generally poor prognosis of elderly patients with GBM, short-course radiotherapy may be a reasonable treatment option. Furthermore, the Nordic Brain Tumor Group compared three separate treatment modalities: standard fractionated radiotherapy (60 Gy in 30 fractions), hypofractionated radiotherapy (34 Gy in 10 fractions), and six cycles of TMZ (5 of 28 days) in their recent phase III study[20]; the findings indicated that the elderly patient treated with standard radiotherapy had worse prognosis than did the elderly patients treated with 34 Gy hypofractionated irradiation or with TMZ alone. In the elderly patients, they found no significant difference in survival between hypofractionated radiotherapy arm and TMZ alone arm. However, both this study and another phase III study (NOA-08 trial), which showed that dose-dense TMZ chemotherapy is noninferior to standard radiotherapy for elderly patients with malignant astrocytoma,[17] demonstrated retrospectively that TMZ treatment seems more effective than radiotherapy alone for the elderly patients with methylated *MGMT* promoter, whereas no significant effect of TMZ was observed for patients with an unmethylated *MGMT* promoter. Methylation of the *MGMT* promoter is reportedly a prognostic and predictive factor for GBM treated with TMZ in elderly cases.[6,15,17,20,21] However, in the present study, *MGMT* methylation was not shown to be a prognostic factor for OS or PFS in elderly patients treated with TMZ and radiotherapy; one reason for this contradictory finding might be the small number of cases in this study; only 19 of 27 elderly patients were evaluated for *MGMT* promoter methylation. The significance of *MGMT* promoter methylation for the treatment of elderly patients with GBM by TMZ and radiotherapy would need to be ascertained in large, prospective clinical trial.

Another remaining question is whether TMZ is effective for elderly patients when concomitantly administered during radiotherapy. Considering recent findings and the frequent Grade 4 adverse events during concomitant TMZ administration with standard radiotherapy in the elderly group, a combined TMZ-based chemotherapy with short-course radiotherapy may be a reasonable treatment option, especially for those elderly patients with a methylated *MGMT* promoter. A currently ongoing randomized controlled trial comparing short-course radiotherapy plus concurrent followed by adjuvant TMZ and short-course radiotherapy alone (NCIC/EORTC 26062) is expected to provide some answer for this question.

The present study has several limitations, including those limitations that are associated with any retrospective study. There was selection bias because patients treated with short-course radiotherapy, radiotherapy alone, or supportive care were excluded. Besides, as age itself is a prognostic factor for GBM, it is difficult to interpret the results of survival comparison between elderly and nonelderly group.

Conclusion

In the elderly patients, especially during the period of concomitant chemoradiotherapy, there was an increased risk of Grade 4 adverse events, which have disrupted the schedule of TMZ administration and in turn may cause the shortening of the survival time. Since probability of severe toxicity seems currently difficult to predict by patient characteristics, such as sex, KPS, or RPA score, the elderly patients who undergo a concomitant course of TMZ must be closely monitored for toxic events. A reduced dose of TMZ might worth considering for elderly patients, and predictive factors for toxicity are expected to be clarified in the future. In addition, the impact of concomitant use of TMZ during short-course radiotherapy, in combination with the *MGMT* promoter methylation status, on the survival of elderly GBM patients needs to be clarified in prospective randomized controlled studies.

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Conflicts of Interest Disclosure

All authors have no conflict of interest to disclose.

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Cancer-specific health-related quality of life in children with brain tumors

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Abstract
Purpose To understand the influence of disease and treatment on the health-related quality of life (HRQOL) of children with brain tumors, compared to the HRQOL of children with other cancers, from the viewpoints of children and parents.
Methods A total of 133 children aged 5–18 years and 165 parents of children aged 2–18 completed questionnaires of the Pediatric Quality of Life Inventory Cancer Module (Pain and Hurt, Nausea, Procedural Anxiety, Treatment Anxiety, Worry, Cognitive Problems, Perceived Physical Appearance, and Communication scales); higher scores indicate a better HRQOL. The Cancer Module scores, weighted by age and treatment status, were compared to those obtained in a previous study of children with other cancers (mostly leukemia).
Results The weighted mean scores for Pain and Hurt (effect size $d = 0.26$) and Nausea ($d = 0.23$) from child reports and the scores for Nausea ($d = 0.28$) from parent reports were higher for children with brain tumors than scores for children with other cancers. The scores for Procedural Anxiety ($d = -0.22$) and Treatment Anxiety ($d = -0.32$) from parent reports were lower for parents of children with brain tumors than the scores for parents of children with other cancers. The child-reported Pain and Hurt score of the Cancer Module was higher ($d = 0.29$) and in less agreement (*intraclass correlation coefficient* = 0.43) with scores from the Brain Tumor Module, indicating that assessments completed with the Cancer Module misesteem pain and hurt problems in children with brain tumors.

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Conclusions The profiles of cancer-specific HRQOL in children with brain tumors differ from those of children with other cancers; we therefore suggest that these children receive specific psychological support.

Keywords Brain neoplasms · Child · Japan · Quality of life · Questionnaires

Introduction

While modern treatment methodologies have improved the outcome for pediatric cancer survival to approximately 70–80 % [1, 2], managing health-related quality of life (HRQOL) during and after treatment becomes a more important part of treatment. Brain tumors are the second most common (27 %) form of pediatric cancer after leukemia (33 %) [3]. Children with brain tumors often experience pain, nausea, lack of energy, and emotional distress [4, 5] and may also experience late effects, such as endocrinological problems, cognitive impairment, neurological (motor and sensory) disability, and posttraumatic stress symptoms [6–8]. Consequently, survivors of brain tumors who receive intensive treatment [9, 10] are at higher risk of physical, psychological, social, and developmental difficulties than survivors of other cancers [11–14]. By understanding the HRQOL profile of these children, medical practitioners can design targeted interventions to maintain and improve HRQOL in this population during and after treatment.

Global profiles of HRQOL (for example, physical, emotional, and social) in children with brain tumors are lower than those of children with other cancers or without cancer [15–18]. However, little information is available on disease-specific HRQOL profiles in children with brain tumors. Meeske et al. compared cancer-specific HRQOL between children with brain tumors and those with acute lymphoblastic leukemia (ALL) using the parent-reported Pediatric Quality of Life Inventory (PedsQL) Cancer Module [17], finding that parents of children with brain tumors and acute lymphoblastic leukemia report different experiences for their children during and after treatment. This highlights the need to understand how children with brain tumors perceive their own HRQOL.

The disease-specific HRQOL of patients with brain tumors can be measured with one of several cancer-specific tools [19–21], such as the PedsQL Cancer Module, or with a brain-tumor-specific tool [15, 22, 23], such as the PedsQL Brain Tumor Module. Different tools may provide different measures of HRQOL, as the questionnaire structure, number, and time of the questions differ among available tools. Here, we compared cancer-specific HRQOL in children with brain tumors with the HRQOL of children with other cancers, the reported views of children and their parents, and the HRQOL as measured by two PedsQL modules—the PedsQL Cancer and the PedsQL Brain Tumor Modules.

Methods

This study was conducted jointly with the development of the Japanese version of the PedsQL Brain Tumor Module [24].

Study population

Children with brain tumors and their parents were recruited from six hospitals across Japan and from the Children's Cancer Association of Japan (CCAJ) between September and December 2008. Inclusion criteria were as follows: age 5–18 years for children (the parent was included if their child was 2–18 years) and at least 1 month had passed since diagnosis. Children and parents were excluded if physicians at the hospital or social workers of the CCAJ determined that the family found the subject of the child's condition too uncomfortable to discuss.

