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Retrospective Analysis of Bevacizumab in Combination with Ifosfamide, Carboplatin, and Etoposide in Patients with Second Recurrence of Glioblastoma

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Abstract

Bevacizumab has been reported to be effective for recurrent glioblastoma. In our hospital, ifosfamide, carboplatin, etoposide (ICE) is the second-line chemotherapy for first recurrence of glioblastoma after temozolomide failure. In the present analysis, we retrospectively investigated the feasibility and effectiveness of bevacizumab combined with ICE in patients with glioblastoma at second relapse during ICE treatment. Between 2010 and 2012, tumor progressions were diagnosed in consecutive 8 patients who were treated with ICE for the first recurrence of glioblastoma. These patients were administered 3 cycles of 10 mg/kg bevacizumab every two weeks in combination with ICE treatment. The objective response rate of bevacizumab combination was 75% in Neuro-Oncology Working Group (RANO criteria), including complete response and partial response. Median progression free survival (PFS) and median overall survival (OS) after second relapse were 3.7 months (95% confidence interval [CI], 2.5–18.5 months) and 6.0 months (95% CI, 3.2–19.7 months), respectively. The 6-month PFS rates were 25% (95% CI, 0–55.0%). The median OS after initial diagnosis was 23.3 months (95% CI, 16.2–55.8 months). The grade 2 or 3 hematologic adverse events were identified in 7 of 8 patients, most of which might be due to ICE chemotherapy. The results of our retrospective analysis suggest that combination treatment with bevacizumab and ICE may be safe and beneficial in patients with recurrent glioblastoma.

Key words: recurrent glioblastoma, bevacizumab, ifosfamide, carboplatin, etoposide (ICE), second recurrence

Introduction

Glioblastomas are primary malignant brain tumors causing poor morbidity and mortality.[17] Current standard treatment in newly diagnosed glioblastoma includes radiotherapy with concomitant and adjuvant temozolomide following surgery. The median survival for patients with glioblastoma remains 14.6 months.[17] The biological nature of glioblastoma is extremely refractory and relapsing. However, there is no consensus on the optimal practice for patients with recurrent glioblastoma. In the literatures, there are many retrospective studies and prospective trials to treat recurrent glioblastoma. An alternative dosing schedule of temozolomide is a reasonable option in patients with glioblastoma who experience progression after conventional 150 or 200 mg/m^2 5/28 dosing schedule.[9,10,24] The RESCUE study showed clinical benefit with 6-month progression free survival (PFS) rates (PFS-6) of 17% and 23.9% with continuous dose-intense temozolomide 50 mg/m^2/d in recurrent glioblastoma.[9] The study of the "week on/week off" dosing schedule of temozolomide at a dose of 150 mg/m^2/day demonstrated clinical benefit with

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a PFS-6 of 43.8% in recurrent glioblastoma.[24]

Based on the highly angiogenic nature of glioblastoma, anti-angiogenic targeted agents have been applied to a treatment approach. Bevacizumab is a humanized monoclonal antibody against the vascular endothelial growth factor.[22] First phase II study of bevacizumab and irinotecan in patients with recurrent malignant glioma showed clinical benefit with a PFS-6 of 38%.[16,19] Following studies showed the efficacy with a PFS-6 of 29–42.6% of single-agent bevacizumab in patients with recurrent glioblastoma who were treated with conventional management with temozolomide.[4,6] Japanese phase II study of single-agent bevacizumab in patients with recurrent malignant glioma also demonstrated a PFS-6 of 33.9%.[8] However, bevacizumab responses are rarely durable.[8,19,20]

Phase II study of ifosfamide, carboplatin, and etoposide (ICE) for recurrent glioblastoma showed a PFS-6 of 35% and mild adverse events.[1] In our institute, ICE is used as second-line chemotherapy in patients with first relapsing glioblastoma treated with conventional management with temozolomide. Bevacizumab has generally been used in combination with cytotoxic agents in the management of solid malignancies. Retrospective studies have shown that regimens containing bevacizumab and carboplatin were effective on recurrent glioblastoma.[3,7,11,12] Therefore, for patients with re-recurrent glioblastoma treated with ICE, we use another chemotherapeutic agents containing bevacizumab combination with ICE. Retrospectively, we investigated the feasibility and effectiveness of bevacizumab combined with ICE in patients with second recurrence of glioblastoma during ICE treatment following temozolomide failure.

Materials and Methods

Patient's demographics, clinical data, radiological, and histopathological findings, type of chemotherapy, number of chemotherapy cycles, and survival data were obtained retrospectively from our hospital medical records. We reviewed consecutive 8 patients diagnosed as second relapse of glioblastoma resistant to ICE, who were treated with bevacizumab in combination with ICE between 2010 and 2012. All patients had undergone previous surgery and were diagnosed histologically with glioblastoma. This retrospective analysis is in compliance with the Declaration of Helsinki (Sixth Revision, 2008). All data were collected retrospectively and in accordance with institutional ethical policies.

Patients were evaluated with magnetic resonance imaging (MRI) every 1 to 2 months or according to clinical symptoms after the initial treatment. Tumor recurrence was diagnosed by MRI and positron emission tomography imaging with 18F-fluorodeoxyglucose (18F-FDG). In the case with suspicious pseudo-progression, the adjuvant chemotherapy was continued.

The initial treatment following the first surgery were three types: radiotherapy with concomitant and adjuvant temozolomide,[17] radiotherapy concomitant and adjuvant nimustine, carboplatin, vincristine, and interferon-beta (VACferon) followed by adjuvant temozolomide, radiotherapy with concomitant and adjuvant temozolomide and interferon-beta.[21] All patients were diagnosed with first recurrence of glioblastoma and received ICE chemotherapy following surgical resection or/and stereotactic radiosurgery (35 Gy, 5 fractions) or no treatment. ICE regimen consisted of ifosfamide (750 mg/m^2/day on day 1, 2, and 3), carboplatin (75 mg/m^2/day on day 1, 2, and 3), and etoposide (75 mg/m^2/day on day 1, 2, and 3) in every 4–6 weeks.[1] All patients were diagnosed with second recurrence of glioblastoma refractory to ICE and received 3 cycles of 10 mg/kg bevacizumab, every two weeks, in combination with the same regimen of ICE as before.

The objective response rate (ORR) to treatment was assessed using the Response Assessment in Neuro-Oncology Working Group (RANO criteria).[23] We evaluated contrast-enhanced T_1-weighted images and fluid attenuated inversion recovery (FLAIR) images at the second relapse and after 3 cycles of bevacizumab. Both complete and partial responses were considered objective responses. Toxicity was evaluated after 3 cycles of bevacizumab according to the National Cancer Institute Common Toxicity Criteria (CTCAE) version 4.0. PFS was measured from the date of image diagnosis to the date of disease progression or death. Patients alive and progression free at last contact are treated as censored in the PFS analysis. Overall survival (OS) was defined as the time from the date of diagnosis to the date of death or last contact. The Kaplan–Meier method was used to estimate survival, which was measured from the time of diagnosis to the date of death. Statistical analyses were with PRISM version 5.0 (GraphPad Software Inc., La Jolla, California, USA).

Results

The characteristic features of 8 patients analyzed in this study are summarized in Table 1. There were 6 males and 2 females, and the median age was 53 years. Six patients received radiotherapy (60 Gy, 30 fractions) with concomitant and adjuvant temozolomide as the initial treatment. Exceptionally,

Table 1 Demographic characteristics of patients With second recurrence of glioblastoma

Case	Age	Sex	First chemotherapy	Radiation (Gy)	First chemotherapy (cycle number)	Salvage treatments at first relapse	ICE cycle number at second relaspe	Salvage treatments at second relapse	KPS at second relapse (%)
1	60	M	VACferon	59.4	VACferon (6), TMZ (27)		6		60
2	27	F	TMZ	60	TMZ (12)	Surgery	12	Surgery	80
3	52	M	TMZ	60	TMZ (11)	Surgery	8		50
4	47	M	TMZ	60	TMZ (6)	Surgery	3		70
5	67	F	TMZ	60	TMZ (7)	Surgery, SRT 35Gy	2		60
6	64	M	TMZ+IFN	60	TMZ+IFN (5)		2		50
7	62	M	TMZ	60	TMZ (16)	SRT 35Gy	4		70
8	51	M	TMZ	60	TMZ (4)	Surgery, SRT 35Gy	4		60

F: female, KPS: Karnofsky performance status, M: male, SRT: stereotactic radiosurgery, TMZ: temozolomide, VACferon: nimustine, carboplatin, vincristine, interferon-beta.

one patient, Case 1, was received ACNU regimen of VACferon with radiotherapy followed by adjuvant temozolomide. Another patient, Case 5, was received interferon-beta in combination with the conventional management with radiotherapy and temozolomide. After the first recurrences were recognized during temozolomide treatment, three patients (Cases 2–4) had tumor resection, two (Cases 5 and 8) had tumor resection followed by stereotactic surgery for the residual tumor (35 Gy, 5 fractions), and one patient (Case 7) had only stereotactic surgery (35 Gy, 5 fractions). All patients were treated with ICE chemotherapy after temozolomide failure. At second relapse diagnosed during ICE treatment, 3 cycles of 10 mg/kg bevacizumab in every two weeks were administered. The median values of Karnofsky Performance status were 60 (50–80). The cycle numbers of ICE were 2–12 before the second relapse of glioblastoma. Only one patient (Case 2) had tumor resection before administration of bevacizumab.

