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High Radiation Dose to the Fornix Causes Symptomatic Radiation Necrosis in Patients with Anaplastic Oligodendroglioma

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Purpose: Surgery, radiotherapy (RT), and chemotherapy have prolonged the survival of patients with anaplastic oligodendroglioma. However, whether RT induces long-term toxicity remains unknown. We analyzed the relationship between the RT dose to the fornix and symptomatic radiation necrosis (SRN).

Materials and Methods: A total of 67 patients treated between 2009 and 2019 were analyzed. SRN was defined according to the following three criteria: 1) radiographic findings, 2) symptoms attributable to the lesion, and 3) treatment resulting in symptom improvement. Various contours, including the fornix, were delineated. Univariate and multivariate analyses of the relationship between RT dose and SRN, as well as receiver operating characteristic curve analysis for cut-off values, were performed.

Results: The most common location was the frontal lobe (n=40, 60%). Gross total resection was performed in 38 patients (57%), and 42 patients (63%) received procarbazine, lomustine, and vincristine chemotherapy. With a median follow-up of 42 months, the median overall and progression-free survival was 74 months. Sixteen patients (24%) developed SRN. In multivariate analysis, age and maximum dose to the fornix were associated with the development of SRN. The cut-off values for the maximum dose to the fornix and age were 59 Gy (equivalent dose delivered in 2 Gy fractions) and 46 years, respectively. The rate of SRN was higher in patients whose maximum dose to the fornix was >59 Gy (13% vs. 43%, p=0.005).

Conclusion: The maximum dose to the fornix was a significant factor for SRN development. While fornix sparing may help maintain neurocognitive function, additional studies are needed.

Key Words: Anaplastic oligodendroglioma, radiotherapy, radiation necrosis, fornix, cognitive function

INTRODUCTION

Oligodendrogliomas are the third most common type of primary glioma, representing 4%–15% of gliomas.[1] The World Health Organization (WHO) categorizes oligodendrogliomas into low-grade well-differentiated (WHO grade II) and ana-

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plastic oligodendrogliomas (AOs) (WHO grade III).[2] AO is uncommon, with approximately 390 new cases predicted in 2020 according to the Central Brain Tumor Registry of the United States.[3] The average age of patients diagnosed with oligodendroglioma is 45 years, which is younger than the average age of patients with grade IV glioblastoma.[4]

The long-term follow-up of the European Organization of Research and Treatment of Cancer (EORTC) 26951 trial showed that six cycles of procarbazine, lomustine, and vincristine (PCV) chemotherapy to radiotherapy (RT) prolonged survival in patients with AO.[5,6] As survival results have improved, interest in long-term toxicity, such as radiation necrosis (RN), has increased. Patients with AO have a higher risk of RN due to higher RT dose compared to that for low-grade gliomas, and the use of PCV chemotherapy.

Assessment of various radiation-induced effects on important white matter tracts, including limbic circuit fibers, helps reduce toxicity by guiding delivery and avoiding regions at high risk for damage.[7] The phase III trial conducted by NRG Oncology CC001[8] showed that hippocampal avoidance (HA) during whole-brain RT significantly lowered the risk of cognitive failure with no differences in intracranial failure. The phase II trial was conducted by the Swiss group for clinical cancer research for HA prophylactic cranial irradiation (PCI) in patients with small cell lung cancer.[9] The results showed no decline in neurocognitive function at 6 and 12 months after HA-PCI and promising brain metastasis-free survival. However, a few study have studied the radiation effect on white matter, although periventricular white matter is very a susceptible to radiation.[10] The fornix and the posterior part of the cingulum are known to be significantly susceptible to radiation damage.[11] Limbic circuit fibers, including the fornix and cingulum, play important roles in emotional association with memory.[12] RT toxicity in such tracts or brain substructures can result in various functional losses.

Therefore, this study analyzed the relationship between the RT dose to the fornix and symptomatic radiation necrosis (SRN) in patients with AO.

MATERIALS AND METHODS

Patients

Between 2009 and 2019, we identified consecutive patients with histologically confirmed AO who underwent surgery, followed by postoperative RT. We excluded patients whose RT plans could not be analyzed. All patients underwent gadolinium-enhanced magnetic resonance imaging (MRI) before and <48 hours after surgery to evaluate the surgery extent. The procedures followed in this retrospective study were in accordance with the Declaration of Helsinki in 1975, as revised in 2000, and the study was approved by our Institutional Review Board (IRB #4-2020-0679), which waived the need for written informed consent due to the retrospective study design.