Procedure

Researchers presented the study aims to 101 children and 122 parents at participating hospitals verbally and in writing, and the CCAJ sent a written notice to all families, inviting them to a meeting regarding brain tumors. Of 55 families from the CCAJ that provided informed consent or assent, 2 families were bereaved, 1 had an adult survivor, 6 children were aged 2–4 years, and 1 child old enough to provide his own consent opted out. A total of 98 children and 120 parents from the hospitals as well as 45 children and 52 parents contacted directly by the CCAJ agreed to participate. Questionnaires were distributed to 143 children and 172 parents.

Questionnaires for children were either self-administered or administered by an interviewer. When providing

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informed consent, parents determined whether or not their child was able to self-administer the questionnaire. In accordance with the PedsQL™ administration guidelines, children aged 5–7 years or who were otherwise determined incapable of self-administration were administered the questionnaire by either their parents or a researcher (children were allowed to decide). In both cases, the instructions and each item were read to the child. Parent report questionnaires were simultaneously self-administered.

The questionnaires were returned by 138 children and 167 parents. We excluded questionnaires from 5 children and 2 parents who did not answer any scales of the PedsQL Cancer Module, and we analyzed answers from 133 children and 165 parents. Next, we analyzed answers from 124 children and 143 parents after omitting questionnaires with missing data for any scale of the PedsQL Cancer Module. Given the lack of any significant differences between the results of the former and latter analyses, we report only the latter.

Ethical considerations

This study was approved by the review boards of all seven participating institutions. Children aged ≥12 years and the parents of all children provided written consent prior to participation. Children aged <12 years provided informed verbal assent.

Measurements

The cancer-specific HRQOL of the PedsQL Cancer Module [21, 25] has eight scales: Pain and Hurt (two items), Nausea (five items), Procedural Anxiety (three items), Treatment Anxiety (three items), Worry (three items), Cognitive Problems (five items), Perceived Physical Appearance (three items), and Communication (three items).

Respondents were asked to describe the extent to which each item troubled them over the past month. Although the PedsQL Cancer Module comprises the standard (covering the previous month) and acute versions (covering the previous 7 days), we used the standard version, because it served as a historical control (described in the next section). For the child reports for ages 8–18 and all parent reports, a 5-point Likert response scale was used (0 = never a problem; 1 = almost never; 2 = sometimes; 3 = often; 4 = almost always). For the child report for children ages 5–7, a 3-point face scale was used. Items were reverse scored and linearly transformed to a 0–100 scale, with higher scores indicating a better HRQOL. To account for missing data, scale scores were computed as the sum of the items divided by the number of items answered. If more than 50 % of the items were missing or incomplete, the scale score was not computed.

Table 1 Characteristics of participants

	This study				Tsuji et al. [25] ($N = 245$)	
	All participants ($N = 165$)		Complete participants ($N = 143$)[a]			
	n	%	*n*	%	*n*	%
Gender						
Male	91	55.5	84	59.2	135	55.1
Female	73	44.5	58	40.8	110	44.9
Age (years)						
2–4	25	15.2	23	16.1	41	16.7
5–7	31	18.8	21	14.7	62	25.3
8–12	56	33.9	48	33.6	75	30.6
13–18	53	32.1	51	35.7	67	27.3
Tumor pathology						
Embryonal tumors	47	29.2	39	27.9	–	–
Germ cell tumors	36	22.4	34	24.3	–	–
High-grade glioma	24	14.9	19	13.6	–	–
Low-grade glioma	39	24.2	33	23.6	–	–
Other tumors	15	9.3	15	10.7	–	–
Treatment status						
On-treatment	63	39.4	56	39.2	88	35.9
Off-treatment ≤ 12 months	23	14.4	21	14.7	33	13.5
Off-treatment > 12 months	74	46.3	66	46.2	124	50.6
Age of guardian (years)						
21–28	7	4.3	4	2.8	5	2.1
29–34	23	14.0	18	12.7	40	16.9
35–39	47	28.7	41	28.9	72	30.4
40–60	86	52.4	78	54.9	120	50.6
≥61	1	0.6	1	0.7	0	0.0
Relationship to patient						
Mother	152	92.1	133	93.0	230	96.2
Father	10	6.1	8	5.6	9	3.8
Other guardian	3	1.8	2	1.4	0	0.0
Guardian's academic background						
Junior high school	3	1.9	2	1.4	4	1.7
High school	63	38.9	49	35.0	87	36.6
Vocational school	28	17.3	27	19.3	44	18.5
Junior college	29	17.9	28	20.0	48	20.2
University	36	22.2	32	22.9	52	21.8
Graduate school	3	1.9	2	1.4	1	0.4
Other	0	0.0	0	0.0	2	0.8

Missing data were excluded

[a] Sample without missing data for any scale of the PedsQL Cancer Module

The PedsQL Brain Tumor Module [15, 24] has six scales. Questions about Nausea, Procedural Anxiety, and Worry scales are identical to those in the PedsQL Cancer Module, whereas questions on the Pain and Hurt scale (three items) and Cognitive Problems scale (seven items)

differ from those in the PedsQL Cancer Module. The parent report for toddlers (ages 2–4) does not include the Cognitive Problems scale. The Movement and Balance scale is not reported here. Agreement between the parent and child reports (intraclass correlation coefficient [ICC]) was described previously as follows: 0.41 (Pain and Hurt), 0.65 (Nausea), 0.62 (Procedural Anxiety), 0.18 (Worry), and 0.49 (Cognitive Problems) [24].

Respondents were asked to describe the extent to which each item troubled them over the previous 7 days. Although the recall period of the questionnaire differed from that of the Cancer Module, no published studies using the Brain Tumor Module as the standard (1 month) version were available when the present study was planned and designed. Because the PedsQL Brain Tumor Module adopts the acute version (covering the previous 7 days) as a standard, we employed the acute version. The respondents, response scale, and scoring method were identical to the PedsQL Cancer Module. Parents were also asked to record their child's gender, date of birth, age, tumor pathology, date of diagnosis, and date of therapy completion.

Historical control

We used data reported by Tsuji et al. [25] as a control. This study reported scores from for Japanese children with cancer (67.8 % had leukemia, 9.0 % had malignant lymphoma, followed by neuroblastoma, Wilm's tumor, rhabdomyosarcoma, and hepatoblastoma) using the Japanese version of the PedsQL Cancer Module. Children with brain tumors were excluded in that study.

The average age of children with cancer was 10.5 years (standard deviation [SD] = 3.9 years), and 55.1 % of patients were boys (Table 1). Mothers answered 93.9 % of the questionnaires, and parents' ages ranged between 40 and 60 years.

Statistical analysis

Statistics were calculated using IBM SPSS software, version 19 (SPSS, Inc., Chicago, IL, USA), and the level of significance was defined as 0.05. We calculated the sample characteristics as follows: age distribution, disease, and treatment characteristics; and scale characteristics as follows: mean, SD, minimum and maximum scores. The internal consistency of each subscale was estimated using Cronbach's alpha coefficient [26] (good consistency > 0.70). The agreement between the child and parent reports was estimated using ICC in a two-way mixed effects model [27] (ICC value of 0.20 indicates fair agreement, 0.40 moderate, 0.60 good, and 0.80 high agreement).