Clinical results in 3 cycles of bevacizumab combination in patients with second recurrence of glioblastoma resistant to ICE are summarized in Table 2. The ORR of bevacizumab including complete response and partial response was 75% in RANO criteria (Fig. 1, Case 2). The median PFS and OS after bevacizumab in combination with ICE were 3.7 months (95% confidence interval [CI], 2.5–18.5 months) and 6.0 months (95% CI, 3.2–19.7 months), respectively. The PFS-6 rates were 25% (95% CI, 0–55.0%). The median OS after onset was 23.3 months (95% CI, 16.2–55.8 months). Two patients (Cases 2 and 7) were treated with additional bevacizumab at third relapse of glioblastoma.

Bevacizumab in combination with ICE did not produce any acute toxic events. Hematologic and nonhematologic grade 2 or 3 adverse events are showed in Table 3. There was no grade 4 or higher adverse events except in one patient (Case 1). The death of the patient (Case 1) was not related to chemotherapy. Hematologic toxicities were identified in 7 of 8 patients and comprised 60% of the grade 2 or 3 adverse events. These adverse events were thought to be attributed to ICE chemotherapy. Cerebral hemorrhage, hypertension, proteinuria, and venous thromboembolism more than grade 3 were not identified in this series.

Discussion

This is the first report to evaluate combined administration with bevacizumab and ICE in patients with second recurrence of glioblastoma during ICE treatment, although it is retrospective analysis in small number cases. These results indicated that bevacizumab combined with ICE improved clinical deterioration in 6 of 8 patients with glioblastoma at second relapse. Furthermore, this combination therapy did not cause any severe adverse events, which means that bevacizumab is well tolerated although during ICE chemotherapy.

Bevacizumab is widely used in recurrent glioblastoma, alone or in combination with other agents. In the meta-analysis of bevacizumab effect for recurrent glioblastoma using 15 studies published

Table 2 Results of bevacizumab in combination with ICE in patients with second recurrence of glioblastoma

Case	Bevacizumab cycles	ICE cycle number after second relaspe	RANO criteria	OS from the initial diagnosis	OS from ICE (months)	OS from bevacizumab (months)	Current status
1	3	2	PR	55.2	8.4	1.6	Dead
2	3 + 4	10	PR	44.2	30.2	18.7	Dead
3	3	17	PR	55.8	45.2	33.0	Alive
4	3	6	PR	20.2	11.1	8.0	Dead
5	3	1	SD	16.6	7.6	3.0	Dead
6	3	2	PR	16.2	8.4	4.8	Dead
7	3 + 2	3	PR	26.3	9.3	6.3	Dead
8	3	3	SD	16.4	9.6	5.6	Dead

ICE: ifosfamide, carboplatin, and etoposide, OS: overall survival, PR: partial response, RANO criteria: Response Assessment in Neuro-Oncology Working Group, SD: stable disease.

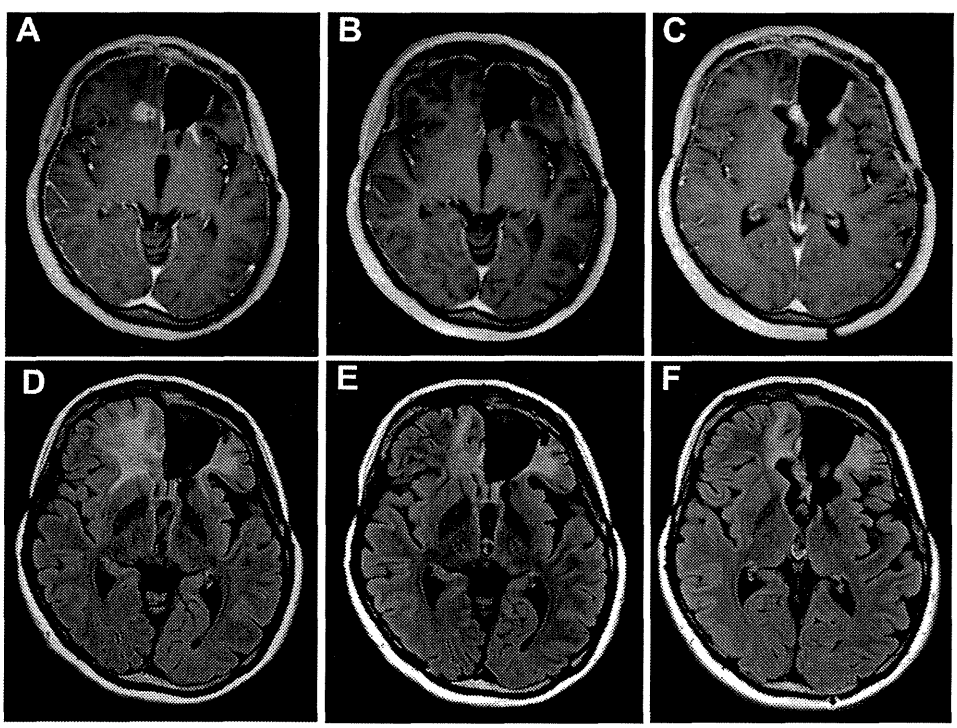

Fig. 1 Illustrative Case 2, 27-year-old female. A, D: Glioblastoma of the patient had rapidly regrown after the third surgery for her second relapsing tumor resistant to ICE. B, E: Her lesion was decreased after 3 cycles of 10 mg/kg bevacizumab combined with ICE. C, F: Her lesion recurred after 3 cycles of ICE following bevacizumab. A, B, C: contrast-enhanced T_1-weighted images. D, E, F: fluid attenuated inversion recovery images. ICE: ifosfamide, carboplatin, etoposide.

from 2005 to 2009, PFS-6 was 45%. The median OS was 9.3 months. The response rate analysis demonstrated 6% complete response, 49% partial response, and 29% stable disease.[25] Japanese phase II study of single-agent bevacizumab showed that PFS-6 was 33.9% and median OS was 3.3 months in 29 patients with recurrent glioblastoma.[8] In our analysis of bevacizumab in combination with ICE chemotherapy, PFS-6 was 25% and median OS was 6.0 months. Regarding the survival endpoints, our results seem to be worse than previously published data. It was a primary factor that the

Table 3 Number of patients who experienced adverse events according to CCTAE grade

Toxicity	Grade 2	Grade 3	Total
Anemia	1	0	1
Lymphopenia	3	3	6
Platepenia	2	0	2
Hypoalbuminiemia	1	0	1
Constipation	5	0	5
Total	12	3	15

CCTAE: Common Terminology Criteria for Adverse Events

subjects were patients with second recurrence of glioblastoma in our analysis. This is compatible with previous reports that the PFS-6 and ORR were numerically higher in patients experiencing first relapse compared to those experiencing second relapse.[4,8]

The phase II study to evaluate effect of bevacizumab-alone and bevacizumab-plus-irinotecan for recurrent glioblastoma demonstrated no significant difference of survival endpoints, median OS times were 9.2 months and 8.7 months, respectively. However, our analysis showed that in two patients (Cases 2 and 3) who received more than 8 cycles of ICE, bevacizumab improved their disease progressions refractory to ICE chemotherapy. Many previous reports also have implied that bevacizumab may have potential to affect tumor in combination with another chemotherapeutic agent.[7,18,19] A possible mechanism is that antiangiogenic therapy affects tumor vascular structure and blood perfusion. The study to assess tumor blood perfusion in recurrent glioblastoma treated with cediranib, a pan-VEGF receptor tyrosine kinase inhibitor, demonstrated that tumor blood perfusion increased in 7 of 30 patients. Increase of tumor blood perfusion was associated with longer survival. Antiangiogenic therapy induced-vascular normalization probably changes the efficacy of the combination drugs.[15]

Recently, two phase III studies, AVAglio and RTOG 0825, to evaluate the addition of bevacizumab to standard temozolomide management in patients with newly diagnosed glioblastoma were performed.[2,5] These studies showed that the addition of bevacizumab did not improve OS but did improve PFS. Based on these results, it is a controversial matter whether bevacizumab is combined with the standard temozolomide management as the initial treatment. And there are clinical questions to resolve. First, what is the factor to bring effect of bevacizumab? Bevacizumab-plus-irinotecan also resulted in high ORR and an increased PFS-6 value, but showed no improvement in OS. Some patients with recurrent glioblastoma and well respond to bevacizumab have survived significantly longer than non-responders.[19] In our analysis, salvage effects of additional bevacizumab tend to be prominent in ICE responders. Second, how do we use bevacizumab to be more effective and less harmful, for example, continuation or short-period administration similar to steroid? The retrospective study demonstrated that bevacizumab continuation beyond initial progression was associated with modestly improved outcome compared with non-bevacizumab therapy.[13] Third, no difference was seen in bevacizumab dose-response benefit between 5 mg/kg and 10 mg/kg to 15 mg/kg. The lack of a dose-response effect would require confirmation in a prospectively conducted clinical trial. A model for the potential therapeutic benefits of low-dose antiangiogenic therapy was introduced.[22] Antiangiogenic therapy is perspective tool in association with tumor vascularity and drug delivery.

