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Prognostic analysis of patients who underwent gross total resection of newly diagnosed glioblastoma

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Abstract

Despite cumulative evidence supporting the idea that gross total resection (GTR) contributes to prolonged survival of patients with glioblastoma (GBM), the survival outcome of such patients remains unsatisfactory. To develop more effective postoperative therapeutic strategies for patients who underwent GTR, identification of prognostic factors influencing survival is urgently needed. Here we retrospectively analyzed prognostic factors for patients who underwent GTR of newly diagnosed GBM, with a particular focus on the influence of the subventricular zone (SVZ) as the tumor location. Forty-eight consecutive patients with newly diagnosed GBM who underwent GTR during the initial operation were investigated. Tumor involvement of the SVZ was significantly associated with overall survival (OS). The SVZ-positive group had a significantly shorter median OS of 12.2 months, compared to 34.9 months for the SVZ-negative group. The occurrence of leptomeningeal dissemination was significantly influenced by tumor involvement of the SVZ, but was not significantly influenced by ventricular opening during surgery. We observed a statistically significant difference in OS according to radiation modality. The median OS was 36.9 months for patients treated with high-dose proton beam therapy, compared with 26.2 months for patients treated with conventional radiotherapy. We demonstrated that tumor involvement of the SVZ was associated with poor survival of patients who underwent GTR of newly diagnosed GBM, suggesting the potential need for therapeutic strategies that specifically target tumors in the SVZ. Further prospective studies to evaluate whether radiotherapy targeting the SVZ improves survival of patients with tumor involvement of the SVZ who had undergone GTR are warranted.

Keywords: glioblastoma, gross total resection, subventricular zone, proton beam therapy

Introduction

In the last several decades, evidence has been accumulating that supports the notion that gross total resection (GTR) leads to prolonged survival of patients with glioblastoma (GBM)[1-4]. Therefore, to achieve GTR, many technologies such as intraoperative neuronavigation systems, 5-aminolevulinic acid, and intraoperative magnetic resonance imaging (MRI) have been introduced. However, the survival outcome of patients with GBM who underwent GTR remains unsatisfactory, with a median survival of 15.2–18.8 months[2, 3, 5]. These results suggest that further efforts should be made to develop more effective postoperative therapeutic strategies for GBM after GTR.

Because individual patient survival varies, identification of prognostic factors for shortened or prolonged survival is urgently needed for the development of appropriate therapeutic strategies. To date, a number of studies have analyzed the prognosis of patients with newly diagnosed GBM, and several different factors (e.g., age, preoperative performance status, tumor location, extent of resection, radiotherapy, and chemotherapy with temozolomide) have been identified as potential prognostic factors[5-7]. We recently demonstrated the prognostic potential of high-dose particle radiotherapies for newly diagnosed GBM[8-10]. However, the prognostic factors for patients who underwent GTR have not been studied in detail.

Previous studies suggest that the heterogeneity in survival and recurrence patterns in patients with GBM may be related to the presence of neural stem cells within the subventricular zone (SVZ) [11, 12]. Furthermore, recent studies demonstrated that GBMs involving the SVZ are associated with earlier recurrence and poor survival[11, 13, 14]. Those studies mainly analyzed patients who did not undergo GTR (the ratio of

patients who underwent GTR varied from 29 to 35%), and thus, the prognostic value of SVZ involvement in patients who underwent GTR remains unclear.

The purpose of the present study was to identify prognostic factors for patients who underwent GTR of newly diagnosed GBM. Specifically, we focused on the influence of tumor involvement of the SVZ.

Materials and Methods

From July 2006 to June 2015, 172 consecutive patients with newly diagnosed GBM were treated at the University of Tsukuba Hospital. Of these 172 patients, 48 underwent GTR of their tumor at the initial operation. The diagnosis of GBM was determined histopathologically based on the classification system of the World Health Organization. Patients with prior lower grade glioma or previous tumor resection were excluded from the analysis. GTR, which is defined as complete removal of the contrast-enhancing portion of the tumor, was confirmed by postoperative MRI that was obtained as soon as possible after surgery within 72 hours. We retrospectively reviewed the clinical and operative charts and radiographic images of these 48 patients.

All patients received radiotherapy with or without chemotherapy. The patients with GBM treated at our institute received one of two postoperative radiotherapy protocols. As conventional radiotherapy (CRT), daily photon radiotherapy of 2.0 Gy was administered five times per week, amounting to a total overall dose of 60.0 Gy. For high-dose proton beam therapy (PBT), a total dose of 96.6 GyE as hyperfractionated concomitant boost PBT was prescribed for the area of the surgical cavity seen on MRI plus a 5-mm margin. A 15-mm margin around the surgical cavity and a 20-mm margin around the region of perifocal edema were irradiated at doses of 73.5 GyE and 50.4 GyE, respectively.