Treatments

All patients underwent primary tumor resection. The extent of surgery was defined as follows: gross total resection (complete resection of the preoperative fluid-attenuated inversion recovery signal abnormality), near-total resection (<3-mm thin residual fluid-attenuated inversion recovery signal abnormality around the rim of the resection cavity only), or subtotal resection (residual nodular fluid-attenuated inversion recovery signal abnormality) based on postoperative MRI.[13]

RT was delivered as either three-dimensional conformal RT (3D-CRT) or intensity-modulated RT (IMRT). RT was planned based on simulation computed tomography (CT) fused with preoperative and postoperative MRI. Regarding target volumes for 3D-CRT, the clinical target volume (CTV)-1 was defined as the low-density area on preoperative CT and/or the high-density area on preoperative T2-weighted MRI scan with a margin of 2 cm. CTV-2 included the non-enhancing tumor area and/or the enhancing area as visible on the postoperative CT scan, in contrast to a 1-cm margin. For setup uncertainty, an additional 3 mm was applied to create the planning target volume (PTV). A dose of 41.4–45 Gy was delivered to PTV-1 in 25 daily fractions of 1.8 Gy at 5 fractions per week. Thereafter, a boost of 14.4–18 Gy (up to a cumulative dose of 59.4 Gy) was delivered to PTV-2 in daily fractions of 1.8 Gy at 5 fractions per week. Since 2011, daily fractions of 2 Gy have been used; therefore, 46 Gy was delivered to PTV-1 and 14 Gy (up to a cumulative dose of 60 Gy) was delivered to PTV-2.

Since IMRT first began to be used for the treatment of AO, the target volumes have changed slightly. PTV-1 was defined as a 3-mm margin to the tumor cavity and enhancing lesion on T1-weighted MRI, while PTV-2 was defined as a 1-cm margin to a high-signal lesion on T2-weighted fluid-attenuated inversion recovery plus a 5-mm margin to PTV-1. In cases of tumor seeding during surgery, PTV-3 was defined as a 5-mm margin to the whole ventricle. The most used RT fractions were 51 Gy in 30 fractions for PTV-2 and 60 Gy in 30 fractions for PTV-1 using a simultaneous integrated boost technique. A dose of 45 Gy in 30 fractions was delivered to PTV-3. When IMRT was administered, megavoltage or kilovoltage cone-beam CT was performed daily before each treatment for all patients for image guidance.

Adjuvant chemotherapy was administered following RT, mainly consisting of PCV chemotherapy, similar to that used in the EORTC 26951 trial.[5] PCV chemotherapy was started within 4 weeks after RT, with each cycle consisting of lomustine 110 mg/m^2 orally on day 1, procarbazine 60 mg/m^2 orally on days 8–21, and vincristine 1.4 mg/m^2 intravenous on days 8 and 29. Cycles were repeated every 6 weeks, with dose reduction for patients who experienced toxicities during chemotherapy.

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Assessment

Various brain substructures were delineated manually on simulation CT fused with preoperative and postoperative MRI scans. Contouring was conducted using MIM version 6.7.14 (MIM Software Inc., Cleveland, OH, USA), with two radiation oncologists cross-checking the contours. The fornix was delineated as follows: the fornix connects longitudinally from the mesial temporal lobe to the diencephalon and basal forebrain and is located medially to the floor of the temporal horn of the lateral ventricle. Fibers from the subiculum and hippocampus merge into the alveus and become the crux of the fornix. The crux arches superanteriorly under the splenium of the corpus callosum and forms the fornix body, which arches over the thalamus and under the septum pellucidum. The fornix body bifurcates into right and left columns, which descend into the basal forebrain.[14] Fig. 1 shows the manual delineation of the fornix. Regarding the location of the tumor and fornix, we defined tumors adjacent to the fornix as those with a distance between the tumor and fornix of <2 cm. Other substructures, such as the corpus callosum, basal ganglia, and septum pellucidum, were also delineated as candidates for organs at risk of RN. Fig. 2 shows the manual delineation of the other substructures.

