Clinical, imaging, and molecular features of radiation-induced glioblastomas developing more than 20 years after radiation therapy for intracranial germinomatous germ cell tumor: illustrative cases

Yoshihiro Tsukamoto, MD, PhD,1 Manabu Natsumeda, MD, PhD,1,2 Haruhiko Takahashi, MD,1,3 Asuka Ueno, MD,1 Kiichi Sakai, MD,1 Kazuki Shida, MD,1 Hiroki Seto, MD,1 Taiki Saito, MD,1 Satoshi Shibuma, MD,1 Yoko Nakayama, MD, PhD,1 Yuki Tanaka, MD,3 Toshimichi Nakano, MD, PhD,4 Atsushi Ohta, MD, PhD,4 Katsuya Maruyama, MD, PhD,5 Masayasu Okada, MD, PhD,1 Takeyoshi Eda, MD, PhD,5 Yasuhiro Seki, MD,5 Yuichirou Yoneoka, MD, PhD,7 Hiroshi Shimizu, MD, PhD,3 Kouichiro Okamoto, MD, PhD,1 Akiyoshi Kakita, MD, PhD,3 and Makoto Oishi, MD, PhD1

Departments of 1Neurosurgery and 3Pathology, Brain Research Institute, Niigata University, Niigata, Japan; 2Advanced Treatment of Neurological Diseases Branch, Brain Research Institute, Niigata University, Niigata, Japan; 4Department of Radiology and Radiation Oncology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; 5Department of Radiology, Niigata Neurosurgery Hospital, Niigata, Japan; 6Division of Pharmacy, Medical and Dental Hospital, Niigata University, Niigata, Japan; and 7Department of Neurosurgery, Uonuma Kikan Hospital, Uonuma Institute of Community Medicine, Medical and Dental Hospital, Niigata University, Niigata, Japan

BACKGROUND Germinomatous germ cell tumor is highly sensitive to chemoradiotherapy; patients are expected to survive for decades. Many radiation-induced malignant gliomas (RIMGs) occur >10 years after radiotherapy. Standard therapy for RIMGs has not been established because of the lesion’s rarity, the patient’s shorter survival period, and the risk of radiation necrosis by repeat radiation.

OBSERVATIONS Two patients, a 32-year-old man and a 50-year-old man, developed glioblastomas more than 20 years after radiation monotherapy for germinoma with or without mature teratoma. The first patient showed a tumor in the left frontotemporal region with disseminated lesions and died 2 months after partial resection of the tumor without responding to the chemotherapy with temozolomide and bevacizumab. Methylation classifier analysis classified the pathology as closest to diffuse pediatric-type high-grade glioma, Rtk1 subtype. The second patient showed a tumor mass in the brainstem and left cerebellar peduncle, which worsened progressively during chemotherapy with temozolomide and bevacizumab. The tumor transiently responded to stereotactic radiotherapy with the CyberKnife. However, the patient died of RIMG recurrence-related aspiration pneumonia 11 months after the biopsy. Methylation classifier analysis classified the pathology as closest to infratentorial pilocytic astrocytoma.

LESSONS Chemoradiotherapy may improve the survival of patients with RIMGs. Furthermore, molecular features may influence the clinical, locoregional, and pathological features of RIMG.

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KEYWORDS radiation-induced glioma; glioblastoma; germinoma; repeat radiation; germ cell tumor

The central nervous system (CNS) is one of the most common sites of extragonadal germ cell tumors (GCTs). However, CNS GCTs are rare, representing 3%–5% of CNS tumors in the pediatric population.1 Pure germinomas and mature teratomas are highly sensitive to chemoradiotherapy. Radiation therapy (RT) plays a central role in the treatment paradigm for the disease.1 Patients with pure germinomas and mature teratomas are expected to survive more than a few decades.2 However, RT can be associated with

ABBREVIATIONS ALL = acute lymphocytic leukemia; BEV = bevacizumab; CNS = central nervous system; CNV = copy number variation; CSR = craniospinal radiation; GCT = germ cell tumor; Gd = gadolinium; GGCT = germinomatous germ cell tumor; IDH = isocitrate dehydrogenase; LI = labeling index; MLPA = multiple ligation-dependent probe amplification; MRI = magnetic resonance imaging; OTA = occipital transtentorial approach; re-RT = repeat radiation therapy; RIMG = radiation-induced malignant glioma; RT = radiation therapy; SMN = secondary malignant neoplasm; SRT = stereotactic radiotherapy; TMZ = temozolomide.