There is no established standard salvage chemotherapy for recurrent glioblastoma after the failure of standard management with temozolomide. Phase II studies of ICE chemotherapy in patients with recurrent glioblastoma showed clinical benefit with a PFS-6 of 35%.[1] In our hospital, we use dose-reduction regimen of ICE as second-line chemotherapy for first relapsing glioblastoma. A Germany retrospective study, which was reported by Schäfer et al., showed that ICE was not effective in patients with recurrent high-grade glioma if applied at second or third relapse.[14] In our analysis, PFS-6 was 37.5% in patients treated with ICE chemotherapy at the first relapse of glioblastoma. Retrospective studies of chemotherapy containing bevacizumab and carboplatin have also shown favorable effect that PFS-6 rates were 22–50% in recurrent glioblastoma.[3,7,11,12] These suppose that the regimen containing carboplatin has potency to be active in malignant glioma, and that the efficacy of regimen combined with bevacizumab and ICE in patients with first relapse of glioblastoma should be addressed.

In conclusion, we consider that the combination of bevacizumab and ICE is well tolerated and may derive some clinical benefits in recurrent glioblastoma patients, in spite of the limitations of our analysis. Bevacizumab seems to be more active with in patients with first recurrence of glioblastoma compared those with its second recurrence. The dose intensity and schedule of bevacizumab and ICE need be optimized in future studies.

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Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices in the article. All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members. This manuscript has no COI that should be disclosed.

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Cancer Medicine

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ORIGINAL RESEARCH

Efficacy of salvage stereotactic radiotherapy for recurrent glioma: impact of tumor morphology and method of target delineation on local control

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Abstract

In this study, we assessed the efficacy of salvage stereotactic radiotherapy (SRT) for recurrent glioma. From August 2008 to December 2012, 30 patients with recurrent glioma underwent salvage SRT. The initial histological diagnoses were World Health Organization (WHO) grades II, III, and IV in 6, 9, and 15 patients, respectively. Morphologically, the type of recurrence was classified as diffuse or other. Two methods of clinical target delineation were used: A, a contrast-enhancing tumor; or B, a contrast-enhancing tumor with a 3–10-mm margin and/or surrounding fluid attenuation inversion recovery (FLAIR) high-intensity areas. The prescribed dose was 22.5–35 Gy delivered in five fractions at an isocenter using a dynamic conformal arc technique. The overall survival (OS) and local control probability (LCP) after SRT were calculated using the Kaplan–Meier method. A univariate analysis was used to test the effect of clinical variables on OS/LCP. The median follow-up period was 272 days after SRT. The OS and LCP were 83% and 56% at 6 months after SRT, respectively. Morphologically, the tumor type correlated significantly with both OS and LCP ($P = 0.006$ and <0.001, respectively). The method of target delineation also had a significant influence on LCP ($P = 0.016$). Grade 3 radiation necrosis was observed in two patients according to Common Terminology Criteria for Adverse Events, version 3. Salvage SRT was safe and effective for recurrent glioma, especially non-diffuse recurrences. Improved local control might be obtained by adding a margin to contrast-enhancing tumors or including increased FLAIR high-intensity areas.

Introduction

The management of recurrent glioma is a challenging issue. In particular, recurrent glioblastoma has a dismal prognosis; the median survival time after progression was 6 months in a clinical trial [1]. Various kinds of chemotherapy and targeted therapy have been tested, but the optimal treatment strategy remains unclear [2, 3]. Radiotherapy is one option. Although re-irradiation may not be a curative approach [4], it could be an attractive option for controlling progressive lesions at areas unsuitable for surgery and those remaining despite repeated chemotherapy. Stereotactic radiotherapy (SRT) may be used to spare as much normal brain tissue as possible. To date, several retrospective or phase I/II studies have been published [5–18]. The overall survival (OS) after salvage re-irradiation is reportedly about 10 months, but assessments of the local control probability (LCP) are rare. Local control and its palliative effect seem to be important endpoints in terms of local treatment. In this retrospective study, we focused on the relationships between LCP and several clinical factors, especially the tumor's morphological type and target delineation.

Methods

Patient population

From August of 2008 to December of 2012, 37 patients with recurrent glioma underwent salvage SRT at our hospital. Among them, seven patients who had disseminated disease at the time of SRT and/or had no follow-up magnetic resonance imaging (MRI) scans at least 1 month after initial SRT were excluded. The remaining 30 patients with 33 lesions were analyzed retrospectively, referring to clinical records. Written informed consent was obtained from the patients for publication of this report and any accompanying images. All patients underwent surgery and received radiotherapy with or without chemotherapy as initial treatments after the time of primary diagnosis. In our hospital, radiotherapy doses are 50.4–54 Gy in 28–30 fractions for low-grade glioma (WHO [World Health Organization] grade II) and 59.4–63 Gy in 30–35 fractions for high-grade glioma (WHO grade III–IV). Concurrent chemotherapy was combining nimustine (ACNU)–carboplatin–vincristine–interferon-β chemotherapy [19] for all grade gliomas, and after the emergence of temozolomide (TMZ) in our country, TMZ has been applied for high-grade gliomas. Two patients had received gamma-knife radiosurgery for low-grade glioma in other hospitals before our initial chemoradiotherapy treatment. Another patient had refused to continue initial radiotherapy and she had received only 18 Gy in 10 fractions. Regarding the morphological patterns of recurrent tumors on conventional MRI, Pope et al. [20, 21] classified them into four categories in the BRAIN trial: local, distant, diffuse, and multifocal. Using a modified version of this classification system, we classified the recurrent tumors into two groups: diffuse and other. Briefly, diffuse recurrence was defined as recurrence either centered or extending more than 2 cm (originally 3 cm) from the primary site or margin of the resection cavity, with ≥50% of the margin of the recurrent tumor qualitatively assessed as poorly defined. In contrast to a diffuse pattern, the margin of a recurrent tumor of another type (local, distant, or multifocal) was defined as mostly or completely well-defined. Details are given elsewhere [21]. Representative cases of diffuse and non-diffuse recurrent tumors are shown in Figure 1.

SRT

Treatment was performed using the Novalis system, equipped with an ExacTrac system and Robotic Tilt Module mounted on the Exact Couch top (BrainLAB AG, Feldkirchen, Germany). Patients were immobilized in a thermoplastic stereotactic head mask with an additional bite block and infrared reflecting markers (BrainLAB AG). Patients were positioned using the Novalis/ExacTrac system, and positional errors, including translations and rotations, were corrected by moving the robotic couch.

