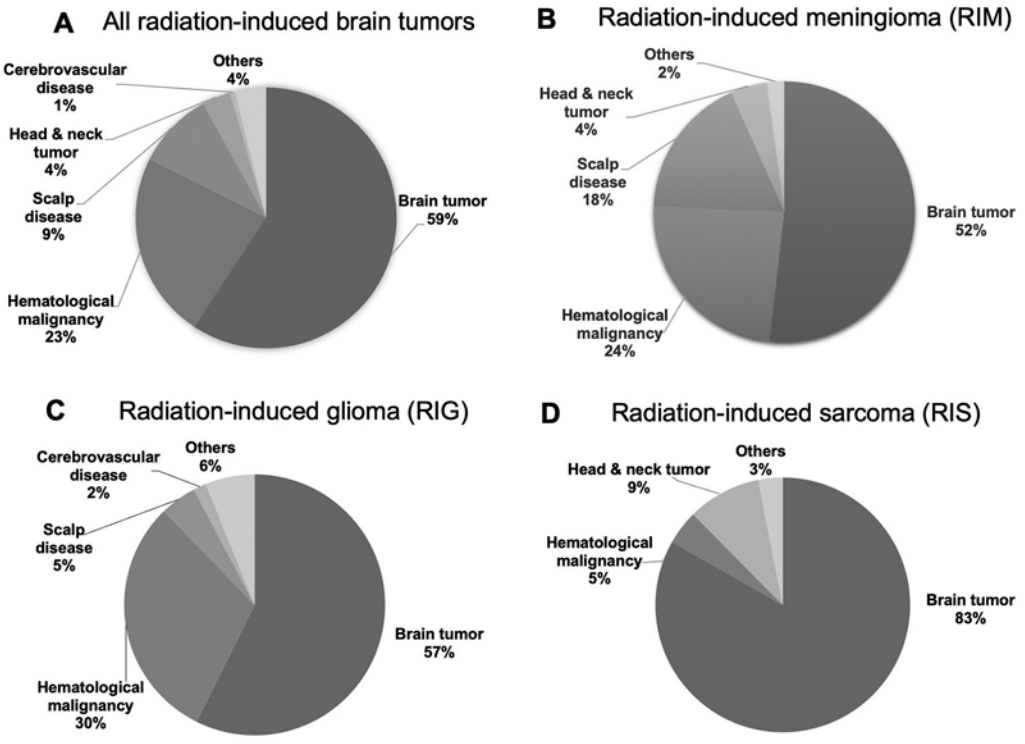

FIG. 4. Types of primary disease in patients with all RIBTs (**A**), RIMs (**B**), RIGs (**C**), and RISs (**D**).

series mainly focused on childhood cancer have shown that a younger age at irradiation was associated with a shorter latency period for the development of RIBTs.[36,37] This was confirmed in our study, in which patients treated with RT at < 5 years of age had the highest reported number of RIBTs. Higher-dose RT at a younger age increases the risk of RIBTs. Hence, treatment strategies that reduce or avoid RT could decrease the risk of secondary neoplasms.[38,39]

RIBTs developed at a younger age than non-RIBTs.[20,21] The mean age for the development of RIG peaked in the 1st decade of life, whereas the age of patients with malignant gliomas (WHO grades 3 and 4) in the Brain Tumor Registry of Japan (BTRJ) 2005–2008 peaked in patients in their 7th decade of life.[21] Similarly, the mean age for the development of RIM peaked in the 3rd decade and the occurrence of meningioma, based on data from the BTRJ, peaked in the 6th and 7th decades.[21] RIS could not be compared with non-RISs because of the low number of cases; primary sarcomas of the central nervous system are extremely rare. The development of RIG may be caused by radiation exposure during the early stages of childhood,[35] when nerves are actively developing. In contrast, RIS develops at a later age compared with RIG, possibly because of the prominence of soft-tissue growth in the later stages of childhood, adolescence, and young adulthood.

Regarding the type of primary disease for RIBTs, brain tumors and hematological malignancies were the two major primary diseases associated with subsequent development of RIBTs. Among patients with RIMs, the third most common primary disease for RT was scalp disease. In the first half of the 20th century, tenia capitis was treated mainly with RT.[40] As radiation exposure was mainly focused on the scalp, the development of RIMs was more likely in these patients than development of RIGs and RISs, which develop mainly in intraparenchymal lesions.