SRN was defined when the following three criteria were met:[15] 1) radiographic findings were confirmed; 2) the patient experienced new or progressive symptoms that were attributable to the progressing lesion; and 3) treatment with corticosteroids, bevacizumab, or surgical resection only resulted in improvement of symptoms without further radiographic progression of the lesion. Multiple studies have made efforts to distinguish recurrence from RN using various imaging methods, including conventional imaging, diffusion-weighted imaging, diffusion tensor imaging, dynamic susceptibility contrast imaging, MR spectroscopy, and positron emission tomography.[16-19] However, there is no gold standard imaging method for the differentiation between recurrence and RN, even with recent radiomics studies.[20-22] Therefore, all cases were reviewed by a specialized neuro-radiologist for the differentiation between recurrence and RN. Fig. 3 shows images of a patient with SRN.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Differences in characteristics and toxicities were compared using chi-square tests, and the Kaplan–Meier method was used to calculate the overall survival (OS) and progression-free survival (PFS). The time to SRN was defined as the time difference between the date of RT completion and the date of SRN. Logistic regression models were fitted to examine whether the RT doses of contours and treatment variables were correlated with SRN development. Owing to the heterogeneity in the prescribed fraction doses, the equivalent dose delivered in 2 Gy fractions (EQD2, where α/β was 3) was calculated. All doses reported in this study are expressed as EQD2. Recent studies have shown that the "point maximum" dose (D_{max}) has a high degree

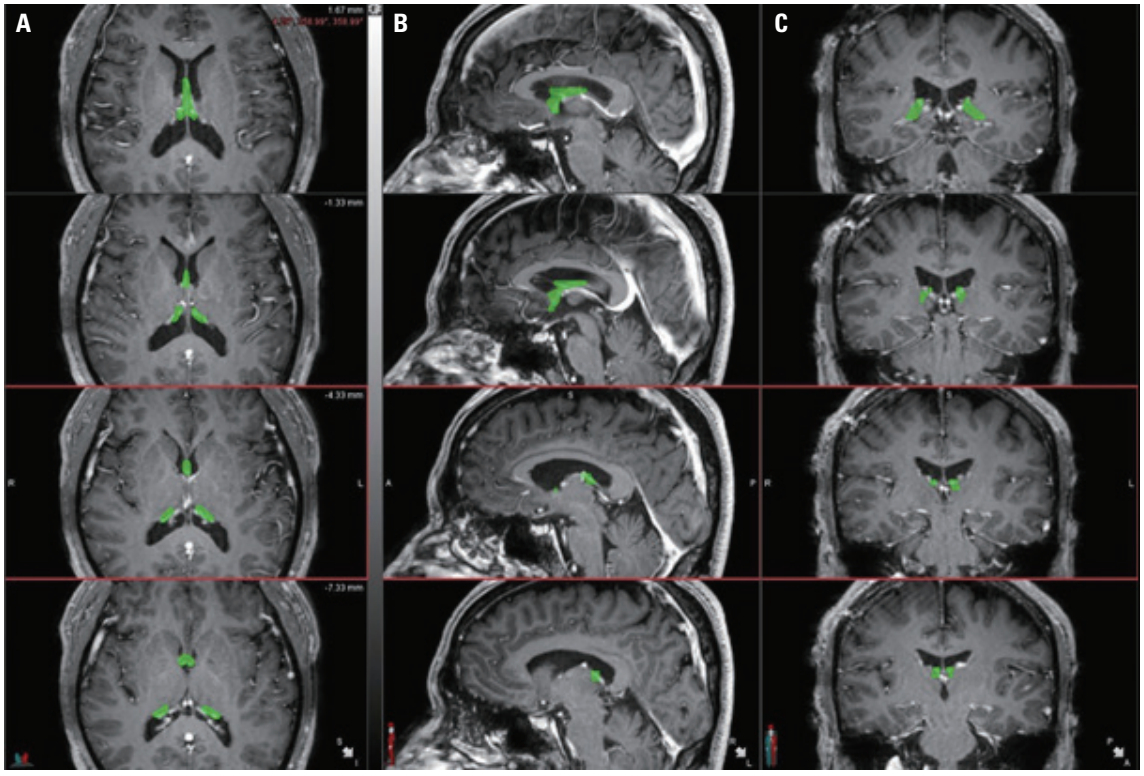

Fig. 1. Fornix delineation. (A) Axial image. (B) Sagittal image. (C) Coronal image. Green contour is a fornix.

of dose uncertainty, whereas a "near-max" dose (e.g., $D_{0.03cc}$) may be associated with less uncertainty;[23] therefore, we used $D_{0.03cc}$ as the maximum dose. Receiver operating characteristic curve (ROC) analysis was used to assess the cutoff values for parameters predicting SRN. Statistical significance was defined as $p<0.05$. Factors with statistical significance in the uni-