The cancer-specific HRQOL of children with brain tumors was compared to the HRQOL of children with other cancers. We compensated for the effect of age (toddler, young child, school child, or adolescent) and treatment status (on-treatment, soon after treatment, or off-treatment) differences using the weighted means and SDs of the PedsQL Cancer Module scale scores, adjusted for age and treatment status. The age distribution of leukemia and brain-tumor onset differs [29, 30], and previous reports have found that treatment status affects the PedsQL Cancer Module score [21, 25]. We also found in this study that the treatment status affected the PedsQL Cancer Module score (see electronic Supplementary Table 1).

These values were calculated by dividing the total sample into different groups based on age and treatment status. The control study sample size (Nc_{total}) was 245, and the brain-tumor sample size (N_{total}) was 165 if all respondents completed the PedsQL Cancer Module scale. The control and study populations were divided into groups (Nc_{ij} and N_{ij}) separated by treatment status (on-treatment, off-treatment $\leq$12 months, or off-treatment >12 months; i = 1–3) and by age (2–4, 5–7, 8–12, or 13–18 years; j = 1–4). The weighted means [31] were calculated as follows:

$$\text{Weighted mean}(\bar{X}) = \sum_{k=1}^{N_{total}} W_k X_k / \sum_{k=1}^{N_{total}} W_k.$$

$$\left(\text{The common mean} = \sum_{k=1}^{N_{total}} X_k / N_{total}\right).$$

$$W_k = \left(\frac{Nc_{ij}}{Nc_{total}}\right) / \left(\frac{N_{ij}}{N_{total}}\right).$$

where X_k was the PedsQL Cancer Module scale score of each respondent that belonged to treatment status i and age j; the weights for each respondent (W_k) were calculated from the ratio of the age and treatment status of the standard population, divided by the proportion of the age and treatment status in this study.

The weighted SDs were calculated using the same weight (W_k) as follows:

$$\text{Weighted SD} = \sqrt{\sum_{k=1}^{N_{total}} W_k (X_k - \bar{X})^2 / \left(\sum_{k=1}^{N_{total}} W_k - 1\right)}.$$

$$\left(\text{The common SD} = \sqrt{\sum_{k=1}^{N_{total}} (X_k - \bar{X})^2 / (N_{total} - 1)}.\right)$$

We compared the cancer-specific HRQOL using Welch's t test and calculated the effect size d from the difference between the two means divided by the pooled SD of both samples.

Table 2 PedsQL Cancer Module scores of children with brain tumors ($N = 143$)

	Mean	SD	Min.	Max.	Alpha[a]	ICC[b]
Child report (n = 124)						
Pain and Hurt	90.4	17.6	0	100	0.62	0.20
Nausea	87.5	20.6	15.0	100	0.86	0.68
Procedural Anxiety	74.5	30.8	0	100	0.88	0.70
Treatment Anxiety	92.8	19.0	0	100	0.88	0.41
Worry	81.9	23.4	0	100	0.76	0.27
Cognitive Problems	73.6	22.4	0	100	0.78	0.44
Perceived Physical Appearance	73.8	26.3	0	100	0.71	0.28
Communication	68.5	29.9	0	100	0.77	0.45
Parent report (n = 143)						
Pain and Hurt	84.5	20.0	0	100	0.83	
Nausea	84.7	22.6	15.0	100	0.93	
Procedural Anxiety	59.8	35.4	0	100	0.96	
Treatment Anxiety	79.7	23.1	0	100	0.93	
Worry	78.3	22.3	0	100	0.86	
Cognitive Problems	66.0	23.8	0	100	0.89	
Perceived Physical Appearance	70.6	24.6	0	100	0.81	
Communication	59.5	29.6	0	100	0.89	

ICC intraclass correlation coefficient, *Max.* maximum, *Min.* minimum, *SD* standard deviation

[a] Cronbach's alpha coefficient

[b] ICC values for child and parent reports in the two-way mixed effects model ($n = 124$)

The agreement of the two modules was evaluated using paired t tests; the effect size d (the mean score difference divided by SD of the mean score difference) [28] designated as small (0.20), medium (0.50), and large (0.80) in magnitude and by the ICC calculated from a one-way random effects model [27].

Results

Sample characteristics

The median age of the children with brain tumors was 10.0 years (range: 2–18) (Table 1), and the sample was heterogeneous for tumor pathology. Most children presented with embryonal tumors, low-grade gliomas, and germ cell tumors. Median age at diagnosis was 6.0 years; 63 children (39.4 %) were still receiving treatment, while 97 (60.6 %) had completed treatment, and the interval from completion of treatment to the survey ranged from 0.1 to 13.3 years. Most children on treatment were younger than the children who had completed treatment.

With the exceptions noted below, no significant differences were observed between the characteristics of the children and their parents and those of the historical control (Table 1). The differences were as follows: The present study enrolled fewer children between the ages of 5 and 7 years and more between the ages of 13 and 18 years ($P = 0.069$, Chi-square test).

Scale descriptions

The child-reported scores were higher than parent-reported scores on all scales of the PedsQL Cancer Module and were internally consistent for all scales except for the Pain and Hurt scale (Cronbach's alpha coefficient = 0.62); parent-reported scores were internally consistent for all scales (Table 2). Agreement between the child and parent reports was good for the Nausea and Procedural Anxiety scales, moderate for the Treatment Anxiety, Cognitive Problems, and Communication scales, and fair for the Pain and Hurt, and Perceived Physical Appearance scales.

Cancer-specific HRQOL in children with brain tumors compared with the HRQOL of children with other cancers

We noted small but significant differences between the children's reports for Pain and Hurt ($d = 0.26$) and Nausea ($d = 0.23$) and the parents' reports for Nausea ($d = 0.28$), Procedural Anxiety ($d = -0.22$), and Treatment Anxiety ($d = -0.32$) (Table 3). The scores for Pain and Hurt and Nausea were higher for children with brain tumors than for children with other cancers, indicating better HRQOL. However, the scores for Procedural Anxiety and Treatment Anxiety were lower for children with brain tumors than for children with other cancers, indicating worse HRQOL. The direction of the effects was the same for the scales reported by parents and children.

Table 3 Comparison of cancer-specific HRQOL in children with brain tumors and those with other cancers

	This study[a]		Tsuji et al. [25][b]			P[c]	Effect size d[d]
	Mean	SD	n	Mean	SD		
$N = 143$							
Child report ($n = 124$)							
Pain and Hurt	89.8	19.3	202	84.7	19.7	0.024	0.26
Nausea	88.0	20.0	199	83.0	24.0	0.044	0.23
Procedural Anxiety	72.5	32.8	203	72.9	31.0	0.910	−0.01
Treatment Anxiety	90.7	22.8	203	93.1	17.0	0.302	−0.12
Worry	81.0	25.8	202	76.6	25.9	0.140	0.17
Cognitive Problems	72.3	23.8	200	71.5	22.1	0.775	0.03
Perceived Physical Appearance	71.9	28.7	204	70.3	28.6	0.639	0.05
Communication	65.5	32.6	204	67.0	27.0	0.656	−0.05
Parent report ($n = 143$)							
Pain and Hurt	84.9	20.9	242	82.9	22.0	0.367	0.09
Nausea	87.0	20.8	233	80.5	25.7	0.008	0.28
Procedural Anxiety	55.7	36.6	242	63.2	31.8	0.043	−0.22
Treatment Anxiety	77.9	24.4	241	84.9	19.0	0.004	−0.32
Worry	79.0	23.6	242	81.4	21.9	0.334	−0.10
Cognitive Problems	65.8	24.9	243	69.4	21.6	0.151	−0.15
Perceived Physical Appearance	71.7	25.3	243	73.8	24.9	0.437	−0.08
Communication	60.1	31.1	241	62.2	25.4	0.496	−0.07