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late treatment-related toxicities such as secondary malignant neoplasms (SMNs), endocrine deficiencies, and stroke, which are particularly relevant in the long term, owing to the favorable prognosis of the patients. With greater years of follow-up, there is increasing mortality attributable to treatment-related causes inducing SMN. The most common radiation-induced CNS SMNs are gliomas and meningiomas. The survival rates for patients who develop gliomas are far worse than those for patients who develop meningiomas, with a 5-year relative survival rate of only 4% for radiation-induced gliomas compared with 77%–84% for radiation-induced meningiomas. Therefore, the development of SMNs, including radiation-induced malignant glioma (RIMG), remains a major concern for patients with GCTs after RT in the long term.

The median survival of patients with RIMG may have improved slightly after the widespread and consistent use of temozolomide (TMZ) since 2005. However, no consistent or optimal treatment regimen has been defined for RIMG. In this report, we describe two cases of RIMG that developed 23 and 29 years after RT for germinoma with or without mature teratoma, respectively. Genetic and epigenetic features of the RIMGs were investigated using multiple ligation-dependent probe amplification (MLPA) and methylation classifier analysis. These results may encapsulate the different clinical, radiological, and pathological findings and prognoses of the patients with RIMG.

Illustrative Cases

Case 1

In a 9-year-old male, bifocal germinomas with a mature teratoma component developed at the pineal and suprasellar regions. The larger pineal tumor was resected via the occipital transtentorial approach (OTA; Fig. 1A). After surgery, craniospinal radiation (CSR) (brain 24 Gy, spine 25.4 Gy) and boost (26.0 Gy) to the bifocal lesions were administered. At the age of 32, he developed generalized convulsions, and magnetic resonance imaging (MRI) revealed left temporal and frontal gadolinium (Gd)-enhancing lesions in the whole-brain and boost field as well as dissemination in the third ventricle (Fig. 1B). RIMG was suspected, and the tumor was partially resected (Fig. 1C). The pathological diagnosis was glioblastoma, isocitrate dehydrogenase (IDH) wild type (Fig. 2A and B), with increased cellularity of small cells with atypical nuclei. Brisk mitotic activity, microvascular proliferation, and hyalinization of vessels suspected to be radiation induced were observed, but necrosis was undetected on hematoxylin and eosin staining. The MIB1 labeling index (LI) was 40%. Immunohistochemistry showed that Olig2 (Fig. 2C), GFAP (Fig. 2D), p53, and MGMT were positive and that IDH1 R132H...
FIG. 2. Case 1. Hematoxylin and eosin (H&E) staining (A, B) and immunohistochemistry of Olig2 (C) and GFAP (D) of the pathological specimen. CVN analysis with methylation classifier analysis (E). The high-power field of H&E staining shows hyalinized vascular formation (white arrowhead, B) and mitosis (black arrow, B). Immunohistochemistry is positive for Olig2 (C) and GFAP (D). Original magnification ×200 (A, C, and D), and ×400 (A in white square and B). CVN analysis shows 7q gain and hemizygous deletion of chromosomes 9p and 13q (black arrowhead, E).