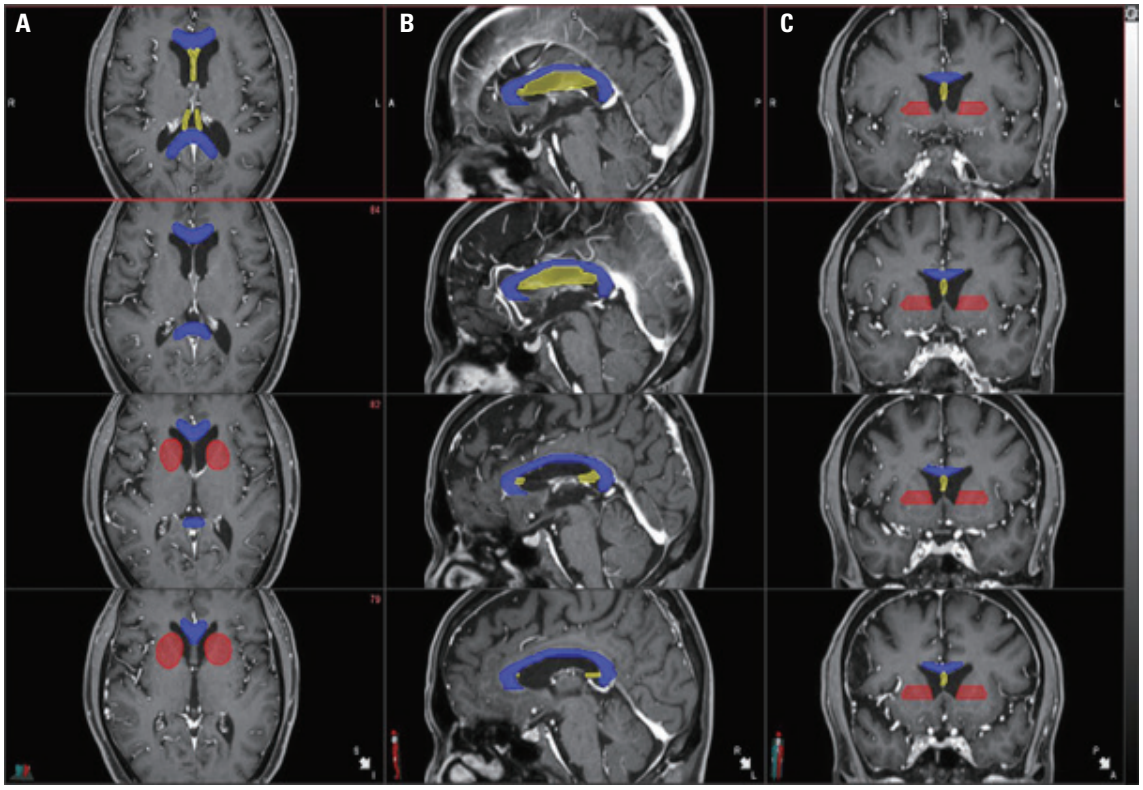

Fig. 2. Other substructures delineation. (A) Axial image. (B) Sagittal image. (C) Coronal image. Blue contour is a corpus callosum. Red contours are basal ganglia. Yellow contour is a septum pellucidum.