HRQOL health-related quality of life, *SD* standard deviation

[a] Means and SDs of the PedsQL Cancer Module score in children with brain tumors adjusted for age and treatment status to subjects reported by Tsuji et al. [25]

[b] Previously reported data in children with the other cancers

[c] P value from the Welch t test

[d] Effect size d defined by Cohen [28] is the difference between two means divided by a pooled SD with two samples. A positive value indicates that children with brain tumors have higher HRQOL scores compared with children with other cancers

Agreement between the PedsQL cancer and the PedsQL Brain Tumor Modules of the PedsQL

Children and parents reported higher Pain and Hurt scores ($d = 0.29$, $P = 0.001$ and $d = 0.22$, $P = 0.010$, respectively) on the Cancer than on the Brain Tumor Module (Table 4). Children reported higher Procedural Anxiety ($d = 0.31$, $P = 0.001$) and Cognitive Problems scores ($d = 0.28$, $P = 0.003$) on the Cancer Module. The agreement between the PedsQL Cancer and the PedsQL Brain Tumor Modules was very high (ICC > 0.80) except for the Pain and Hurt scale for the child report where the agreement was moderate (ICC = 0.43). The agreement according to treatment status is shown in Supplementary Table 2.

Discussion

We report here that children with brain tumors perceive their HRQOL differently from children with other cancers. Several aspects of HRQOL were more difficult (for example, procedural and treatment anxiety) for patients with brain tumors, while other aspects (nausea, pain and hurt) were less difficult, and a number of factors may be responsible for these differences. In particular, the brain is the center of multiple functions. The brain integrates the information received from, and coordinates the physical and mental activity of, the whole body. Thus, the unique HRQOL of children with brain tumors likely reflects the vast complexity of brain function. Knowledge of these differences should help medical practitioners design-specific support and care strategies for these children.

A total of 29 % of children in this study suffered from embryonal tumors (mainly medulloblastomas), and treatment for these tumors requires surgery, radiation, and chemotherapy [32, 33]. The main treatments for children with germ cell tumors (mainly germinomas) include surgery, radiation, and chemotherapy [34], with chemotherapy representing the main treatment for children with leukemia (controls). Each treatment method will affect a child's HRQOL differently.

Table 4 Comparison of cancer-specific HRQOL using the PedsQL cancer and PedsQL Brain Tumor Modules

	n	Dif.[a]	95 % CI of the Dif.		*P*[b]	Effect size *d*[c]	ICC (5–18 years)[d]	ICC (2–18 years)[e]
			Lower	Upper				
$N = 143$								
Child report ($n = 124$)								
Pain and Hurt	124	5.41	2.12	8.70	0.001	0.29	0.43	–
Nausea	124	0.91	−0.91	2.72	0.325	0.09	0.88	–
Procedural Anxiety	123[f]	4.34	1.80	6.87	0.001	0.31	0.89	–
Worry	124	1.95	−0.39	4.30	0.102	0.15	0.84	–
Cognitive Problems	124	3.64	1.29	5.99	0.003	0.28	0.81	–
Parent report ($n = 143$)								
Pain and Hurt	143	2.50	0.60	4.40	0.010	0.22	0.82	0.91
Nausea	143	0.59	−1.20	2.39	0.515	0.05	0.91	0.89
Procedural Anxiety	142[f]	2.14	−0.77	5.05	0.148	0.12	0.88	0.87
Worry	143	1.46	−0.20	3.11	0.084	0.15	0.90	0.90
Cognitive Problems	124[g]	−0.99	−2.89	0.91	0.304	−0.09	0.89	–

CI confidence interval, *Dif.* difference, *HRQOL* health-related quality of life, *ICC* intraclass correlation coefficients, *PedsQL* pediatric quality of life inventory, *SD* standard deviation

[a] Mean score differences (PedsQL Cancer Module—PedsQL Brain Tumor Module). A positive value indicates that participants (children with brain tumors or parents of children with brain tumors) have higher scores in the PedsQL Cancer Module (fewer problems) than in the PedsQL Brain Tumor Module

[b] *P* value from the paired *t* test

[c] Effect size *d* defined by Cohen [28] is the mean score difference divided by SD of the mean score difference. A positive value indicates that participants (children with brain tumors or parents of children with brain tumors) scored higher in the PedsQL Cancer Module (fewer problems) than the PedsQL Brain Tumor Module

[d] ICC values for the PedsQL Cancer Module and the PedsQL Brain Tumor Module in the one-way random effects model among children aged 5–18 years

[e] ICC values for the PedsQL Cancer Module and the PedsQL Brain Tumor Module in the one-way random effects model among children aged 2–18 years

[f] Missing data for the Brain Tumor Module ($n = 1$) were excluded

[g] The PedsQL Brain Tumor Module parent report for toddlers (ages 2–4) does not include the Cognitive Problems scale

Children with brain tumors reported less difficulty with pain and hurt than children with other cancers; however, we believe it unlikely that these children actually experienced less pain, as here and in a previous study [17], parents reported similar difficulty with pain and hurt irrespective of cancer type. Children with brain tumors reported pain and hurt more frequently than children with lymphoma at a similar frequency to children with leukemia and less frequently than children with solid tumors [4]. These inconsistencies may arise due to scale characteristics. The agreement between Pain and Hurt scores in the Cancer and Brain Tumor Modules was moderate, while the agreement on other scales was high. These findings suggest that the Pain and Hurt scale of the PedsQL Cancer Module may not consider problems for children with brain tumors compared with the Brain Tumor Module.

The Pain and Hurt scale of the Cancer Module asks about generalized body pain but does not localize the pain. For example, "I ache or hurt in my joints and/or muscles," versus "I hurt a lot." Further, the Brain Tumor Module measures two items present in the Cancer Module and, uniquely, "I get headaches." Thus, the Brain Tumor Module includes a question about headaches, which are frequent in patients and survivors of brain tumors [35]. Headache is the most frequently reported initial symptom of pediatric brain tumors in children aged ≥2 years and may be interpreted with particular meaning for these children [36]. Headache would remind the children and parents of the first brain tumor and induce worry about a relapse. Such headaches cause physical distress and psychosocial concern. Therefore, we prefer to use the Brain Tumor to the Cancer Module to measure disease-specific HRQOL for these children.

Children with brain tumors and their parents reported less difficulty with nausea than children with other cancers. Causes of nausea may include side effects of chemotherapy, radiation sickness, postoperative reactions, tumors close to the area postrema, intracranial hypertension, gastrointestinal pathology, and anxiety [37, 38]. Here, at least 1 month had passed since diagnosis, and factors such as

postoperative reaction, brain-tumor activity, and intracranial hypertension would have been controlled, resulting in less difficulty with nausea [39, 40].

Patients may experience strong nausea and vomiting at the onset of brain tumors as well as in the perioperative period; therefore, pediatric patients may evaluate their experience with treatment-induced nausea and vomiting as less trying than that experienced perioperatively. In contrast, children with ALL (control group majority) are treated at the first remission-induction phase using moderately emetogenic chemotherapy (i.e., vincristine, daunorubicin, L-asparaginase) [41], and severe emetogenic chemotherapy (i.e., cyclophosphamide, ifosfamide) is added during the intensification phase. Treatment type and course will affect a child's experience, so a longitudinal study will be required to assess how the experience of children with brain tumors changes after diagnosis and treatment.