Case 2

A 20-year-old man underwent tumor resection for a pineal pure germinoma via the OTA (Fig. 3A). After surgery, CSR (34.8 Gy) and boost (21.6 Gy) were performed. By the time he turned 50, the patient complained of ataxia, and MRI revealed a brain tumor involving the brainstem and cerebellum (Fig. 3B). The tumor developed in the CSR field but outside the boost area. RIMG was suspected. The pathological diagnosis of glioblastoma, IDH wild type, was confirmed by a biopsy (Fig. 4A and B). Pathological examination showed highly cellular astrocytic cells and microvascular proliferation without necrosis. The MIB1 LI was 30%. Tumor cells were positive for Olig2 (Fig. 4C), GFAP (Fig. 4D), and p53 and negative for IDH1 R132H and MGMT. ATRX was retained. No GCT components were identified in any specimen. MLPA revealed PDGFRA amplification. Clinically, cancer genome panel analysis by FoundationOne CDx revealed CDKN2A/B loss, PDGFRA amplification, PDGFRA C235Y mutation, FGF19 amplification, FGF3 amplification, FGF4 amplification, KIT amplification, and CCND1 amplification. Although PDGFRA amplification was detected, methylation classifier analysis classified the tumor as closest to infratentorial pilocytic astrocytoma; however, the calibrated score was 0.42. As in case 1, this score might be acceptable as an indication of a specific diagnosis. The CNV profile revealed hemizygous deletion of CDKN2A/B; gain of PDGFRA; and hemizygous deletions of chromosome 1p, 9p, and 13q (Fig. 4E). Combined TMZ and BEV chemotherapy was initiated. Because the tumor progressed after 2 months (Fig. 3C), stereotactic radiotherapy (SRT) with CyberKnife (20 Gy/4 fractions) was administered. After a partial response to SRT (Fig. 3D), the RIMG relapsed 5 months later. The patient died 11 months after the biopsy because of aspiration pneumonia.

Immunohistochemistry, DNA direct sequence, and MLPA were performed, as described previously. Methylation classifier analysis was also performed, as described previously. In brief, DNA was extracted from frozen tissue. The Infinium Methylation EPIC (850k) BeadChip array (Illumina) was used according to the manufacturer’s instructions. Brain tumor classifier version 12.5 was applied for tumor classification with the free web platform system supplied by the German Cancer Research Center (https://www. molecularneuropathology.org).

Patient Informed Consent

The necessary patient informed consent was obtained in this study.

Discussion

Observations

Both patients had undergone radiation monotherapy, at the ages of 9 and 20 years, respectively, for intracranial GCTs. They had no genetic history of cancer predisposition (including Li-Fraumeni syndrome or neurofibromatosis), although they had developed glioblastoma 23 and 29 years after RT, respectively.

The patient in case 1 harbored RIMG in the frontotemporal region subjected to 50 Gy as the RT and died 2 months after the tumor resection without responding to chemotherapy. The patient in case 2 developed RIMG in the brainstem and cerebellum, outside the boost-dose area, which had received CSR (34.8 Gy), and responded to re-RT transiently while surviving for 11 months after the RIMG diagnosis. The diagnoses of methylation classifier analyses with a lower calibrated score for both cases were acceptable as an indication of a specific diagnosis, and the molecular features seemed...
to reflect the clinical, imaging, and pathological findings and the prognoses of the patients.

**Lessons**

**Rare Radiation-Induced Intracranial Neoplasms and Longer Latency Period of RIMG After GCT Treatment**

The most common CNS SMNs of childhood cancer are gliomas and meningiomas. However, cranial SMN is very rare in patients with intracranial GCT seen in follow-up for <20 years. No CNS SMN was reported in 153 patients with cranial GCT treated and monitored by Matsutani et al. for more than 9 months (range 9 months to 27 years, median 8.1 years). In our previous report of 48 patients with intracranial germinomas treated by radiation monotherapy, no RIMG was encountered during a follow-up period of up to 20 years. However, at 25 years, the cumulative incidences of death caused by cancer (either SMN or primary recurrence) and SMN were 16% and 6.0%, respectively, in the SEER (Surveillance, Epidemiology, and End Results) study analyzing 405 germinomatous GCTs (GGCTs) and 94 non-GGCTs. Among the patients with GGCTs, 1 patient developed glioblastoma (0.2%) and another developed malignant meningioma (0.2%). Similarly, 3 intracranial SMNs were reported in a study of 418 intracranial GCTs with a median follow-up of 8.9 years: 2 meningiomas (0.5%) and 1 glioma (0.2%). A large, single-center study of 189 patients diagnosed with intracranial GCTs showed that SMNs developed in 10 patients (5.3%), including 5 glioblastomas (2.6%) with a latency period of 20 years (range 4–26 years), which caused death in 6 of the 10 patients.

As for previously presented case reports or case series, 10 additional RIMGs were described after RT for intracranial germinoma (Table 1). The median latency period was 11.5 years (range 7–30 years) in these patients (age range 5–20 years, mean 11.8 years). RIMGs occurred within 10 years in 3 patients who had undergone RT at the age of 8 or younger, although the longest latency periods of 29 and 30 years were observed in patients who had undergone RT at ages 11 and 15 years, respectively.