For treatment planning, computed tomography (CT) scans (1.25 mm slice thickness) were acquired using a Light Speed RT scanner (GE Healthcare, Milwaukee, WI). Treatment planning was performed using iPlan or BrainScan software (BrainLAB AG). Images produced by conventional MRI were fused with the planning CT scans. The gross tumor volume (GTV) was defined as contrast-enhancing tumor. Delineation of the clinical target volume (CTV) was done at the discretion of the treating physician. We classified the groups retrospectively by two methods: A, contrast-enhancing tumor only (i.e., identical to the GTV); and B, contrast-enhancing tumor plus a margin of 3–10 mm and/or surrounding fluid attenuated

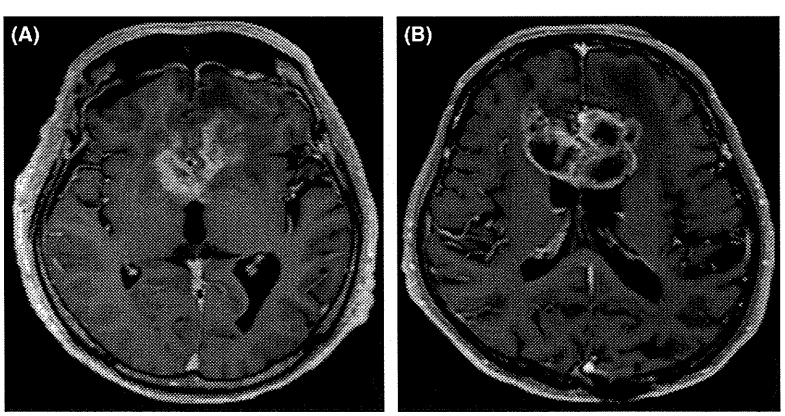

Figure 1. Examples of tumor morphological types. Representative cases of (A) diffuse and (B) non-diffuse recurrent tumors are shown. Diffuse recurrent tumors extended more than 2 cm from the primary site, with ≥50% of the margin qualitatively assessed as poorly defined.

inversion recovery (FLAIR) high-intensity increasing lesions. Then, the CTVs were expanded 1–2 mm to create the planning target volumes (PTVs) in consideration of setup error and patient motion. In one patient who had an absolutely non-contrast-enhancing tumor, the CTV was delineated based on a growing FLAIR high-intensity lesion (i.e., method B). The prescribed doses were specified at the isocenter; 22.5–35 Gy in five daily fractions was prescribed (median, 35 Gy). The PTV was covered by the 70–80% isodose line of the prescribed dose. In all patients, the dynamic conformal arc technique was used.

Follow-up and assessment

We analyzed the intracranial status and disease progression after salvage SRT retrospectively, in accordance with "Response Assessment in Neuro-Oncology Working Group of the American Society of Clinical Oncology" (RANO) criteria [22]. Briefly, progression was defined as an increase in 25% of the product of perpendicular diameters of enhancing lesions, a significant increase in the T2/FLAIR non-enhancing component, appearance of new lesions, and clinical deterioration not attributable to causes other than the tumor or a reduction in the corticosteroid dose. The assessment of local control was also based on RANO criteria, considering contrast-enhancing lesions and/or T2/FLAIR components. Local recurrence patterns were operationally defined as "central" if the recurring tumors were centered within the initial contrast-enhancing tumor and otherwise as "marginal." Treated lesions contrast-enhanced peripherally or heterogeneously, with no continuous progression, were diagnosed as radiation necrosis. Nuclear medicine tests, including positron emission tomography, were conducted as necessary for differential diagnosis. The severity of radiation necrosis was evaluated according to Common Terminology Criteria for Adverse Events (CTCAE), version 3, which defines asymptomatic central nervous system (CNS) necrosis with only radiographic findings as grade 1 toxicity. Grade 2 CNS necrosis is defined as symptomatic, but not interfering with the activities of daily living (ADL). Grade 3 CNS necrosis is symptomatic and interferes with ADL. Grade 4 CNS necrosis is defined as life-threatening and requires operative intervention. The level of steroid treatment and Eastern Cooperative Oncology Group performance status (PS) were also evaluated at the time of salvage SRT (baseline) and at 1 and 3 months after salvage SRT.

Statistical analysis

OS, progression-free survival (PFS), and LCP were estimated using the Kaplan–Meier method. OS was calculated from the date of initial SRT to that of death or last follow-up. PFS was calculated from the date of initial SRT to that of disease progression, defined by RANO criteria, or last follow-up. LCP was calculated from the date of initial SRT to local failure or last imaging follow-up. A univariate analysis was used to estimate the association of OS or LCP with various clinical factors; P-values <0.05 were considered to indicate statistical significance. All analyses were performed with EZR (Saitama Medical Center, Jichi Medical University; http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/manual.html; Kanda, 2013), a graphical user interface for "R" software, version 2.13.0 (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of "R" Commander (version 1.6-3), designed to add statistical functions frequently used in biostatistics [23].

Results

Patient and tumor characteristics

The characteristics of 30 patients with 33 lesions are shown in Table 1. All patients received radiotherapy with

Table 1. Characteristics of 30 patients with 33 lesions.

Characteristics	Number or value
Gender	
Male/female	17/13
Age (years)	
Median (range)	52.5 (19 81)
Primary diagnosis	
WHO grade II/III/IV	6/9/15
Most recent histological diagnosis	
WHO grade II/III/IV	2/10/18
Performance status	
0/1/2/3/4	9/10/5/4/2
Tumor location	
F/P/T/O/CC/BG/CB	9/1/5/3/6/5/4
Tumor morphological type	
Diffuse/other	11/22
Contrast-enhancing tumor volume (cc)	
Median (range)	3.2 (0 36.1)
PTV volume (cc)	
Median (range)	9.0 (1.0 140.0)
Target delineation	
Method A/B	16/17
Dose per fraction (Gy)	
4.5/5/6/7	1/3/8/21
Concurrent chemotherapy with SRT	
None/TMZ/ICE/Others	17/4/4/5

BG, basal ganglion; CB, cerebellum; CC, corpus callosum; F, frontal lobe; ICE, ifosfamide, carboplatin, and etoposide; O, occipital lobe; P, parietal lobe; SRT stereotactic radiotherapy; T, temporal lobe; TMZ, temozolomide; WHO, World Health Organization.

or without chemotherapy at the time of primary diagnosis. In total, 24 recurrent tumors were within the initial radiotherapy field and the remaining nine were outside the field. The median time from initial radiotherapy to salvage SRT was 755 (range, 127–3571) days. SRT was performed for first recurrent tumors in nine (30%) patients and for repeated recurrent tumors in the remaining 21 (70%), who had already undergone salvage chemotherapy (20 patients) and/or salvage surgery (14 patient) more than 1 month before SRT. At the time of SRT, six patients underwent partial resections or biopsies with a histological diagnosis of recurrence while the remaining 24 patients were diagnosed radiographically or clinically because of difficulty in approaching the tumor location surgically or a poor PS. All recurrent tumors except one had a progressive contrast-enhancing component and were diagnosed clinically as WHO grade III or higher. One patient was initially diagnosed with anaplastic astrocytoma (WHO grade III). The median follow-up time from the start of SRT to death or last follow-up was 273.5 (range, 61–702) days, while the median MRI imaging follow-up period from SRT was 238 (range, 47–699) days.

Outcomes of SRT and influencing factors

The median OS was 316 days (95% confidence interval [CI], 252–389); at 6 and 12 months, the OS was 83% (95% CI, 64–93) and 34% (95% CI, 17–53), respectively. The median PFS was 91 days (95% CI, 75–121); at 6 and 12 months, the PFS was 19% (95% CI, 7.6–35) and 10% (95% CI, 2.2–26), respectively. The median LCP was 210 days (95% CI, 141–491); at 6 and 12 months, the LCP was 56% (95% CI, 37–71) and 38% (95% CI, 21–55), respectively. Local control failures were observed in 22 of 33 lesions (67%) within the follow-up time. The local failure patterns were central in eight (36%) and marginal in 14 (64%) lesions. Marginal recurrence after salvage SRT was observed in eight of 13 patients (62%) with method A and six of nine patients (67%) with method B. Kaplan–Meier curves of LCP for methods A and B are shown in Figure 2. Peripheral dose (minimum dose) of contrast-enhancing tumor was a median of 29.7 Gy (range, 17.8–31.3) in method A and 29.1 Gy (range, 18.8–32.2) in method B with no significant difference (Mann–Whitney U test; $P = 0.79$). A univariate analysis for OS and LCP was performed considering various clinical factors believed to be important; the results are summarized in Table 2. Morphological classification (diffuse or not), most recent WHO grade (II–III or IV), and PS were significantly associated with OS. On the other hand, morphological classification, PS, method of target delineation (contrast-enhancing tumor only or

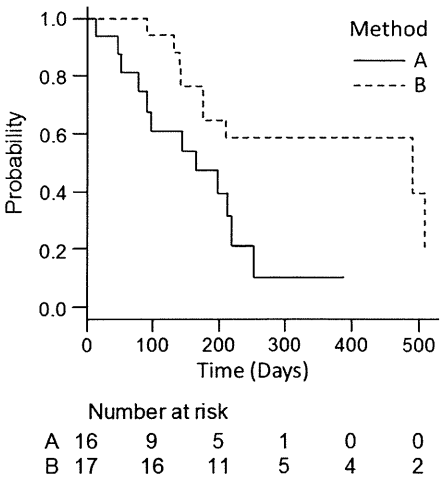

Figure 2. Local control probability depending on methods of target delineation. Local control probability of 33 lesions from the date of salvage stereotactic radiotherapy was estimated using the Kaplan–Meier method depending on methods of clinical target delineation: A, contrast-enhancing tumor only; or B, contrast-enhancing tumor plus a margin of 3–10 mm and/or surrounding fluid attenuated inversion recovery high-intensity increasing lesions.