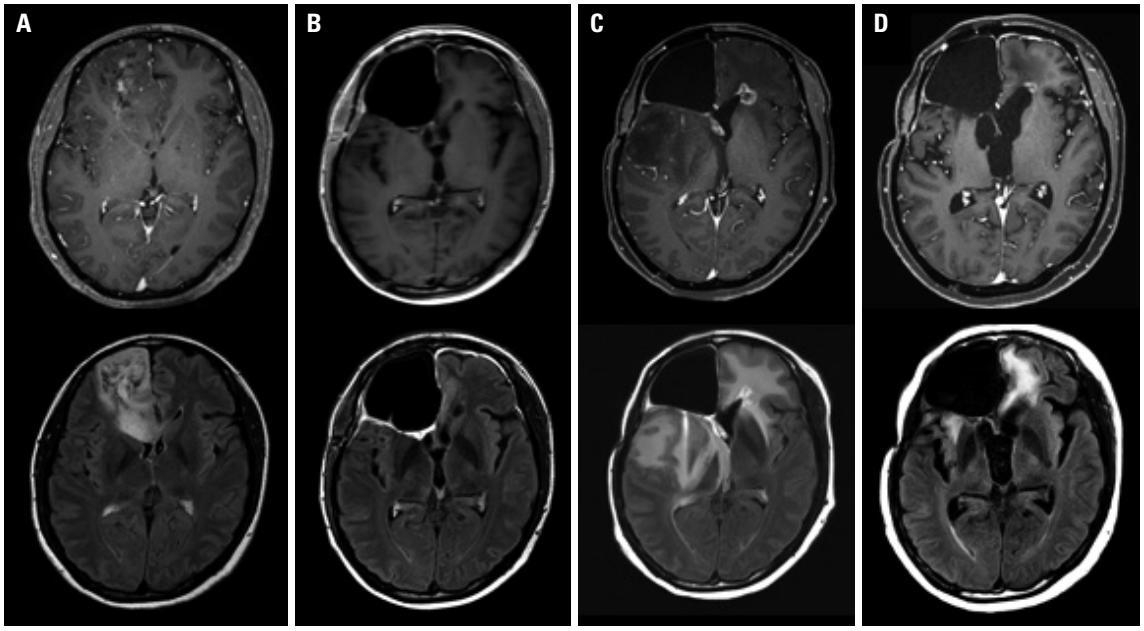

Fig. 3. Images of a patient with symptomatic radiation necrosis (SRN). (A) Preoperative images. (B) Post-radiotherapy 1 month follow-up images. (C) Post-radiotherapy 30 months follow-up images with SRN. (D) Post-radiotherapy 39 months follow-up images with SRN.

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variate analyses were included in the multivariate analyses.

RESULTS

Patient, tumor, and treatment characteristics

Patient and tumor characteristics are summarized in Table 1. The median patient age was 41 years, and the median Karnofsky Performance Status Score was 90 (range, 50–100). The most common tumor location was the frontal lobes (n=40, 60%), with 70% and 82% IDH1 mutant and 1p/19q LOH, respectively. The treatment details are summarized in Table 2. Maintenance chemotherapy was administered to 42 patients (63%); 39 patients received PCV chemotherapy, while three patients received temozolomide chemotherapy due to poor performance status. Patients received 3D-CRT (n=17, 25%) or IMRT (n=50, 75%) with a median total RT dose of 60 Gy (range, 52.5–70.0 Gy) and EQD2 of 60 Gy (range, 53.5–77.0 Gy). The maximum dose to the fornix ($D_{0.03cc}$) was 58.15 Gy (range, 41.6–78.0 Gy).

Table 1. Patient and Tumor Characteristics (n=67)

Variables	Value
Age (yr)	41 (17–78)
Sex	
Male	32 (48)
Female	35 (52)
Karnofsky Performance Status	
≤70	12 (18)
>70	55 (82)
Tumor location	
Frontal lobe	40 (60)
Parietal lobe	16 (24)
Limbic lobe	4 (5)
Temporal lobe	3 (5)
Occipital lobe	3 (5)
Cerebellum	1 (1)
IDH1	
Mutant	56 (84)
Wild	11 (16)
1p/19q LOH	
Deleted	58 (87)
Intact	9 (13)
MGMT	
Methylation	58 (87)
Unmethylation	9 (13)
EGFR	
Amplification	16 (24)
No amplification	42 (63)
Unknown	9 (13)

IDH, isocitrate dehydrogenase; LOH, loss of heterozygosity; MGMT, O^6-methylguanine-DNA methyltransferase; EGFR, epidermal growth factor receptor.
Data are presented as n (%) or median (range).

SRN

Sixteen patients (24%) had SRN. The median time to SRN was 17 months (range, 4–54). Most SRN cases (n=11, 69%) occurred within 12–24 months. The most common symptom of SRN was cognitive function impairment (n=12, 76%), followed by gait disturbance (n=11, 65%), emotional fluctuation (n=2, 12%), and persistence of seizures (n=1, 12%).