Tumor involvement of the SVZ was defined if the contrast-enhancing lesion contacted the lateral walls of the lateral ventricle[11, 15]. The O^6-methylguanine-DNA-methyltransferase (*MGMT*) methylation status was determined by methylation-specific PCR. Isocitrate dehydrogenase-1 (*IDH1*) R132H mutation status was determined by immunohistochemistry using IMab-1[16].

Statistical analyses were performed using SPSS software (version 22; SPSS, Inc.). Overall survival (OS), defined as the time from surgery until death, was used to investigate the prognostic value of the analyzed variables. Survival probabilities were calculated using the Kaplan-Meier method, and differences among patient groups were evaluated using the log-rank test. The difference in categorical variables was evaluated using the Fisher's exact test. The difference in continuous variables was evaluated using the non-paired Student's t-test. A value of $p < 0.05$ was considered statistically significant in all analyses.

Results

The demographic, clinical, and treatment characteristics of the 48 patients are shown in Table 1. The mean age of the patients was 56.9 years (range, 14-76 years). Twenty-four patients were males, and 24 were females. The median Karnofsky performance status was 80 (range, 40-100). Nineteen (39.6%) patients had tumors involving the SVZ (SVZ-positive), and 29 (60.4%) had tumors located outside the SVZ (SVZ-negative). In 34 (70.8%) patients, the lateral ventricle was opened during surgery. Thirty-one (64.6%) patients received CRT, and 17 (35.4%) received PBT. Forty-two (87.5%) patients received concomitant chemotherapy with temozolomide, two patients (4.2%) received chemotherapy with nimustine hydrochloride alone, one patient (2.1%) received chemotherapy with a combination regimen of procarbazine, nimustine hydrochloride, and vincristine, and three patients (6.3%) received no chemotherapy. In three (6.3%) patients, biodegradable carmustine wafers were implanted during surgery. Nine (18.8%) patients received bevacizumab upon recurrence. Thirty-three (68.8%) patients developed recurrences during the follow-up period, of which 23 (69.7%) patients developed local or distant recurrences, and 10 (30.3%) developed leptomeningeal dissemination.

The median OS for all patients was 28.6 months (95% confidence interval, 18.0–39.1 months). The 1- and 2-year survival rates were 78.3% and 65.8%, respectively. Age, gender, Karnofsky performance status, tumor involvement of the SVZ, ventricular opening during surgery, *MGMT* methylation status, R132H mutant *IDH1* expression, radiation modality, temozolomide, biodegradable carmustine wafer implantation, and bevacizumab administration upon recurrence were examined as prognostic factors for survival using univariate analysis. The results of the analysis based on the Kaplan-Meier

method and the log-rank test are summarized in Table 2. Tumor involvement of the SVZ was significantly associated with OS. The SVZ-positive group had a significantly shorter median OS of 12.2 months compared to 34.9 months for the SVZ-negative group ($p = 0.007$) (Fig. 1A). We also observed a statistically significant difference in OS according to radiation modality. The median OS was 36.9 months for patients treated with PBT compared with 26.2 months for those treated with CRT ($p = 0.015$) (Fig. 1B). Regarding other factors, age was the only significant factor associated with OS. Although we observed tendencies for an association between the *MGMT* methylation status or R132H mutant *IDH1* expression and OS, these tendencies did not reach statistical significance. In relation to the association between tumor involvement of the SVZ and other factors, age, ventricular opening during surgery, radiation modality, and biodegradable carmustine wafer implantation were significantly correlated. The SVZ-positive group included more elderly patients than the SVZ-negative group. In the SVZ-positive group, ventricular opening during surgery was likely performed, whereas PBT and biodegradable carmustine wafer implantation were less likely to be undertaken. With regard to the association between radiation modality and other factors, no factors were significantly correlated other than tumor involvement of the SVZ. The occurrence of leptomeningeal dissemination was significantly influenced by tumor involvement of the SVZ, but was not significantly influenced by ventricular opening during surgery.

Discussion

In the present study, we identified the prognostic significance of tumor location with involvement of the SVZ and high-dose radiotherapy using PBT in consecutive patients in our institution who underwent GTR of newly diagnosed GBM. In addition, tumor involvement of the SVZ was significantly associated with leptomeningeal dissemination at recurrence.

Several previous studies demonstrated a correlation between tumor involvement of the SVZ and poor survival in patients with both newly diagnosed and recurrent GBM[14, 17, 18]. Furthermore, an association between distant and multifocal recurrence patterns in GBM and tumor involvement of the SVZ has been reported[12, 15]. Consistent with those previous reports in which patients who did not undergo GTR were mainly analyzed, we demonstrated the prognostic significance of tumor involvement of the SVZ, even in a series of patients who underwent GTR of newly diagnosed GBM.