Parents of children with brain tumors reported more procedural and treatment anxiety for their children than did the parents of children with other cancers. The PedsQL Cancer Module evaluates children's and parents' perception of a child's anxiety about needle sticks, blood tests, seeing a doctor, and hospitalization, which relate to trauma and stressor-related symptoms that are classified as anxiety disorders. Perceived life threat and treatment intensity are directly associated with posttraumatic stress disorder [42]. We assume that intensive symptoms and the treatment of pediatric brain tumors increase anxiety.

Our findings here of increased anxiety in children with brain tumors differ from those of a previous study conducted in the United States [17]. Although we cannot explain the reason for this discrepancy, pediatric oncology practice differs between the United States and Japan [43], and patients in Japan may not be fully informed of the diagnosis, which affects posttraumatic stress disorder [44]. Cognitive problems of children with brain tumors might also limit their understanding of disease and treatment course. Each child's psychological readiness for each stage of the diagnosis and treatment may be affected by the information provided and by the child's cognitive ability.

Several limitations of the present study warrant mention. First, the study and controls were heterogeneous and included various pathologies. All children in this study suffered central nervous system damage from invasion, compression, or hydrocephalus as well as from therapy. Further investigations of tumor types and treatment should reveal how HRQOL differs between children with brain tumors and those with other cancers.

Second, data obtained from children and parents were not completely equivalent; the ages of self-reporting children ranged between 5 and 18 years, whereas parental-reporting included children 2–18 years of age. Further, the varying degrees of patients' impairments prevented optimum accuracy of reporting [17]. However, the number of children participating in the present study (133) was similar to that of participating parents of children aged 5–18 years (140) because of assisted administration. Further, HRQOL reporting by children is not significantly influenced by the administration technique [24, 45].

Third, the PedsQL Cancer and Brain Tumor Modules employ different recall periods, as described above [15, 25]. This difference must be taken into account when interpreting data. Although the items on the Procedural Anxiety subscale are identical in both modules, children with brain tumors studied here reported less difficulty with procedural anxiety using the Cancer than with the Brain Tumor Module. The recall period may alter a child's perception of procedural anxiety. Further research is required to determine why children reported less anxiety over the past month than over the previous 7 days.

Fourth, our ability to generalize the data is limited. For example, at the CCAJ, several hundred families, including those not eligible to participate, were notified of this study; therefore, the true response rate is unknown. Families were excluded if doctors or social workers determined that the family found the child's condition too uncomfortable to discuss. Although the number of such excluded families was not recorded, this exclusion may have limited data collection.

Fifth, when comparing children with brain tumors to those with other cancers, certain parental characteristics could not be taken into account, as Tsuji et al. [25] did not report them. Parental reports might have been influenced by factors such as parental mental health, which may limit comparability. However, all child and parent characteristics reported here, except for age and tumor pathology, were similar.

Conclusion

Here, we found that children with brain tumors reported less difficulty with the categories of pain and hurt and nausea than children with other cancers that included mostly leukemia. Parents of the children with brain tumors reported more procedural and treatment anxiety. The information will help medical professionals and researchers to understand the influence of the disease and treatment on the HRQOL of children with brain tumors regardless of age and treatment status.

This study is the only comparison, to our knowledge, of the PedsQL Cancer and Brain Tumor Modules. The PedsQL Cancer Module compares cancer-specific HRQOL of children with brain tumors and those with other cancers. However, the PedsQL Brain Tumor Module is more

sensitive for brain-tumor-specific aspects of the HRQOL and should be used to assess HRQOL in children with brain tumors.

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The Association of Subventricular Zone Involvement at Recurrence with Survival after Repeat Surgery in Patients with Recurrent Glioblastoma

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Abstract

Surgical resection is identified as an important prognostic factor for survival in patients undergoing initial resection of glioblastoma (GBM). However, in patients with tumor recurrence, the benefits of repeat surgery remain unclear. Recent reports have stated that the association between initial surgery for GBM and subventricular zone (SVZ) influences survival. The current study examined the relationship of SVZ involvement in recurrent GBM to survival time after reoperation. We conducted a retrospective review of 61 consecutive patients who had undergone repeat surgery for recurrent GBM at our institution between 1997 and 2010. Survival after repeat surgery were compared between patients with (n = 29) and without (n = 32) SVZ involvement at recurrence using univariate analysis with known prognostic factors, including sex, age, Karnofsky Performance Status (KPS) score at recurrence, recurrent tumor size, initial SVZ involvement, and adjuvant therapy after repeat surgery, as variables. All 26 SVZ-positive tumors at initial diagnosis recurred as SVZ-positive tumors, while 32 of 35 SVZ-negative tumors at initial diagnosis remained SVZ-negative at recurrence; the remaining three were SVZ-positive at recurrence. Survival after repeat surgery was decreased in patients with recurrent GBM involving the SVZ at recurrence (p = 0.022). No other prognostic factors for survival after repeat surgery were identified in this study. This finding may have prognostic and therapeutic significance.

Key words: glioblastoma, recurrence, repeat surgery, subventricular zone

Introduction

Glioblastoma (GBM) is the most common central nervous tumor in adults. Despite therapeutic advances, the median survival time continues to be approximately 14 months.[1] Younger age and higher Karnofsky Performance Status (KPS) scores are widely accepted independent predictors of prolonged survival.[2–4] A significant association between the extent of resection and survival has also been shown in several retrospective studies.[5–7] As several papers have reported, GBM is a histopathologically, radiographically, and genetically heterogeneous disease.[8,9] Recent studies have demonstrated that the heterogeneity of GBM may be related to the cell of origin, which has stem cell-like characteristics.[10,11]

The adult human brain harbors neural stem cells within the subventricular zone (SVZ), which is located under the ependyma of the lateral ventricle.[12] Recently, Lim et al. proposed a classification system based on the relationship of the contrast-enhanced lesion to the SVZ and the cortex on magnetic resonance imaging (MRI).[13] They found that tumors contacting the SVZ and involving the cortex more often tended to be multifocal at diagnosis as well as recurrence. In addition, lower overall survival (OS) and progression-free survival have been reported in patients with GBM involving SVZ.[14,15]

In cases of tumor recurrence, treatment options are individualized because no standard protocol has been developed. Till date, the benefits of repeat surgery for the treatment of recurrent GBM have not been fully established. Previous studies have retrospectively assessed patient outcomes after resection of recurrent GBM. The variables that were significantly associated with OS in at least one of these studies were preoperative KPS, extent of surgical resection, age, and time interval between the first and second

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surgeries.[16–19] However, whether or not location of the recurrent lesion is associated with survival after repeat surgery remains unclear. We, therefore, aimed to determine whether SVZ involvement in patients with recurrent GBM is related to decreased survival after repeat surgery.