The latency period >10 years in most RIMGs after treatment for GCTs is longer than that for other brain tumors or other cranial diseases. In a review of 172 RIMGs in patients with various brain tumors from 1960 to 2013, the median latency period was 9 years. RIMGs occurred within 15 years in 82% of patients. The median latency period for acute lymphocytic leukemia (ALL; 8 years) was significantly shorter than those for medulloblastoma (9.5 years) and pituitary adenoma (10.5 years). The shortest reported latency period was 2.5 years in a patient with ALL who had received 24 Gy, and the longest was 61 years in a patient with tinea capitis, who had received a radiation dose of 3 Gy. A longer latency period >20 years was recorded in 17 cases, including 7 cases of tinea capitis treated with a total dose of 3 Gy as minimum-dose RT.

**FIG. 3.** Case 2. (A) Axial and sagittal Gd-enhanced T1WI on admission. (B) Axial Gd-enhanced T1WI and FLAIR image at the development of radiation-induced glioblastoma. (C) Axial Gd-enhanced T1WI and FLAIR image after chemotherapy with TMZ and BEV. (D) Axial Gd-enhanced T1WI and FLAIR image after SRT with the CyberKnife. Gd-enhancing germinoma is shown at the pineal lesion (A). Radiation-induced glioblastoma developed at the left middle cerebellar peduncle and left cerebellar hemisphere involving the brainstem (B). The radiation-induced glioblastoma progressed for chemotherapy (C). The glioblastoma regressed after SRT with the CyberKnife (D).
Radiation Dosage Range for Original Tumors in RIMGs

Several large cohort studies have demonstrated a direct correlation between the cumulative dose of radiation received and the risk of subsequent CNS tumor development. In RIMG, the frequent RT dosage range for original tumors was 21–30 Gy, including the most common condition of ALL, and 41–60 Gy for brain tumors. In our two patients, RT doses for the site where RIMG developed were 50 Gy and 34.8 Gy, respectively. The estimated mean, median, minimum, and maximum radiation thresholds for RIMG are 63.3 Gy, 66.7 Gy, 13.6 Gy, and 110 Gy, respectively. Interestingly, a peak SMN frequency of approximately 31% was identified in volumes that had received <2.5 Gy. No risk factors have been conclusively identified as predictors of RIMG development.

Pathogenesis of Radiation-Induced Neoplasm

Ionizing radiation directly damages DNA by inducing both single- and double-strand breaks, with the latter being the most deleterious. Indirect DNA damage can also occur via radiolysis of water molecules, which produces reactive oxygen species, in turn causing single-strand breaks and other DNA alterations. Imperfect repair of this damage can result in point mutations, gene fusions, large-scale deletions, or translocations, subsequently activating oncogenes or inactivating tumor-suppressor genes. These changes are often associated with ongoing genomic instability and thus can increase the risk of developing cancer. In the case of radiation-induced SMNs, genomic instability is thought to persist for multiple generations of cells over many years prior to oncogenic transformation, resulting in a significant latency period between the exposure event and the development of radiation-induced cancer.

Molecular Analysis of RIMG

The RIMGs in the two patients had both common and different molecular features. The common molecular feature was PDGFRA alteration. PDGFRA is an important molecule for RIMG occurrence. Our patient in case 1 harbored hemizygous deletion detected by MLPA, and the patient in case 2 harbored amplification verified by both MLPA and CNV profile. Whitehouse et al. analyzed 102 patients with radiation-induced gliomas identified from 1727 records through a systematic literature review. The most frequent genetic alterations were PDGFRA or TP53 mutation, PDGFRA or CDK4 amplification, and CDKN2A deletion, along with 1q gain, 1p loss, and 13q loss. López et al. reported that 5 of 10 patients with RIMG showed PDGFRA amplification, 2 showed PDGFRA hot spot mutation, and 1 showed EGFR amplification. The alteration of the PDGFRA tyrosine kinase receptor is considered frequent, but mutation or alteration of the TERT promoter and EGFR amplification were not observed. This finding may imply that PDGFRA is an important molecule for RIMG occurrence.