The latency period from irradiation was statistically longer for the development of RIMs than for the development of RIGs and RISs. Given that almost 70% of the RIMs were WHO grade 1[20] and almost 90% of the RIGs were WHO grades 3 or 4,[21] the characteristics of tumor biology might influence the latency periods from irradiation to development of RIBTs. Although age at irradiation was not associated with the latency period in the patients with RIGs and RISs, age at irradiation and age at development of RIBTs were significantly younger for patients with RIGs. A previous study also reported that younger age at irradiation increased the risk of RIG development.[35] Younger age at irradiation may be especially associated with the development of RIGs. The brain undergoes significant development during infancy and childhood,[41] so the brain may be more sensitive to cranial irradiation during these periods and induce development of RIBT.

In this study, the mean latency periods from irradiation to the development of RIMs, RIGs, and RISs were 22.2, 12.0, and 11.8 years, respectively. Therefore, an appropriate follow-up program should be established for patients who have undergone cranial irradiation. In a previous study on the follow-up practices of the member institutions of the COG in the United States, almost 50% of patients with medulloblastomas treated with RT never received or received < 5 years of MRI surveillance.[42] Regarding the transition practice for childhood cancer survivors, two-thirds of COG member institutions transferred adult-aged survivors to another institution for cancer-related follow-