Table 2. Univariate analysis of overall survival and local control probability.

	Outcomes at 6 months (95% CI) and *P*-values			
Factors	Overall survival		Local control	
Age (years)				
<50	85% (53–94)	0.69	60% (29–81)	0.60
≥50	82% (51–96)		53% (29–72)	
Performance status				
0–1	95% (68–99)	0.026[1]	76% (52–89)	<0.001[1]
2–4	61% (27–84)		14% (1–43)	
Most recent histological diagnosis				
WHO grade II–III	92% (54–99)	0.016[1]	64% (30–85)	0.21
WHO grade IV	78% (51–91)		52% (29–71)	
Time from initial RT to progression				
<600 days	80% (51–93)	0.21	53% (29–72)	0.25
≥600 days	86% (54–96)		61% (30–82)	
Concurrent chemotherapy				
Yes	68% (36–87)	0.20	38% (13–63)	0.24
No	94% (65–99)		68% (43–84)	
Tumor morphological type				
Diffuse	62% (28–84)	0.006[1]	21% (0.3–48)	<0.001[1]
Others	95% (68–99)		72% (49–87)	
Contrast-enhancing tumor volume (cc)				
<4 cc	81% (51–93)	0.85	73% (46–88)	0.018[1]
≥4 cc	86% (54–96)		33% (11–58)	
Target delineation				
Method A	73% (43–89)	0.084	47% (22–69)	0.016[1]
Method B	93% (61–99)		65% (38–82)	

CI, confidence interval; RT, radiotherapy; WHO, World Health Organization.

[1]Regarded as statistically significant ($P < 0.05$).

not), and the contrast-enhancing tumor volume (<4 cc vs. ≥4 cc) were significantly correlated with the LCP.

Toxicity

Radiation necrosis was grade 1 in 13, grade 2 in five, and grade 3 in two lesions, according to CTCAE, version 3. No case of grade 4 toxicity was observed. Thus, the crude proportion of radiation necrosis ≥grade 3 was 6.1% (2/33 lesions) and no uncontrollable radiation necrosis was observed in the follow-up period. Fifteen patients received bevacizumab (BEV) after SRT and one before SRT. The median time from SRT to BEV was 148 (range, −15 to 514) days. One patient received BEV for the treatment of grade 3 radiation necrosis and the others did so as salvage treatment for progressive recurrent disease. A median PTV size was 7.2 cc (range, 1.4–47.8) in method A and 9.3 cc (range, 1.0–140.0) in method B with no significant difference (Mann–Whitney U test; $P = 0.40$). Radiation necrosis in method A was grade 1 in four patients, grade 2 in five patients and grade 3 in one patient. On the other hand, radiation necrosis in method B was grade 1 in nine patients and grade 2 in no patient, and grade 3 in one patient. In addition, there was no difference in usage of BEV between two groups (9/16 lesions in method A and 9/17 lesions in method B).

The steroid dose 1 month after SRT was decreased in three (10%), increased in three (10%), unchanged in five (17%), and was none in 19 (63%) patients. The reasons for increasing the steroid dose were a symptomatic edematous change surrounding the SRT-treated lesion in two patients and progressive disease in one. At 3 months after SRT, two patients had died of progressive disease: diffuse-invasive and infiltrative progression in one patient and disseminated progression in the other. The steroid dose was decreased in five and increased in five patients compared with the baseline dose. The remaining 18 patients needed no steroid treatment. The reasons for the increased steroid dose were progressive disease in three patients and a possible radiation-induced edematous change in two patients.

The PS 1 month after SRT was improved in four (13%), worsened in five (17%), and unchanged in 21 (70%) patients. The reasons for a decreased PS score were local or intracranial progression in four patients and acute radiation effects in one patient, as mentioned above. The PS score at 3 months after SRT was available in 28 patients (two had died, as mentioned above). Patients with an improved PS at 1 month after SRT remained so. An additional three patients had a worsened PS because of progressive disease in two patients and a complex partial seizure in one. The seizure was not the first, but the focus was considered to be the treated lesion and could have been due to an acute irradiation effect.

Discussion

In this report, the presence of a diffuse-type tumor had significant effects on both OS and local control after salvage SRT. The definition of diffuse recurrence was based on Pope's classification in the BRAIN trial [20]. Although that system was created specifically for patients with recurrent glioblastoma who received BEV, it is useful for classifying various and complex morphological characteristics before and after salvage treatment. In some reports [24–26], diffuse-type recurrence has been discussed as a negative effect of antiangiogenic therapy. On the other hand, Wick et al. [27, 28] reported that diffuse-invasive recurrence (i.e., "gliomatosis-like phenotype") might be a feature of late-stage glioma rather than a specific property of antiangiogenic treatment. In this study, we did not use antiangiogenic therapy at the time of first SRT except in one patient, and the poor outcomes observed in patients with a diffuse recurrence supports their finding. In our clinical course, about half of the patients (16 out of 30) received BEV treatment, but the OS was not significantly different from that of patients who did not receive BEV ($P = 0.9$ by univariate analysis).

In a univariate analysis, PS was also one of significant influencing factors on local control but it may be difficult to understand intuitively. In post hoc analysis, morphological type (diffuse or not) and PS (0–1 or 2–4) were strongly correlated with each other (Fisher's exact test; $P = 0.001$) and then an apparent influence of PS on LCP should be a reflection of that of morphological type on LCP. Diffuse-invasive recurrence and lower PS might also be two sides to a feature of late-stage recurrent glioma.

Delineation of the CTV has been limited to contrast-enhancing lesions in most recent reports [5, 9, 11, 14, 18]. In the re-irradiation setting, a smaller irradiated volume is obviously preferable in terms of toxicity, while limiting treatment to contrast-enhancing lesions might lead to a lower LCP, considering the invasiveness of gliomas. Especially in the case of diffuse tumors, a precise understanding of tumor spread is often difficult and supposedly amenable to local failure. In our analysis, the method of target delineation had an impact on LCP. There was no significant difference in background (PS, tumor morphological type, and contrast-enhancing volume) between the two methods of target delineation (Fisher's exact test; $P > 0.1$). There are few reports of target delineation using conventional MRI in the setting of salvage radiotherapy for recurrent glioma. Koga et al. [29] reported that extended-field stereotactic radiosurgery (SRS) yielded better local control for recurrent glioblastoma. They attached a 0.5- to 1-cm margin to contrast-enhancing lesions, and the toxicity profiles were reportedly tolerable, while the proportion of radiation necrosis in extended-field SRS

seemed to be higher than with conventional SRS, approaching a significant level. Patel et al. [10] assessed 10 patients with recurrent glioblastoma who underwent SRT, and the re-irradiation volume was defined as a contrast-enhancing tumor with a rapid increase in the FLAIR imaging signal. The median PTV was 51.1 cc and the prescribed dose was 36 Gy in six fractions, twice weekly, with 90% coverage of the PTV. They reported that patients tolerated the treatment well with limited toxicity, while one patient underwent a biopsy and mixed residual tumor and necrosis was seen 11 months after SRT. Hundsberger et al. [17] reported that adding small margins to the gross target volume were counterintuitive and less appropriate. They attached a 2.5-cm margin to contrast-enhancing tumors and the surrounding edema. Despite this very large re-irradiation field, radiation necrosis was not observed in 10 patients treated with BEV while one patient of four that did not receive BEV showed radiation necrosis. Considering these findings, re-irradiation with an extended field and based on the premise of BEV treatment may be an attractive option for effective and safe salvage treatment.

In our series, the proportion of marginal recurrence was higher than that of central recurrence. A representative case of marginal recurrence is shown in Figure 3. In such a case, adding margins to the contrast-enhancing tumor or target delineation based on successive FLAIR imaging might yield better local control. Although the risk of radiation necrosis might be increased, the incidence of radiation necrosis in our series was not different between methods A and B. On the other hand, marginal recurrence after salvage SRT was similarly observed between methods A and B; thus, method B might yield extended control over tumor recurrence compared to method A, but it did not change the local failure pattern after salvage SRT. Additionally, whole intracranial control (PFS) was very poor (the 6-month PFS was only 19%). This was a reflection of other new multifocal, subependymal, or disseminated recurrences after SRT. Most patients (21/30; 70%) suffered from resistant recurrent tumors despite repeated salvage treatment before SRT. These dismal patterns of recurrence may also be a feature of late-stage glioma; therefore, not only improved local therapy but also effective systemic therapy should be considered.