The methylation classifier analysis did not clearly classify our two cases. However, the specific diagnoses indicated by methylation classifier analysis reflected clinicoradiological features of the two patients. RIMG in case 1 was classified as diffuse pediatric-type high-grade glioma, RTK1 subtype, which comprises H3 wild-type and IDH wild-type diffuse gliomas, typically occurring in children, adolescents, and young adults. PDGFRA amplification was detected in 33% of these subtype cases. The patient in case 1 was a young adult, and the RIMG developed in the frontotemporal region with PDGFRA hemizygous deletion in MLPA. The characteristics of location, age, and PDGFRA alterations in case 1 agreed with the methylation classifier diagnosis. There is a reported radiation-induced glioma that shares many genetic features with pediatric glioblastoma, RTK1. The RIMG in case 2 was classified as infratentorial pilocytic astrocytoma, which is located mostly in the posterior fossa with favorable prognosis in general. In case 2, the pathological diagnosis was different from that of the methylation classifier, but, interestingly, the tumor originated in the posterior fossa and showed a more favorable prognosis than that in case 1. FoundationOne CDx panel analysis revealed CDKN2A/B loss, PDGFRA amplification, and PDGFRA C235Y mutation. These alterations are rare in pediatric low-grade glioma, including pilocytic astrocytoma. The analysis also revealed other important molecular alterations. CCND1 was reported as a possible molecule for glioma progression. FGF family amplification might be related to the tumorigenesis, as a previous paper reported activating FGFR1 mutation in posterior fossa pilocytic astrocytoma.

In the CNV profile, case 1 showed a hemizygous deletion of chromosome 1p, and case 2 showed a hemizygous deletion of chromosome 13q.
<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Tumor (location)</th>
<th>Radiation (dose)</th>
<th>RIG Age (yrs)</th>
<th>RIG Period (yrs)</th>
<th>Pathological Diagnosis</th>
<th>Chemo</th>
<th>RIG Radiation (Gy)</th>
<th>Survival (mos)</th>
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<tr>
<td>You et al., 2013&lt;sup&gt;26&lt;/sup&gt;</td>
<td>8</td>
<td>M</td>
<td>Germinoma (BG, T)</td>
<td>WB, 20 Gy, local 30.4 Gy, WS 20 Gy</td>
<td>17</td>
<td>9</td>
<td>High-grade glioma</td>
<td>Chemo</td>
<td>30.6</td>
<td>18</td>
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<td>11</td>
<td>M</td>
<td>Germinoma (BG)</td>
<td>WB, 40 Gy, local 10 Gy, WS 34.4 Gy</td>
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<td>29</td>
<td>Glioblastoma</td>
<td>TMZ</td>
<td>45</td>
<td>NA</td>
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<tr>
<td>You et al., 2013&lt;sup&gt;26&lt;/sup&gt;</td>
<td>5</td>
<td>F</td>
<td>Germinoma (suprasellar)</td>
<td>WB, 30 Gy, local 19.8 Gy, WS 30 Gy</td>
<td>14</td>
<td>9</td>
<td>Glioblastoma</td>
<td>Vincristine/lomustine/cisplatin</td>
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<td>13</td>
<td>M</td>
<td>Germinoma (pineal lesion)</td>
<td>WB, 34 Gy, local 20 Gy</td>
<td>20</td>
<td>7</td>
<td>Anaplastic astrocytoma</td>
<td>—</td>
<td>Preop 10, postop 28</td>
<td>14 (alive)</td>
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<td>M</td>
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<td>M</td>
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<td>TMZ + BEV + CPT-11</td>
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<td>M</td>
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<td>15</td>
<td>M</td>
<td>Germinoma (suprasellar)</td>
<td>Local 41 Gy/23 fr (15 yrs); local 60 Gy/34 fr (17 yrs)</td>
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<td>20</td>
<td>M</td>
<td>Germinoma (suprasellar)</td>
<td>WB 50 Gy</td>
<td>33</td>
<td>13</td>
<td>Glioblastoma, IDH wild type</td>
<td>CBDCA + VP-16</td>
<td>No</td>
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<td>6</td>
<td>F</td>
<td>Germ cell tumor (suprasellar)</td>
<td>WV, 30 Gy, local 20 Gy</td>
<td>16</td>
<td>10</td>
<td>Glioblastoma</td>
<td>Chemo</td>
<td>No</td>
<td>6</td>
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</table>