According to brain lobe, 10 of 40 (25%) patients developed SRN in the frontal lobe, 3 of 16 (19%) in the parietal lobe, and 3 of 4 (75%) in the limbic lobe. According to the tumor distance to the fornix, 16 of 40 (40%) patients with tumors adjacent to the fornix developed SRN, while none of 27 with a tumor far from the fornix developed SRN (p=0.001). Most patients (n=13, 81%) with SRN were treated with corticosteroids and levetiracetam (Keppra), which is used for epilepsy treatment. Two patients were treated with Avastin and levetiracetam, and one patient was initially treated with temozolomide and levetiracetam for suspected recurrence rather than RN; however, follow-up revealed SRN. Even with these treatments, there was a slight improvement in symptoms. Analysis of the target volume of RT and the fornix dose in patients with SRN showed that six patients (35%) had their fornix within PTV-1 (Group 1), nine patients (53%) had within PTV-2 (Group 2), and one patient (12%) had outside PTV-2 (Group 3). The mean of maximum doses to the fornix for Groups 1, 2, and 3 were 64.6, 60.6, and 46.4 Gy, respectively (p=0.015).

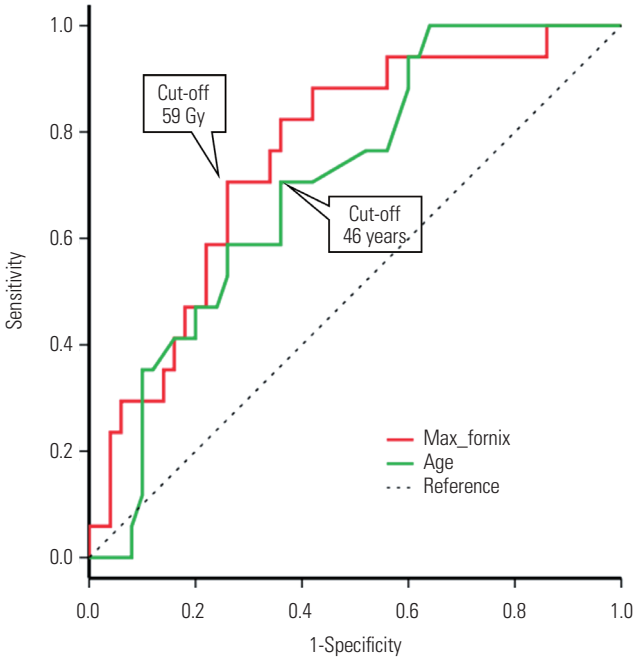
Table 2. Treatment Details (n=67)

Variables	Value
Surgery extent	
GTR/NTR	38 (57)
STR	23 (34)
Partial resection	6 (9)
Chemotherapy	
No	23 (34)
Maintenance	42 (63)
Concurrent	2 (3)
Radiotherapy (Gy)	
Total dose	60 (52.5–70.0)
Total BED	100 (89.3–128.3)
Total EQD2	60 (53.6–77.0)
Fractional dose	2 (1.8–2.5)
Dose of fornix (Gy)	
Maximum dose	58.7 (44.3–68.2)
Mean dose	48.0 (19.0–59.1)
Radiotherapy modality	
3D-CRT	17 (25)
IMRT	50 (75)

GTR, gross total resection; NTR, near-total resection; STR, subtotal resection; BED, biologically effective dose where α/β was 3; EQD2, equivalent dose delivered in 2-Gy fractions where α/β was 3; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy.
Data are presented as n (%) or median (range).

Of the 16 patients with SRN, 10 (63%) had undergone maintenance chemotherapy. Nine and one patients received maintenance chemotherapy with PCV and temozolomide, respectively.

The results of univariate and multivariate analyses of SRN are summarized in Table 3. Univariate analysis revealed that age, EGFR, and mean and maximum doses to the fornix were significant factors for SRN, while the use of PCV chemotherapy was not. Since the maximum and mean doses to the fornix were correlated (p<0.001), both the maximum and mean doses were included in the multivariate analysis separately, and the model of maximum dose was selected. In multivariate analysis, age and maximum doses of the fornix were associated with the development of SRN. Multivariate analysis, including mean dose of the fornix, is summarized in Supplementary Table 1 (only online). ROC analysis showed that the area under the curve (AUC) for the maximum dose of the fornix was 0.755 [95% confidence interval (CI), 0.628–0.883; p=0.002], with a cut-off value for SRN of 59 Gy (EQD2). The rate of development of SRN was significantly higher in patients whose maximum dose to the fornix was >59 Gy (13% vs. 43%, p=0.005). The AUC for age was 0.706 (95% CI, 0.576–0.836; p=0.012), with a cut-off value of 46 years (Fig. 4).



	AUC	95% CI	*p* value
Max_fornix (EQD2)	0.755	0.628–0.883	0.002
Age	0.706	0.576–0.836	0.012

Fig. 4. Receiver operating characteristic curve for symptomatic radiation necrosis. AUC, area under the curve; CI, confidence interval.