Radiation necrosis is a major concern in the re-irradiation setting. In this report, two lesions in two patients had CTCAE grade 3 necrosis. Both were within the initial radiotherapy field (63 Gy in 35 fractions and 60 Gy in 30 fractions) and treated at a dose of 35 Gy in five fractions

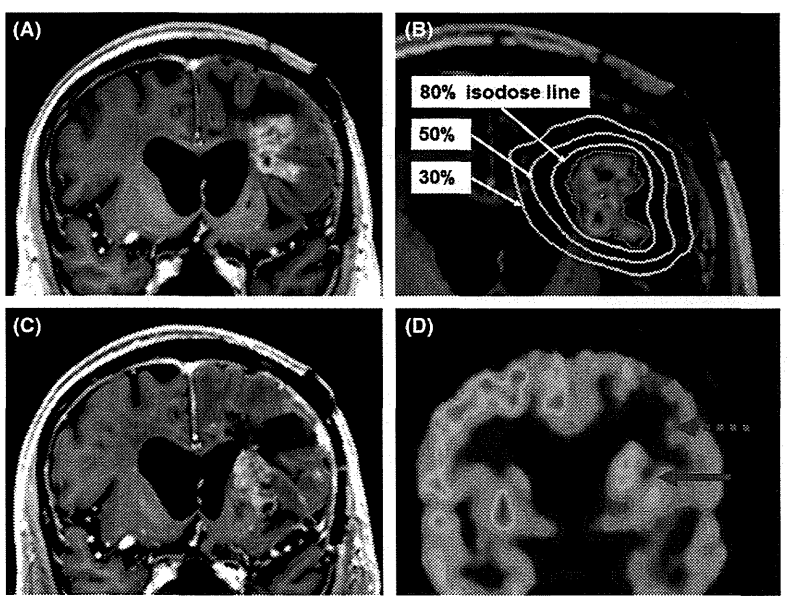

Figure 3. Representative case of marginal recurrence. (A) A recurrent tumor from an anaplastic oligoastrocytoma located in the left frontal lobe, adjacent to the initial surgical cavity and within the field of the initial radiotherapy. (B) The tumor was treated with salvage stereotactic radiotherapy (SRT). Target delineation of the planning target volume (PTV, indicated by the magenta line) was classified as method A (contrast-enhancing lesion plus a 1-mm margin); the prescribed dose was 35 Gy in five fractions with 80% coverage of the PTV. (C) At 10 months after treatment, a new recurrent tumor at the left basal ganglion emerged, adjacent to the previously treated lesion (marginal recurrence). (D) L-Methyl-^{11}C-methionine positron emission tomography supported the diagnosis of recurrence (indicated by a solid arrow), while the SRT-treated area was determined to be radiation necrosis (indicated by a dashed arrow).

with methods A and B for target delineation. The PTVs were 6.8 and 3.0 cc, respectively. The crude proportion of grade 3 necrosis (6.1%) here was comparable with that in recent reports. The dose per fraction in our report was higher than that in other recent series, whereas the PTV was smaller. Our prescribed dose might have a higher risk when applied to much larger tumors. Ernst-Stecken et al. [5] reported outcomes for nearly the same dose-fraction schedule (35 Gy in five fractions with 90% covering the PTV) and for larger volumes (a median PTV of 22.4 cc) and showed acceptable toxicity and maintenance of quality of life (QOL). They also reported that the PTVs were larger than 60 cc in all patients with increased edema after 3 months, with no apparent progression. Considering the difficulty of intracranial control, salvage SRT alone is not a curative approach and the balance between better local control and acceptable toxicity is important. The palliative effect and QOL after SRT should be evaluated in a prospective manner.

As is typical, this retrospective study has some limitations. The small sample size, selection bias, lack of biological information, and various treatment factors, including chemotherapy before and after SRT, made it difficult to interpret the patient outcomes. However, there are few data about salvage SRT for recurrent glioma and the sample size in our study was similar to those in the literature. In particular, our analysis provides additional data about LCP in terms of tumor morphology and method of target delineation.

In conclusion, salvage SRT for recurrent glioma was safe and yielded better outcomes in patients with non-diffuse recurrent tumors. Improved local control may be obtained by adding a margin to contrast-enhancing tumors or including increased FLAIR high-intensity areas, while the overall intracranial control was very poor. Thus, there is continuing need for systemic therapy or a new modality to prevent remote recurrences.

Conflict of Interest

None declared.

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Pineal parenchymal tumor of intermediate differentiation: Treatment outcomes of five cases

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Abstract. Pineal parenchymal tumor of intermediate differentiation (PPTID) is a rare disease, first classified by the World Health Organization in 2000. The number of available studies on the treatment of PPTID is currrently limited and the optimal management for this disease has not yet been determined. We retrospectively evaluated the treatment outcomes for PPTID at our institute and analyzed the roles of radiation therapy and chemotherapy for this disease. The clinical data on five patients diagnosed with PPTID since 2000 were retrospectively reviewed. Patients with cerebrospinal dissemination at diagnosis received biopsy-only surgery, craniospinal and whole-ventricular irradiation and chemotherapy. Patients with locally limited disease at diagnosis received local or whole-ventricular irradiation after surgery. The median relapse-free and overall survival were 72.9 and 94.1 months, respectively. Two of the five patients developed a relapse of cerebrospinal dissemination after treatment and succumbed to the disease. All the patients who received both craniospinal and whole-ventricular irradiation exhibited evidence of cerebral white matter abnormalities in magnetic resonance imaging and developed neurocognitive disorders after treatment. Although PPTID may be aggressive and has cerebrospinal fluid seeding potential, PPTID patients may survive long-term, even after recurrence. Considering the long survival time and the late adverse effects due to intensive treatment, the irradiation field and usage of chemotherapy after surgery require optimization.

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Introduction

Pineal parenchymal tumors are rare, accounting for <0.3% of all primary central nervous system tumors (1). Pineal parenchymal tumors are heterogeneous entities, exhibiting considerable morphological variation. According to the WHO classification for tumors of the central nervous system (2007 revision), these tumors are histologically subdivided into pineocytoma (grade I), pineoblastoma (grade IV), papillary tumor of the pineal region (grade II or III) and pineal parenchymal tumor of intermediate differentiation (PPTID) (grade II or III) (2,3). PPTID is a fairly recently defined disease. It was first classified by the WHO in 2000 as a pineal parenchymal tumor with an intermediate prognosis between pineocytoma and pineoblastoma. Determination of the mitotic index and immunohistochemistry are used to pathologically classify PPTIDs as grade II or III (2,3).

The treatment for pineal parenchymal tumors is histology-dependent. Pineocytomas are treated with surgical resection. If complete or subtotal resection is accomplished, the outcome is favorable, even without adjuvant treatment (4,5). By contrast, the treatment of pineoblastomas should consist of surgery as well as adjuvant treatment, including chemotherapy and craniospinal irradiation. Occasionally, even more aggressive treatment, including myeloablative chemotherapy with stem cell rescue, may be required for the treatment of pineoblastomas (6).

Unlike other histological subtypes, the optimal management for PPTIDs remains to be determined, as it was relatively recently characterized and is rather rare. In one series, patients with PPTID who were treated with surgery alone survived free of disease (7). At the other extreme, another study described PPTIDs as tumors with seeding potential and recommended postoperative treatment in a manner similar to that for pineoblastomas (1). To the best of our knowledge, the number of available studies on the treatment of PPTID is limited, particularly regarding radiation therapy and chemotherapy (8-10), whereas there are currently no treatment reports for PPTID cases alone. The aim of this study was to retrospectively evaluate the treatment outcomes of patients with PPTID who received treatment at our institute and analyze the effects of radiation therapy and chemotherapy on this disease.

Materials and methods

Record review. We conducted a retrospective record review for patients who were diagnosed with PPTID and treated with radiation therapy at our institute from 2000 onwards. Clinical data, including Eastern Cooperative Oncology Group performance status and Karnofsky performance status, pathological results, imaging [computed tomography (CT) and magnetic resonance imaging (MRI)], initial treatment, resection status, details of chemotherapy, details of radiation therapy, initial response to treatment, recurrence pattern and late adverse toxicities, were collected.

The extent of surgical resection was assessed according to the surgical and pathological reports and postoperative imaging. The resection status was classified as previously described: 'gross total resection' was defined as no evidence of contrast-enhancing tumor on postoperative images; 'R2-resection' was any surgical tumor resection less than gross total resection; and 'biopsy only' was no surgical tumor resection due to inoperability, with a biopsy performed to determine tumor histology (10). The response to treatment was assessed based on serial measurements of CT or MRI scans.