Materials and Methods

We retrospectively reviewed the medial records of 269 adult patients who had undergone surgical resection of a supratentorial GBM at the Tohoku University Hospital from January 1, 1997 to August 31, 2010. After initial surgery, patients had received involved-field external beam radiation therapy and either nitrosourea or temozolomide chemotherapy. Repeat surgery has been considered by the following points: (1) resectable tumor without severe morbidity and (2) younger patients or older patients with high KPS. Of the 269 patients, 61 received one or more additional resective surgeries for the treatment of histologically confirmed recurrent tumor. Medical charts were reviewed for information concerning patient age at the time of initial surgery, sex, additional therapy, KPS score at recurrence, and median survival time after repeat surgery. The degree of resection was retrospectively classified as follows on the basis of MRIs obtained < 72 h after repeat surgery: gross-total resection (GTR) if no residual enhancement was noted on postoperative MRI or subtotal resection if any residual enhancement was noted on postoperative MRI.[7] Perioperative mortality was defined as death within 30 days of repeat surgery.

MRI sequences were acquired on a 1.5T scanner and typically included axial T_1-weighted, T_2-weighted fast spin-echo, and fluid-attenuated inversion-recovery sequences as well as gadopentetate dimeglumine-enhanced (Magnevist, Bayer Health Care, Leverkusen, Germany) axial and coronal T_1-weighted images. As previously reported, tumors were classified as involving the SVZ (SVZ-positive) if the contrast-enhanced lesion contacted the lining of the lateral ventricle.[2] Tumor recurrence was defined as the appearance or enlargement since prior imaging of a contrast-enhanced mass on T_1-weighted MRI. The size of the contrast-enhanced lesion was approximated using the formula for the volume of an ellipsoid (4/3 × radius × radius × radius).

Parametric data are expressed as mean ± standard deviation (SD). Nonparametric data were expressed as median [interquaritile range (IQR)]. Percentages were compared using the χ^2 test. Continuous variables were compared using Student's *t*-test or the Mann-Whitney U test where appropriate. To determine the relative impact of multiple variables on OS and survival after repeat surgery, a Cox proportional hazards model was constructed. For the univariate analysis of potential prognostic factors, time-to-event distributions of the patients were estimated using Kaplan-Meier plots, and p values were obtained using log-rank tests. Variables with significance at the 0.20 level were selected for inclusion in the multivariate model and were entered in a forward stepwise fashion. Only variables with significance at the p = 0.05 level were accepted in the final model. All statistical tests were performed using SPSS version 21 (IBM, Chicago, Illinois, USA).

Results

Among 269 patients with GBM, we obtained pre- and post operative MRI at initial surgery and follow-up MRIs from 223 patients. As shown in Fig. 1, 102

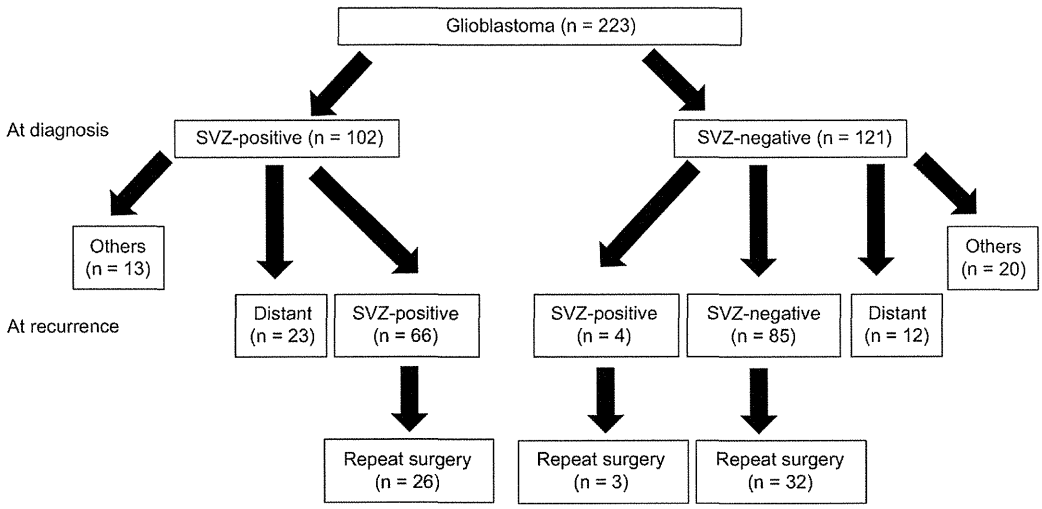

Fig. 1 Flowchart illustrating the subventricular zone (SVZ) involvement of glioblastoma at diagnosis and recurrence. Distant included the patients recurred at locations noncontiguous with the recurrent lesion [cerebrospinal fluid (CSF) dissemination or contralateral invasion]. Others included the patients survived without recurrent lesion or died from other disease.

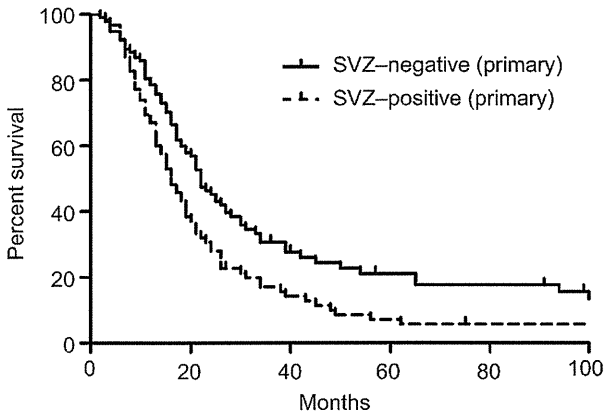

Fig. 2 Kaplan-Meier plots of OS comparing patients with SVZ-positive and SVZ-negative glioblastoma at diagnosis. Median OS was 16 months in patients with SVZ-positive lesions and 22 months in patients with SVZ-negative lesions (p = 0.005). OS: overall survival, SVZ: subventricular zone.

GBMs were SVZ-positive and other 121 GBMs were SVZ-negative. During follow-up period, 66 of 102 SVZ-positive GBMs also recurred as SVZ-positive and 23 tumors recurred at locations noncontiguous with the recurrent lesion. In other 13 patients, 5 were still alive without recurrence and 8 were dead by other disease. Finally, 26 of 66 patients with SVZ-positive recurrent GBM received repeat surgery. On the other hand, repeat surgery was performed for 3 of 4 SVZ-positive and 32 of 85 SVZ negative recurrent tumors from primary SVZ-negative tumors. Twelve tumors recurred at locations noncontiguous with the recurrent lesion. In other 20 patients, 16 were still alive without recurrence and 4 were dead by other disease. There was no significant difference for frequency of repeat surgery between SVZ-positive and negative tumors at diagnosis [22/102 (21.5%) vs. 35/121 (28.9%), p = 0.22, Fig. 1]. Median OS of SVZ-positive tumors was significantly shorter than that of SVZ-negative tumors (16 vs. 22 months, p = 0.005, Fig. 2).

The baseline demographic, clinical, and MRI characteristics of the patients evaluated and treated in this study are summarized in Table 1. The mean age (± SD) of the patients was 50.6 ± 14.6 years, and 38 patients (62%) were male. The median

Table 1 Summary of clinical, treatment, and magnetic resonance imaging characteristics of 61 patients with glioblastoma

Parameter	All patients	SVZ-positive	SVZ-negative	p
Patients				
No. (%)	61	29 (48)	32 (52)	
Sex				0.18
Male	38	21	17	
Female	23	8	15	
Age (years, mean + SD)	50.6 + 14.6	52.4 + 13.6	49.0 + 15.6	0.37
KPS at recurrence (IQR)	70 (60–80)	60 (50–70)	70 (60–90)	**0.034**
Tumor size (cm^3) (mean + SD)	15.6 + 21.4	19.4 + 21.3	12.2 + 21.1	0.19
Extent of resection (%)				0.39
Gross total	44 (72)	19 (66)	25 (78)	
Subtotal	17 (28)	10 (34)	7 (22)	
Primary lesion (%)				**< 0.0001**
SVZ-positive	26 (43)	26 (90)	0	
SVZ-negative	35 (57)	3 (10)	32 (100)	
Therapy after repeat surgery				
Chemotherapy (%)	54 (89)	25 (86)	29 (91)	0.69
SRT (%)	27 (44)	8 (28)	19 (59)	**0.019**
3rd resective surgery (%)	17 (28)	4 (14)	13 (41)	**0.024**

GBM: glioblastoma, IQR: interquatile range, KPS: Karnofsky Performance Status, MRI: magnetic resonance imaging, SD: standard deviation, SRT: stereotactic radiotherapy, SVZ: subventricular zone.