ACNU = nimustine hydrochloride; BG = basal ganglia; CBDCA = carboplatin; chemo = chemotherapy; CPT-11 = irinotecan; fr = fraction; HGG = high-grade glioma; NA = not available; NOS = not otherwise specified; RIG = radiation-induced glioma; T = thoracic spinal cord; VP-16 = etoposide; WB = whole-brain radiation; WS = whole-spine radiation; WV = whole-ventricular radiation.
13q. The most frequent copy number changes reported in radiation-induced gliomas were loss of 13q (59%), gain of 1q (53%), and loss of 1p (47%).\(^3\) Paugh et al.\(^{36}\) reported that PDGFRα amplification and 1q gain occurred at significantly higher frequencies in radiation-induced tumors, suggesting that these are the initiating events in childhood gliomagenesis.

**Re-RT for RIMG After Germinoma Treatment**

Treatment of RIMG, particularly with or without re-RT, is problematic because these patients previously received radiation doses \(\geq 50\,\text{Gy}\), as in our patients. On the basis of our limited but practical treatment experience in the two patients with RIMG combined with the literature review, re-RT is recommended for RIMG development in patients with GCTs previously treated with RT.

The radiation oncologist can be hesitant to deliver further RT, being wary of complications, including the possibility of brain necrosis and blindness. Radiation necrosis is a major concern associated with re-RT. However, there have been just a handful of reports of re-RT for RIMG. Such radiation necrosis has been reported with re-RT in patients with high-grade gliomas or other brain tumors, who survived for a longer period,\(^7\) but not in patients with GCTs. In general, the tolerance to re-RT increased with an increasing time to re-RT and a decreasing initial radiation dose.\(^{37}\) In patients with GCTs, the longer latency period and shorter survival of RIMG may contribute to the rare occurrence of radiation necrosis after re-RT.

Previous reports recommended re-RT in addition to chemotherapy for RIMG.\(^2,23\) A study regarding the role of RT in the treatment of patients with RIMG showed that 1-, 2-, and 5-year overall survival rates were 58.9%, 20.5%, and 6.8%, respectively, in the patients undergoing re-RT, which were higher than those in patients not undergoing re-RT (15.1%, 3%, and 0%, respectively).\(^7\) Another article showed that the median progression-free survival time of patients treated with re-RT and chemotherapy tends to be longer than that of patients who received chemotherapy alone (17.0 versus 8.1 months). However, the median survival periods were similar (29.6 versus 27.4 months).\(^23\) According to previous case reports and case series of RIMG in patients with intracranial germinoma (Table 1), 4 patients received re-RT of 30.6–50.0 Gy for RIMG with or without chemotherapy, and 6 were treated with chemotherapy only. Furthermore, of the 9 cases describing survival, 1-year survival rates were 67% and 33% in the RT and non-RT groups, respectively. The patient in case 1 died 2 months after resection of the RIMG without responding to TMZ and BEV combination chemotherapy. In contrast, the patient in case 2 showed a transient response to SRT with the CyberKnife and survived 11 months after the biopsy.

**Prevention of Complications for Re-RT After High-Dose Radiation**

Modern treatment technologies are expected to reduce the risk of radiation necrosis.\(^{36}\) SRT such as CyberKnife or intensity-modulated RT may restrict lesion growth while minimizing radiation exposure to the surrounding brain.\(^{39}\) Interestingly, a recent study showed a lower incidence of SMNs, including RIMGs, because of recent efforts to reduce RT doses.\(^{16,20}\) Compared with previous findings, the incidence of SMNs in a study by Koh et al.\(^{16}\) was lower than that reported by Lee et al.,\(^7\) which may reflect a recent trend for lower RT doses. However, the incidence may have been underestimated, owing to the retrospective multicenter nature of the studies.\(^{16}\) Recently, re-RT with BEV for recurrent high-grade glioma was reported to reduce the risk of necrosis and edema from high-dose re-RT\(^{41–43}\) and may be applicable to RIMG after GCT RT.

In conclusion, rare RIMGs occur after a long latency period \(>20\) years in patients treated with RT for intracranial germinomas. Re-RT with TMZ and BEV would be recommended for RIMG treatment to improve the prognosis.

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