The criteria for response were as follows: complete response (CR), disappearance of tumor; partial response (PR), >50% decrease in tumor size; progressive disease, >25% increase in tumor size or any appearance of new sites; stable disease, all other situations. Relapse-free and overall survival were calculated from the initiation of radiation therapy to the date of relapse and to the date of death or last follow-up, respectively. The endpoint of the analysis was the date of either the last follow-up or the patient's death.

The appearance or exacerbation of cerebral white matter abnormalities in MRI after treatment, neurocognitive effects, pituitary function and incidence of cerebrovascular disease were investigated as late effects of treatment, according to the grading system of Radiation Therapy Oncology Group (RTOG) common toxicity criteria and Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. The details of the classification according to neurocognitive disorders are as follows: RTOG (neurological/cortical) grade 1, mild somnolence or agitation; grade 2, moderate somnolence or agitation; grade 3, severe somnolence, agitation, confusion, disorientation or hallucinations; and grade 4, coma, seizures and toxic paralysis; and CTCAE (cognitive disturbance) grade 1, mild cognitive disability, not interfering with work/school/life performance, specialized educational services/devices not indicated; grade 2, moderate cognitive disability, interfering with work/school/life performance but capable of independent living, specialized resources indicated on a part-time basis; grade 3, severe cognitive disability, with significant impairment of work/school/life performance; and grade 4, unable to perform activities of daily living, with full-time specialized resources or institutionalization indicated.

Patients. Five patients were diagnosed with PPTID and treated at our institute between 2000 and 2011. Table I summarizes the patients' backgrounds, tumor pathological characteristics and treatment received. Two patients were male and three were female. The median age at diagnosis was 52 years (range, 30-55 years). Two patients had evidence of cerebrospinal dissemination at diagnosis, as assessed by radiological findings or cerebrospinal fluid (CSF) cytology. A cytological examination of the CSF was performed prior to chemotherapy and radiation therapy and craniospinal imaging was performed throughout the therapy. The grade of the disease was determined according to the number of mitoses and immunostaining for neurofilaments (grade 2, <6 mitoses and strongly immunopositive for neurofilaments; grade 3, >6 mitoses or <6 mitoses, but without strong immunostaining for neurofilaments) (2). The five patients were pathologically classified as WHO grade 2 according to pathological criteria (Table I).

Treatment. None of the patients underwent a gross total resection, due to the difficulty of tumor location and invasion toward the thalamus or the surrounding eloquent area. Three of the five patients had an R2-resection and the remaining two patients, who had cerebrospinal dissemination at diagnosis, had biopsy-only surgery (Table I).

All the patients were treated with external beam radiation therapy with a 1.8-Gy fraction dose after surgery. Among the five patients, two received 54 Gy directed at the primary lesion following R2-resection; the two patients with cerebrospinal dissemination at diagnosis received 36 Gy of craniospinal irradiation and 18 Gy of whole-ventricular irradiation after biopsy-only surgery. The remaining patient was initially planned to receive 59.4 Gy of whole-ventricular irradiation with concurrent chemotherapy following R2-resection; however, irradiation was discontinued after administering 34.2 Gy due to severe sepsis after chemotherapy.

Four of the patients received six courses of combination chemotherapy with vincristine (0.6 mg/m^2), nimustine (60 mg/m^2), carboplatin (110 mg/m^2) and interferon β ($3x10^6$ IU) on day 1 and the same dose of vincristine and interferon β on days 8 and 15 (Table I). The remaining patient was administered radiation therapy alone following R2-resection. The two patients with cerebrospinal dissemination at diagnosis received sequential chemotherapy after radiation therapy and the two patients without dissemination received concurrent chemotherapy with radiation therapy after surgery.

All five patients underwent follow-up MRI or CT every 2 months during the first year after treatment. Further MRI or CT follow-up were performed every 4-6 months after the first year of follow-up.

Results

Outcome. Table II summarizes the treatment results of the five PPTID patients included in the present study. The patients appeared to have long-term survival. The median relapse-free and overall survival were 72.9 and 94.1 months, respectively (mean relapse-free survival, 65.1 months; range, 13.9-108.6 months; and mean overall survival, 79.9 months; range, 13.9-108.6 months). Three of the five patients achieved a CR and two attained a PR as an initial response to treatment (Table II). Although two of the patients developed a recurrence after treatment, they survived long-term after treatment, with overall survival times of 106.1 and 76.8 months (Table II). These results demonstrated that, with optimized surgery, radiation therapy and chemotherapy, PPTID patients have the potential for long-term survival.

Table I. Patients' backgrounds, tumor pathological characteristics and treatment details.

Case no.	Age/gender [PS/KPS] (years)	Tumor size (mm)	Dissemination at time of diagnosis	Pathology				Surgery	Radiation therapy	Chemotherapy
				WHO grade	NFI	Mitoses (/10 HPF)	Ki-67 (%)			
1	46/M [3/70]	38	-	2	Focal	0	1	R2	Local 54 Gy	-
2	55/F [1/90]	37	-	2	+	0	15	R2	WVI 34.2 Gy	Concurrent
3	52/F [1/90]	22	+	2	+	0	10-15	Biopsy	CSI 36 Gy + WVI 18 Gy	Sequential
4	55/F [1/90]	30	+	2	+	0-1	5	Biopsy	CSI 36 Gy + WVI 18 Gy	Sequential
5	30/M [2/80]	25	-	2	+	0-1	1-2	R2	Local 54Gy	Concurrent

PS, Eastern Cooperative Oncology Group performance status; KPS, Karnofsky performance status; M, male; F, female; WHO, World Health Organisation; NFI, neurofilament immunostaining; HPF, high-power fields; R2, R2-resection; WVI, whole-ventricular irradiation; CSI, craniospinal irradiation.

Table II. Treatment outcomes and late adverse events after treatment.

Case no.	Initial response	Alive (recurrence)	Relapse-free survival (months)	Overall survival (months)	Late effects after treatment			
					White matter abnormalities (time after RT)	Neurocognitive disorders (time after RT)	Pituitary function disorders	Cerebrovascular disorders
1	CR	No (yes)	36.0	106.1	-	-	-	-
2	CR	Yes (no)	108.6	108.6	Yes (6 months)	-	-	-
3	PR	Yes (no)	94.1	94.1	Yes (7 months)	Yes (6 years)	GH deficiency Hypothyroidism	-
4	PR	No (yes)	72.9	76.8	Yes (5 months)	Yes (4 years)	GH deficiency	-
5	CR	Yes (no)	13.9	13.9	-	-	-	-

RT, radiotherapy; CR, complete response; PR, partial response; GH, growth hormone.

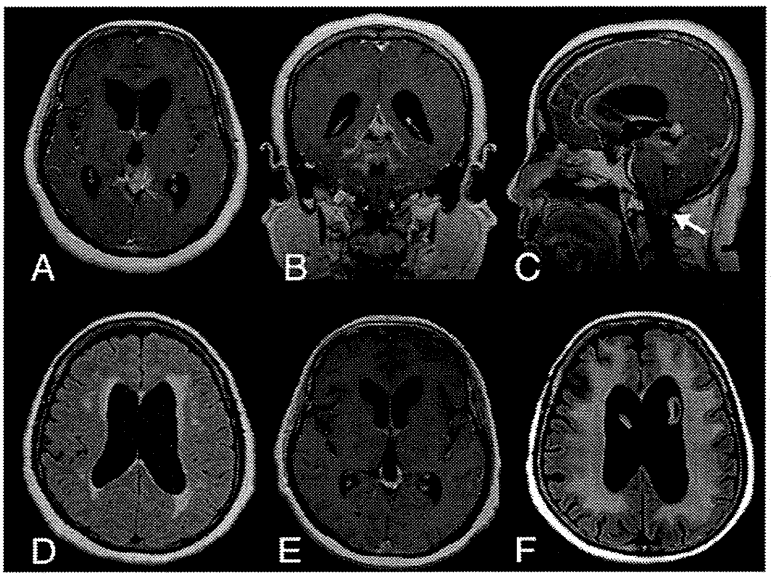

Figure 1. Example of treatment response and a late adverse effect. (A-D) Magnetic resonance imaging at the time of diagnosis (Tables I and II, case 3). (A, B and C) Contrast-enhanced T1-weighted imaging prior to treatment revealed spinal dissemination on the dorsal side of the medulla oblongata, appearing as a contrast-enhanced region (arrow). (D) The patient had slight periventricular white matter abnormalities on fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging. (E) Contrast-enhanced T1-weighted magnetic resonance imaging 2 months after treatment demonstrated a complete response. (F) The patient clearly showed exacerbated periventricular white matter abnormalities on FLAIR imaging and gradually developed a neurocognitive disorder in the 6 years following treatment.