Patterns of recurrence

With a median follow-up of 42 months (range, 9–125 months)

Table 3. Prognostic Factors for Radiation Necrosis

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Patient factors						
Age	1.053	1.009–1.100	0.018	1.079	1.020–1.141	0.008
KPS	0.997	0.935–1.044	0.905			
Tumor factors						
Location (frontal vs. other)	0.857	0.270–2.722	0.794			
IDH1 (mutant vs. wild)	0.273	0.032–2.321	0.235			
1p/19q LOH (deleted vs. no)	0.898	0.167–4.831	0.900			
MGMT (methyl vs. unmethyl)	0.488	0.053–4.509	0.527			
EGFR (no vs. amp)	4.250	1.222–14.781	0.023	3.196	0.731–13.979	0.123
Treatment factors						
Surgery extent (total vs. other)	0.347	0.099–1.219	0.099			
PCV maintenance (no vs. yes)	0.900	0.289–2.798	0.856			
RT dose (total)	1.001	0.998–1.004	0.542			
RT dose (EQD2)	1.091	0.910–1.309	0.346			
Maximum dose (fornix)	1.168	1.038–1.315	0.010	1.156	1.017–1.315	0.027
Mean dose (fornix)	1.142	1.038–1.256	0.006			
Maximum dose (corpus callosum)	0.986	0.957–1.016	0.370			
Maximum dose (basal ganglia)	1.021	0.971–1.074	0.420			
Maximum dose (septum pellucidum)	1.044	0.976–1.118	0.212			
RT modality (IMRT vs. 3D-CRT)	2.182	0.649–7.333	0.207			

OR, odds ratio; CI, confidence interval; KPS, Karnofsky Performance Status; IDH, isocitrate dehydrogenase; LOH, loss of heterozygosity; MGMT, O^6-methylguanine-DNA methyltransferase; EGFR, epidermal growth factor receptor; PCV, procarbazine, lomustine, and vincristine; RT, radiotherapy; EQD2, equivalent dose in 2 Gy fraction; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy.

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for surviving patients, the median OS and PFS were 74 and 74 months, respectively (Supplementary Fig. 1, only online). The results of the univariate and multivariate analyses of OS are summarized in Supplementary Table 2 (only online). The results of the univariate and multivariate analyses of PFS are summarized in Supplementary Table 3 (only online).

Nine patients experienced disease recurrence. One patient was treated in our institution but had follow-up abroad; while we were informed that the patient had experienced recurrence, no details of the recurrence were provided. Analysis of the recurrence site for eight patients showed that most (n=7) had in-field recurrence, while one patient experienced leptomeningeal seeding. Five of seven patients had recurrent disease within PTV-1, while two patients had recurrent disease within PTV-2. In patients with recurrent disease within PTV-1 (n=5), 2 (40%) had recurrent disease adjacent to the fornix and 3 (60%) had recurrent disease not adjacent to the fornix. Patients with recurrent disease within PTV-2 (n=2) showed a recurrent tumor adjacent to the fornix.

DISCUSSION

This study investigated the correlation between the RT dose and SRN in a homogenous group. We selected patients with AO other than glioblastoma or brain metastasis, since 1) the average age at AO diagnosis is generally low and better OS was anticipated compared to glioblastoma or metastatic brain tumor. Therefore, patients with AO are considered good candidates for observing RT-induced long-term toxicities, as long-term follow-up is possible. 2) The standard treatment for patients with AO comprises surgery and postoperative RT with a dose of 60 Gy, followed by the sixth cycle of maintenance PCV chemotherapy. Since a higher RT dose and long-term chemotherapy can increase the possibility of RN and impairment of neurocognitive function, we selected patients with AO for this study.

The function of the white matter tracts has not yet been accurately identified. Moreover, the problems arising in RN of the white matter tracts have not been studied. Our study began with the hypothesis that patients with AO who have completed standard treatment often have impaired cognitive function or gait disturbance—side effects that may be caused by RN of some anatomical structures. We found that the RT dose exceeding the tolerance to the fornix could explain these symptoms. Our results provide valuable information to doctors from various departments who treat and follow up with patients with AO. Surgeons and medical oncologists would be beneficial considering that older patients or those who have undergone maintenance chemotherapy are more likely to develop SRN. Although it was not statistically significant in our analysis, as many patients (65%) with SRN received maintenance chemotherapy, these patients require more careful observation. For radiation oncologists, this study may be used to provide the information to prevent SRN by determining the target volume and dose of various normal substructures.