(IQR) KPS score at recurrence was 70 (60–80), while the mean tumor size (± SD) at recurrence was 15.6 ± 21.4 cm^3. GTR was performed in 44 patients (72%).

Of the 61 patients, SVZ-positive tumors were identified in 29 (48%) while SVZ-negative tumors were identified in 32 (52%). No significant difference in sex, age at recurrence, recurrent tumor size, or extent of resection at repeat surgery was observed between the two groups. However, preoperative KPS score in patients with SVZ-positive tumors was significantly lower than that in patients with SVZ-negative tumors. All 26 SVZ-positive tumors at initial diagnosis recurred as SVZ-positive tumors (Fig. 3). Only three primary SVZ-negative tumors showed SVZ involvement at recurrence; the other primary SVZ-negative tumors were still SVZ-negative at recurrence (Fig. 4).

No perioperative mortality was observed in this study. All patients underwent follow-up MRIs for postoperative evaluation. Of the 61 patients, 54 (89%) received additional chemotherapy (temozolomide, ifosfamide + cisplatin + etoposide or intrathecal methotrexate) while 27 (44%) received stereotactic radiotherapy (SRT) following repeat surgery. During the follow-up period (24–206 months), second recurrence occurred in 57 patients and a third resective surgery was done in 17 (28%) of them. Of the 29 SVZ-negative tumors with second tumor recurrence, 23 (85%) re-recurred at locations contiguous with the recurrent lesion. Therefore, a third resective surgery was possible in 13 of the 23 patients (41%).

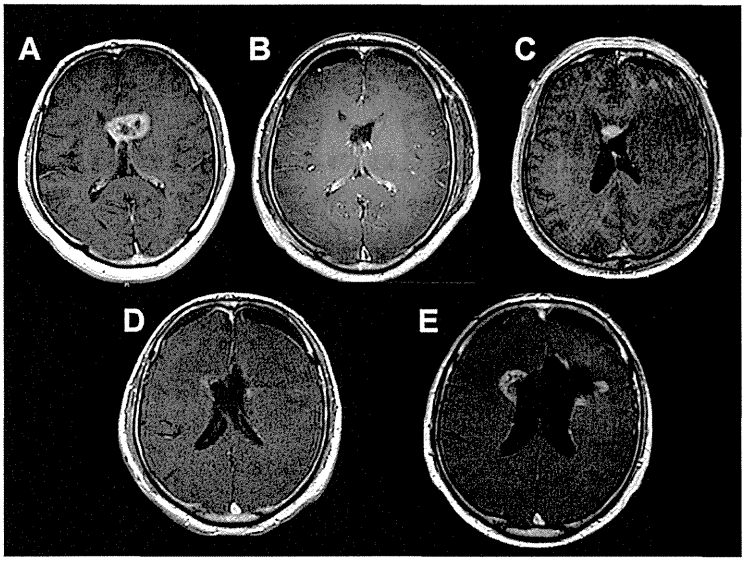

Fig. 3 A: Preoperative axial contrast T_1-weighted magnetic resonance (MR) image of a patient with primary subventricular zone (SVZ)-positive glioblastoma (GBM). The contrast-enhanced lesion contacts the anterior horn of SVZ. B: Postoperative axial contrast T_1-weighted MR image of a patient with primary SVZ-positive GBM. No residual tumor is noted on MR imaging. C: Four months after surgery, an enhanced lesion in the SVZ of the anterior horn was observed. D: Postoperative axial contrast T_1-weighted MR image of a patient with recurrent SVZ-positive GBM. Subtotal resection was performed. E: Three months after surgery, an enhanced lesion can be observed in the SVZ of the bilateral wall of the lateral ventricle.

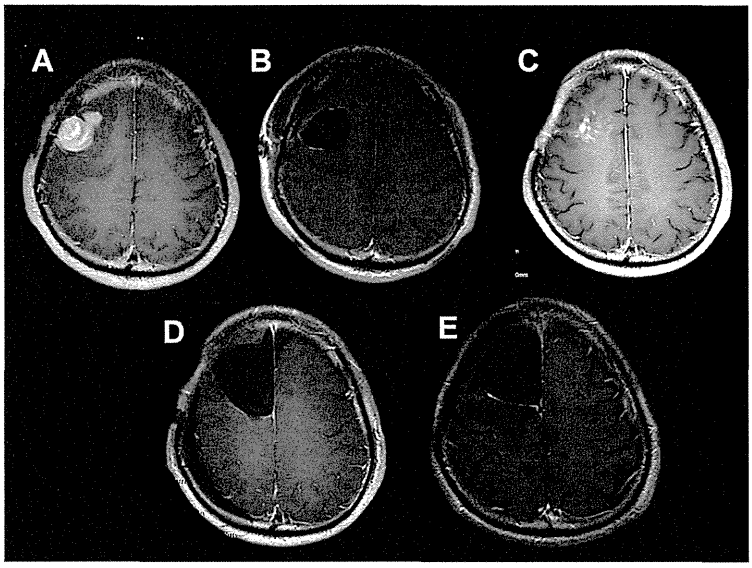

Fig. 4 A: Preoperative axial contrast T_1-weighted magnetic resonance (MR) image of a patient with primary subventricular zone (SVZ)-negative glioblastoma (GBM). The contrast-enhanced lesion does not contact the SVZ. B: Postoperative axial contrast T_1-weighted MR image of a patient with primary SVZ-negative GBM. No residual tumor is observed on MRI. C: Five months after surgery, an enhanced lesion is evident around the resection cavity. D: Postoperative axial contrast T_1-weighted MR image of a patient with recurrent SVZ-negative GBM. No residual tumor is visible on MR imaging. E: Four months after surgery, an enhanced lesion around the resection cavity can be observed.

On the other hand, in the 28 SVZ-positive GBMs with second recurrence, 21 tumors re-recurred at locations noncontiguous with the recurrent lesion [cerebrospinal fluid (CSF) dissemination in 11 and contralateral invasion in 5]. Therefore, only four patients (14%) received a third resection in this group. There was no significant difference in the number of patients who received chemotherapy after repeat surgery between the two groups. However, the number of patients who received SRT and/or underwent a third surgery was lower in the SVZ-positive group than in the SVZ-negative group (Table 1).