As regards treatment selection and outcome, the two patients who received craniospinal and whole-ventricular irradiation after biopsy-only surgery exhibited a long-term survival of ≥6 years (Table II, cases 3 and 4). However, two patients experienced relapses consisting of cerebrospinal dissemination after treatment and eventually succumbed to the disease (Table II, cases 1 and 4). Of the two patients with recurrence, one had only received local irradiation at the site of the pineal tumor without chemotherapy after R2-resection. These outcomes suggest that the irradiation field may affect recurrence, although we cannot clearly establish an association between the irradiation field and the outcome, due to the limited number of cases.

Toxicity. All the patients recovered from surgery without significant problems. No lethal events or serious intracranial bleeding were recorded in the perioperative period.

Table II outlines the late adverse effects after treatment. The two patients who received 36 Gy of craniospinal irradiation and 18 Gy of whole-ventricular irradiation had evidence of cerebral white matter abnormalities in MRI and grade 3 cognitive disturbance according to RTOG and CTCAE toxicity grading, at 5-7 months and at 4-6 years after radiation therapy (Table II, Fig. 1). Although the patient who received only 34.2 Gy of whole-ventricular irradiation had evidence of cerebral white matter abnormalities at 6 months after radiation therapy, the patient exhibited no evidence of a neurocognitive disorder, even 9 years after the treatment. The patients who were irradiated locally had no evidence of cerebral white matter abnormalities or neurocognitive disorders. The two patients who received craniospinal and whole-ventricular irradiation also exhibited evidence of hypopituitarism after treatment: one developed a growth hormone deficiency 8 months after radiation therapy and the other developed a thyroid-stimulating hormone deficiency 7 years after radiation therapy. However, the latter patient already had a lack of growth hormone when he was diagnosed with PPTID. There were no reported cerebrovascular disorders after treatment.

Discussion

As the number of available studies on the treatment of PPTID is limited, the present study may add noteworthy evidence regarding viable treatment outcomes with radiation therapy and chemotherapy in PPTID. In our cohort, two patients experienced relapses with cerebrospinal dissemination and eventually succumbed to the disease; this was consistent with previous studies suggesting the potentially aggressive behavior of PPTID and its tendency for CSF seeding (8,11). In a previous report analyzing patterns of prognostic factors and treatment failures, five of 37 patients with PPTID relapsed >5 years after the initial treatment (11). The role of craniospinal and whole-ventricular irradiation for patients with PPTID remains to be determined. However, the importance of irradiation for patients with pineal parenchymal tumors, excluding pineocytoma, was investigated in a previous study on a series of 30 patients with pineal tumors and 105 with other germ cell tumors (12). That study demonstrated an association between the radiation dose administered and survival time in patients with pineal parenchymal tumors: the patients who received doses >50 Gy had a significantly higher 3-year survival rate compared to those who received lower doses (94 vs. 56%, respectively; P=0.03). In the present study, almost all the patients, even those with cerebrospinal dissemination

at diagnosis, survived long-term after radiation therapy (Table II). In our cohort, one of the two patients diagnosed with cerebrospinal dissemination received a total of 54 Gy of craniospinal and whole-ventricular irradiation with a combination of sequential chemotherapy after biopsy-only surgery and survived for >7 years. Doses >50 Gy and wide irradiation fields, such as craniospinal and whole-ventricular irradiation, combined with sequential chemotherapy, may be an effective treatment for PPTID with dissemination, although the number of cases analyzed was limited.

Whether all PPTID patients should be treated with chemotherapy remains controversial. Among the five PPTID patients in the present study, one did not receive chemotherapy; this patient developed spinal seeding after treatment and succumbed to the disease. In this patient, a radiation dose of 54 Gy was directed at the pineal region. Given the CSF seeding potential of PPTID and the outcome of this case, either systemic chemotherapy or a wider irradiation field may be required to prevent recurrence, although a definitive conclusion cannot be reached from only five cases regarding the exact indication of chemotherapy and the width of the irradiation field.

There is currrently no standard systemic therapy for PPTID patients. In this study, we used a combination regimen of vincristine, nimustine, carboplatin and interferon β as a systemic treatment for PPTID. The safety of the regimen used in this study was previously confirmed by a phase II study in patients with glioblastoma multiforme (13). Previous studies demonstrated promising results with the combination of vincristine, nitrosoureas and platinums in children diagnosed with primitive neuroectodermal tumors and low-grade gliomas (14,15). Interferon β was reported to act as a drug sensitizer for nitrosourea and alkylating agents, whereas interferon β and nitrosourea combination therapy has been used for the treatment of gliomas in Japan (16). Moreover, interferon β was shown to enhance chemosensitivity to alkylating agents by downregulating the expression of a DNA repair protein, O^6-methylguanine DNA methyltransferase, via p53 induction (17).

A previous study used combination chemotherapy with cisplatin and vinblastine as systemic treatment of pineal parenchymal cell tumors (18), whereas a clinical study on childhood pineoblastoma used a regimen including ifosfamide, etoposide, high-dose methotrexate, cisplatin and cytarabin followed by radiation therapy, or a regimen including vincristine, lomustine and carboplatin (19). These regimens may represent other chemotherapeutic options for pineal parenchymal tumors. A recent study suggested that molecular-targeted therapies, in addition to chemotherapy, may be a viable treatment option for PPTID tumors. A mutation of epidermal growth factor receptor (in-frame deletion of exons 2-7) was detected in PPTID tumors by flow cytometry, western blot analysis and reverse-transcription polymerase chain reaction (20). Patients with PPTID may benefit from a combination of chemotherapy and molecular-targeted therapy in the future.

Although almost all the patients in the present study were long-time survivors, they experienced some late adverse effects. The two patients who received craniospinal irradiation exhibited severe cognitive impairment (grade 3, RTOG and CTCAE toxicity grading) 4-6 years after radiation therapy. This result is consistent with previous reports regarding neurobehavioral outcomes following cranial irradiation (21). Neurocognitive disorder due to treatment is a multifactorial consequence, although data suggest that injury to neural progenitor cells plays an important role in treament-related neurocognitive toxicity (22,23). Associations between radiation dose to neural progenitor cell niches and the temporal lobes were previously reported (24). From this viewpoint, radiation delivery technique modifications, including hippocampal avoidance, may carry the potential to mitigate cognitive neurotoxicity by sparing normal neural stem cells, as in the RTOG 0933 trial, which was a phase II trial investigating whether avoiding the hippocampus during whole-brain radiation therapy lowers the incidence of long-term neurocognitive toxicity in the management of brain metastases.

In addition to the neurocognitive toxicity effect of radiation therapy, certain types of chemotherapy potentially contribute to neurocognitive toxicity due to the different sensitivity of normal neural stem cells (25). Newer chemotherapy agents, such as the epidermal growth factor receptor tyrosine kinase inhibitor and the proteasome inhibitor, were reported as potentially neurotoxic, compared to conventional chemotherapeutic agents (25). Moreover, irradiation may enhance chemotherapeutic neurocognitive toxicity. The majority of chemotherapeutic agents do not effectively penetrate the blood brain barrier; however, there is evidence that brain irradiation causes radiation-induced damage to the capillary bed (26). The concurrent or subsequent administration of neurotoxic chemotherapy while the blood brain barrier is disrupted by radiation therapy is likely to result in the sensitization of the brain to chemotherapy (21). As PPTID patients have the possibility of long-term survival even after recurrence, as shown in this study, whether patients should receive systemic chemotherapy and craniospinal and whole-ventricular irradiation should be carefully considered, depending on the patient's pathological characteristics, disease extent and potential to develop severe late adverse effects. As there are several available methods to enhance treatment intensity and reduce the possible effects on long-term toxicity, more detailed prospective future studies with a larger number of cases are required to investigate the optimal irradiation field and chemotherapeutic strategy for PPTID.

There were potential limitations to this study. First, we could not prospectively evaluate the cognitive disorders with a general neurocognitive function assessment, such as the Mini-Mental State Examination, the Montreal Cognitive Assessment, the Hopkins Verbal Learning Test and Trail Making Tests, or a more detailed objective patient-reported quality of life outcome assessment. Second, this was a retrospective study with a limited case series. Although this disease entity is rare, we should prospectively investigate larger cohorts to determine the appropriate treatment options.

In conclusion, we evaluated the outcomes of multimodality treatment for PPTID. Patients with PPTID in this study survived long-term, even after experiencing a recurrence. However, some patients developed serious neurocognitive disorders a few years after the treatment. Taking into account the rarity of this disease and the long-term survival of recurrent patients, a prospective multi-institutional study including a large patient cohort is required to determine the optimal width of the irradiation field and the use of chemotherapy after surgery, weighing the serious late adverse events and survival time.