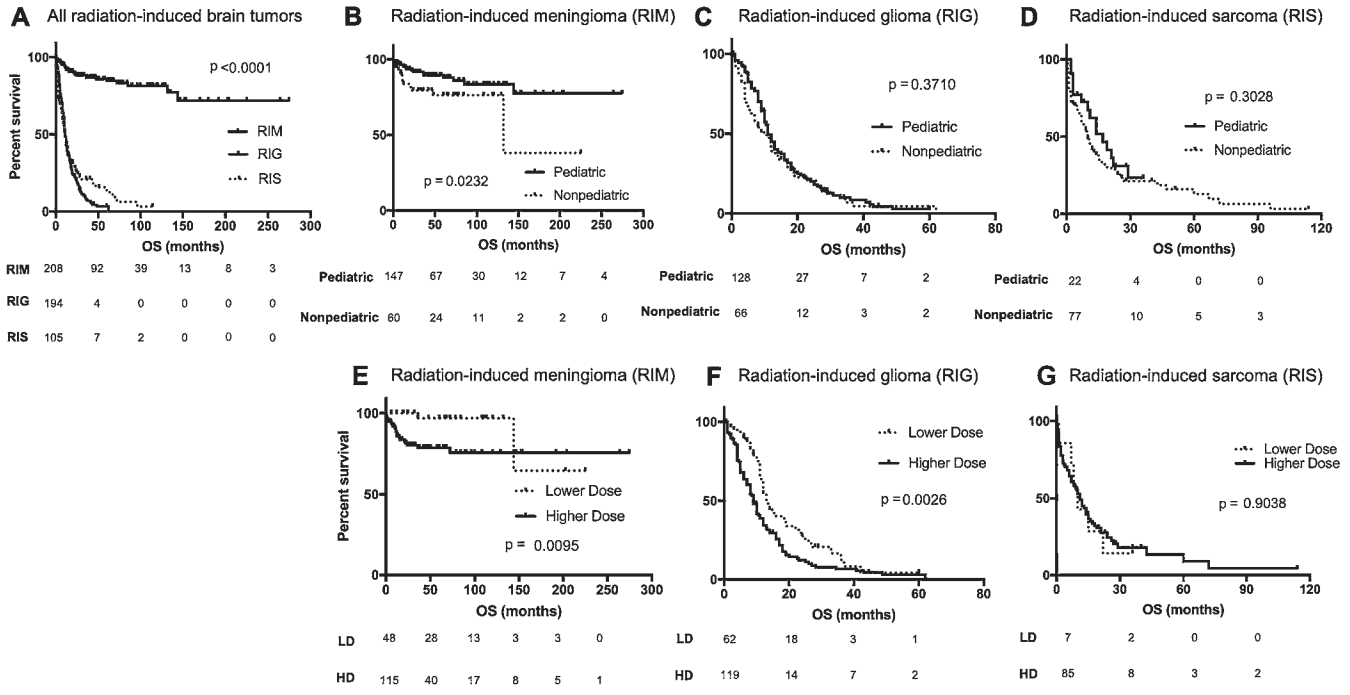

FIG. 5. Kaplan-Meier analysis of the OS of patients with RIBTs. Patients were classified according to the type of RIBT (**A**). Patients were divided into the pediatric group (age at RT < 15 years) and nonpediatric group (age at RT ≥ 15 years) among patients with RIMs (**B**), RIGs (**C**), and RISs (**D**). Patients with RIMs (**E**), RIGs (**F**), and RISs (**G**) were divided into higher irradiation dose (≥ 30 Gy) and lower irradiation dose (< 30 Gy) groups.

up care.[43] One of the major barriers to transitioning survivors to adult care was previously reported to be the lack of late-effect knowledge among clinicians.[43] Most RIBTs develop several decades after cranial irradiation; therefore, physicians should recognize the importance of long-term follow-up for patients who have undergone cranial irradiation.

Our results also showed a poorer prognosis for patients with RIGs and those with RISs than for patients with RIMs. In addition, the prognosis was longer for younger patients with RIMs than for those with RIGs and RISs, and patients with RIGs and those with RISs had a poor prognosis regardless of age. The molecular characteristics of RIG have been previously reported. Excluding only 1 case,[44] the isocitrate dehydrogenase (IDH) status of the RIGs was IDH-wildtype which has a prognosis worse than that of IDH-mutant gliomas.[20,45] The comprehensive molecular characteristics of RIG are related to the loss of CDKN2A,[46,47] which reportedly is a poor prognostic factor in IDH-wildtype glioblastomas.[48] In genetic analysis of sarcomas of the entire body, loss of CDKN2A/B was shown to be more frequent in postradiation sarcomas than in sporadic sarcomas[49] and is a poor prognostic factor.[50] Because of the malignant behavior of tumor cells, the prognosis might be worse for RIG and RIS than for RIM. Among patients with RIGs and those with RIMs, the patients who received a higher irradiation dose for primary disease had a poor prognosis. DNA damage induced by radiation might influence the prognosis of patients who received higher-dose RT.

There are some study limitations that should be considered when interpreting our results. Some details regarding the radiation dose or location and some clinical information were lacking in some of the studies reviewed. Second, our study did not identify the patients at higher risk for RIBTs, and we did not suggest the appropriate follow-up programs for RT-treated patients. The rate of RIBT development in patients who underwent brain irradiation could not be determined because of the retrospective design of the study. Therefore, the differences between patients with RIBTs and patients with non-RIBTs have not been clarified. We excluded patients with cancer predisposition syndrome; however, germline analysis was not well-described and/or not performed in the reviewed reports. Further studies are needed to clarify the characteristics of RIBT in patients with cancer predisposition because such patients were excluded. Because of the meta-analysis approach, publication, availability, and selection bias are potential concerns. Despite these limitations, the strength of this study is the comprehensive analysis of these rare tumors. Further prospective studies and construction of a genetic database for RIBTs are necessary to establish effective follow-up programs for irradiated patients.

Conclusions

Our study showed that the prognosis was poor and worse for patients with RIGs and RISs than for those with RIMs, and the prognosis was poor in patients with RIBTs that developed after exposure to high irradiation doses for primary disease. Given that RIBTs develop more than a decade after cranial irradiation, long-term follow-up is crucial, especially for younger patients.

Acknowledgments

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Yamasaki, Onishi. Acquisition of data: Yamasaki, Onishi, Go. Analysis and interpretation of data: Yamasaki, Onishi. Drafting the article: Onishi. Critically revising the article: Yamasaki. Reviewed submitted version of manuscript: Yamasaki, Onishi, Kinoshita, Amatya, Yonezawa, Taguchi, Ozono, Maeda, Khairunnisa, Takeshima, Horie. Approved the final version of the manuscript on behalf of all authors: Yamasaki. Statistical analysis: Onishi, Maeda. Administrative/technical/material support: Onishi, Kinoshita, Amatya, Yonezawa, Taguchi, Ozono, Horie. Study supervision: Yamasaki, Horie.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplemental Table 1. https://thejns.org/doi/suppl/10.3171/2024.3.JNS232934.

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