The median OS and survival after repeat surgery was 25 months and 11 months, respectively, in this study. Patient age, sex, KPS score at recurrence, recurrent tumor size, resection rate at recurrence, SVZ involvement at initial and repeat surgery, and therapy after repeat surgery were examined as prognostic factors for survival using univariate analysis. The results are shown in Table 2. A significant difference in median survival after repeat surgery was noted between patients with SVZ-positive recurrence and patients with SVZ-negative recurrence (Kaplan-Meier estimates: 10 months vs. 14 months; p = 0.022; Fig. 5). Median OS and survival after repeat surgery for patients with SVZ-positive recurrence of tumors that were SVZ-negative at diagnosis were 17 and 8 months, respectively. Only KPS at recurrence and SVZ involvement for survival from repeated surgery at the p = 0.20 level and were included in the multivariate model. Hazard ratios (HRs) from the multivariate results for each factor are shown

Table 2 Outcomes of 61 patients with GBM who underwent repeat surgery

Parameters	Survival from repeat surgery (months)	p
Sex		0.23
Male (n = 38)	12	
Female (n = 23)	11	
Age		0.82
< 50 (n = 27)	11	
> 50 (n = 34)	11	
KPS at recurrence		0.11
70–100 (n = 37)	9	
40–60 (n = 24)	12	
Tumor size (cm^3)		0.88
< 10 cm^3 (n = 38)	11	
> 10 cm^3 (n = 23)	11	
Resection rate		0.23
Total (n = 44)	11	
Subtotal (n = 17)	11	
Primary lesion		**0.021**
SVZ-positive (n = 26)	9.5	
SVZ-negative (n = 35)	13	
Recurrent lesion		**0.022**
SVZ-positive (n = 29)	10	
SVZ-negative (n = 32)	14	
Therapy after 2nd operation		0.87
SRT (+) (n = 19)	11	
SRT (–) (n = 38)	11	
3rd operation (+) (n = 20)	11	
3rd operation (–) (n = 37)	11	

KPS: Karnofsky Performance Scale, SRT: stereotactic radiotherapy, SVZ: subventricular zone.

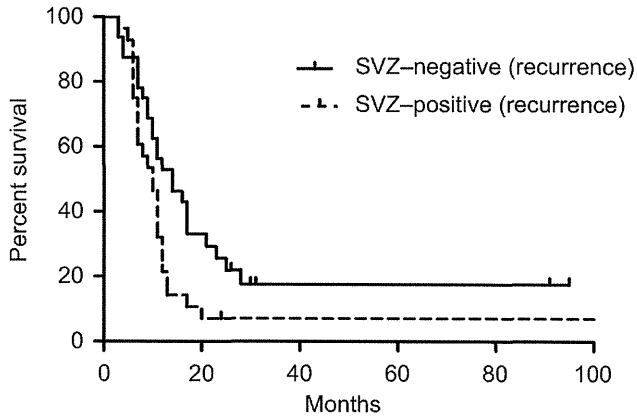

Fig. 5 Kaplan-Meier plots of survival after repeat surgery in patients with SVZ-positive and SVZ-negative GBM at recurrence. Median survival after repeat surgery was 10 months in patients with SVZ-positive recurrent GBM and 14 months in patients with SVZ-negative recurrent GBM (p = 0.022). GBM: glioblastoma, SVZ: subventricular zone.

Table 3 Multivariate analysis of survival from repeat surgery

Parameters	HR	95%CI	p
KPS at recurrence			0.13
KPS < 70	1.54	0.88–2.68	
KPS > 70	1		
SVZ (recurrent lesion)			**0.029**
SVZ-positive	1.87	1.06–3.28	
SVZ-negative	1		

CI: confidence ratio, HR: hazard ratio, KPS: Karnofsky Performance Scale, SVZ: subventricular zone.

in Table 3. When adjusting for all factors, only SVZ involvement at recurrence was a significant predictor of survival after repeat surgery (HR, 1.87; 95%CI, 1.06–3.28; p = 0.029).

Discussion

Several papers in the past decade have emphasized the importance of surgical resection for primary GBM.[5–7] However, the benefits of repeat surgery for recurrent GBM have not been completely determined. Previous papers have identified age, preoperative KPS score, and resection rate at recurrence as important prognostic factors.[16–20] However, these factors were not identified as significant prognostic factors in our study, although the results of this study are subject to the limitations of a retrospective study, only SVZ involvement at recurrence was associated with decreased survival after repeat surgery. Previous papers have reported associations between SVZ involvement, aggressive tumor behavior, and shorter OS in patients with GBM.[13–15] Lim et al. reported that contrast-enhanced lesions contacting both the cortex and SVZ were most likely to be multifocal at the time of initial diagnosis. In addition, recurrent tumors were more likely to develop at locations distant to the initial lesion in patients with SVZ involvement. In contrast, GBMs not involving the SVZ or cortex were not multifocal at initial diagnosis and always recurred within 2 cm of the resection margin.[13] Chaichana et al. reported an association between periventricular tumor location (SVZ involvement) and poor survival.[14] They proposed a classification system including periventricular involvement for the prediction of outcome in patients with primary GBM.[21] Our study confirmed that SVZ involvement at diagnosis was an important predictor of OS.

In our result, the frequency of repeat surgery in patients with SVZ-positive GBMs was lower than that in patients with SVZ-negative GBMs, however, there was no significant difference. Other factors such as invasion to eloquent lesions could be also important for indication of repeat surgery. In this study, SVZ involvement was identified at recurrence in all patients who had primary SVZ-positive GBMs. In addition, most of these tumors re-recurred at locations noncontiguous with the recurrent lesion (CSF dissemination or contralateral invasion). As a result, a third resection was possible in only four patients in this group. In contrast, except for a few cases, SVZ-negative GBMs recurred within the SVZ-negative region. In addition, the tumor location at the second recurrence was quite similar to that of the primary and first recurring lesions. Therefore, a third resection was possible in approximately half the patients with SVZ-negative recurrent GBMs. In addition, SVZ involvement was associated with survival after repeat surgery in patients with recurrent GBM. Although a third resection was not associated with survival after the second repeat surgery, more aggressive tumors with SVZ involvement may have been associated with poorer survival after repeat surgery. On the other hand, median OS and survival after repeat surgery for patients with SVZ-positive recurrence of tumors that were SVZ-negative at diagnosis were 17 and 8 months, respectively. These results suggest that OS for patients with SVZ-negative tumors at diagnosis was relatively favorable; however, if the tumors recurred with SVZ involvement, the chances of survival became low. Despite the limited availability of cases, these results may be of interest. However, what remains less well known is why SVZ involvement is associated with poorer survival. In basic science studies, Sanai et al. demonstrated that cells obtained from the lateral wall of the lateral ventricle, which is called the SVZ, harbors cells with stem cell-like features of self-renewal and multi-potentiality.[12] While some GBMs may arise from transformed SVZ stem cells, other GBMs may be initiated by neoplastic transformation of astrocyte precursor cells or dedifferentiated mature astrocytes.[22] The aggressive behavior of SVZ-positive GBMs may be related to the recruitment of neural stem cells from the SVZ that have a tendency toward invasive proliferation. However, Kappadakunnel et al. found no relationship between stem-cell gene expression and SVZ grade, but they did find an association between stem-cell gene expression and survival.[23] As these researchers noted, more research is required to clarify the relationship among SVZ, cancer stem cells, and survival.

Despite its retrospective design, this study is the first to report a possible association between recurrent GBM tumors adjacent to the SVZ and decreased survival after repeat surgery. Nonetheless, larger prospective studies may provide further relevant information. However, the findings of this study may be helpful to determine therapeutic strategies for recurrent GBM. With regard to recurrence, SVZ-negative recurrent GBMs may be good candidates for repeat surgery.

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Conflicts of Interest Disclosure

The authors report no conflict of interest. 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.

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