The incidence of RN is affected by the RT total dose, RT fractional dose, and irradiation volume. A phase III trial conducted by the Radiation Therapy Oncology Group (RTOG) to compare high-dose RT (total dose ≥64.8 Gy) versus low-dose RT (50.4 Gy) in patients with low-grade glioma[24] observed a higher incidence of RN with high-dose RT (5% vs. 2.5%, respectively). Retrospective studies of patients with metastatic brain tumors reported higher RN rates in patients who received higher RT doses (4.7–9.2%).[25-27] Regarding fractional dose, multi-fractionated stereotactic radiosurgery (SRS) not only leads to lower RN rates but has also been shown to achieve a higher local control rate compared to single-fraction SRS.[28] Regarding the irradiation volume, results from RT to arteriovenous malformations indicated that the fraction of brain volume receiving >10 Gy is statistically correlated with increased RN rates.[29,30] The results of the RTOG 90-05 phase I study showed that tumors >3 cm were associated with a 16-fold increased risk of RN compared to tumors <2 cm.[31] In our analysis, a high maximum dose to the fornix was correlated with SRN, which may be due not only to its high RT dose but also to the high volume of RT administered, since the fornix is in the center of the brain.

In addition to RN, impaired cognitive function is associated with patients who receive RT, especially those expected to have long lives after treatment, such as children or adolescents. Higher doses of RT and larger volumes of irradiation are associated with cognitive deficits, as observed in RN. For example, young children treated with 36 Gy of craniospinal irradiation have a lower intelligence quotient (IQ).[32,33] In addition to the dose and volume, RT to specific regions such as the temporal lobes and hippocampus may affect long-term IQ.[34,35] Jacola, et al.[36] reported that the volume of normal-appearing white matter could explain neurocognitive deficits. Since the white matter tract is vulnerable to RT, a decline in working memory ability is associated with white matter tract loss after RT.[37] However, few studies have reported on the fornix. Therefore, our study is the first to investigate the relationship between RT and the fornix. Our results showed that most of the patients with SRN experienced impairment of cognitive function (76%), and two patients had RN in both the fornix and hippocampus. Necrosis of the hippocampus may be related to decreased cognitive and memory function.

Modern RT techniques, such as IMRT or proton therapy, enable an organ-saving plan compared to two-dimensional RT or 3D-CRT. The hippocampus, hypothalamus, and pituitary gland could be spared with volumetric modulated arc therapy.[8,9,38] Since RT to the hypothalamic-pituitary gland can result in hormonal dysfunction, a planning study showed simultaneous dose reduction of the hippocampus, hypothalamus, and pituitary, as well as adequate target coverage. Therefore, research on brain substructures that have not yet been studied is required. Specific organ sparing, such as a small part of the brain, was im-

possible with previous RT techniques; however, recent advances in RT techniques and understanding of RT toxicities have enabled physicians to spare normal organs to maintain patients' quality of life and function with the coverage of sufficient target volume guaranteed for oncologic outcomes.

However, our study had several limitations. First, due to disease rarity, the number of patients included in this study was insufficient to obtain statistically significant results regarding dose differences in the fornix. Other diseases, such as meningioma, which has a long survival period, and glioblastoma, the survival of which is increasing due to the development of treatment methods, should be assessed for similar results. Second, since this was an analysis of patients who were already treated, therapeutic intervention for fornix-sparing was impossible. This concept requires validation in prospective settings to demonstrate that fornix-sparing RT results in comparable survival and recurrence rates with decreased SRN. In addition, due to the retrospective nature of the study, the radiation-induced toxicities could be underestimated. Finally, considering the OS of AO patients shown in other studies, our study requires more time for follow-up. Despite these limitations, our study had several strengths. First, it is the first to examine the effects of RT on the white matter tract. Second, most patients were treated with IMRT with a consistent protocol, guaranteeing the quality of treatment. Finally, our study provides important cut-off values for clinicians to treat patients with AO.

In conclusion, the maximum fornix dose was a significant factor in the development of SRN. Fornix sparing using modern techniques may help reduce various neurocognitive dysfunction following RT. Further study is needed to evaluate the differences in recurrence and survival in fornix sparing.

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AUTHOR CONTRIBUTIONS

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