Although the underlying cause of aggressive GBM behavior and tumor involvement of the SVZ is not yet completely understood, several hypotheses have been proposed. Lim et al. suggested that tumor cells near the SVZ may be closely related to neural stem cells, and the tumor cells may be highly migratory and invasive[12]. Chaichana et al. proposed another hypothesis that the SVZ region may have a different cellular environment that is more conducive to tumor proliferation and invasion[14].

In the present study, ventricular opening during surgery was not correlated with leptomeningeal dissemination at recurrence or poor survival, consistent with previous reports[15, 19, 20]. Our results suggested that surgical difficulty based on close proximity to subcortical fibers and critical neurological tissue, as well as surgical intervention including ventricular opening along with tumor involvement of the SVZ, were less likely

to contribute to poor survival than the biological nature of tumor cells and the anatomical environment of the SVZ. However, the molecular basis of this clinical phenomenon remains unclear.

The potential benefit of high-dose particle radiotherapy using hyperfractionated, concomitant boost PBT for patients with newly diagnosed GBM has been demonstrated in several previous studies[9, 10, 21, 22]. In those studies, only a selected population of patients who met the eligibility criteria were enrolled, and patients who did not undergo GTR were mainly analyzed. Our previous reports showed that high-dose, 96.6-GyE, concentric PBT, which was the same treatment protocol as in the present study, has high potential to improve survival in GBM patients with residual tumor after surgical resection[9, 22]. In our PBT protocol, the residual tumor plus a 5-mm margin was irradiated with 96.6 GyE, and in cases without residual tumor, the surgical cavity as seen on MRI plus a 5-mm margin was irradiated with 96.6 GyE. In the present study, we demonstrated the potential survival benefit of high-dose, 96.6-GyE, concentric PBT compared to CRT, even in cases without residual tumor.

To overcome the negative influence of tumor involvement of the SVZ on survival, alternative approaches specifically targeting the SVZ will be needed. Several retrospective studies have analyzed the relationship between the radiation dose to the SVZ and the outcome of patients with newly diagnosed GBM [23-26]. Those studies were designed based on the hypothesis that therapy targeting GBM stem cells from the SVZ may be beneficial because these cells potentially initiate or contribute to GBM and worsen patient outcome. Thus, for comparison, the patients analyzed in those studies were not restricted to patients with tumor involvement of the SVZ. In three previous reports, an association between a higher radiation dose to the ipsilateral SVZ and significantly

improved OS, progression-free survival, or both was demonstrated[23, 25, 26]. On the contrary, a conflicting report showed no association between the radiation dose to the ipsilateral SVZ and survival[24]. Although whether a higher radiation dose to the SVZ is generally beneficial for the outcome of GBM patients remains controversial, Chen et al. stated that a higher radiation dose to the ipsilateral SVZ positively impacts the survival of only patients who had undergone GTR[23]. Particularly for GBM patients with tumor involvement of the SVZ, radiotherapy targeting the SVZ after GTR may play a critical role in survival. The potential benefit of high-dose radiotherapy using PBT in terms of the dose to the SVZ has not been investigated well. Our study has some limitations. The potential confounding between tumor involvement of the SVZ and high-dose radiotherapy using PBT may influence our results because PBT was less likely to be undertaken in the SVZ-positive group. However, patients with tumor involvement of the SVZ treated with PBT tended to survive longer than those treated with CRT, although these tendencies did not reach statistical significance due to the relatively small sample size. Also, we could not evaluate the association between the dose of PBT to the SVZ and survival of patients with tumor involvement of the SVZ because of the relatively small sample size. Further evaluation will be needed to determine whether radiotherapy targeting the SVZ including PBT has the potential to increase survival in patients with tumor involvement of the SVZ who had undergone GTR.

In conclusion, we demonstrated that tumor involvement of the SVZ was associated with poor survival of patients who underwent GTR of newly diagnosed GBM, suggesting the potential need for therapeutic strategies that specifically target the SVZ. We also demonstrated that high-dose PBT for the surgical cavity after GTR has a potential benefit on survival. Further prospective studies are warranted to evaluate whether radiotherapy

targeting the SVZ including PBT improves survival of patients with tumors involving the SVZ who had undergone GTR.

Figure Captions

Fig. 1: The results of univariate analysis based on the Kaplan-Meier method

A: Kaplan-Meier estimates of overall survival according to tumors involving the SVZ or not. B: Kaplan-Meier estimates of overall survival according to radiation modality.

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Table 1
Demographic, clinical, and treatment characteristics of the 48 patients analyzed in this study

Characteristics	No. of patients	%
Age (yrs)		
Mean ± SD	56.9 ± 13.2	
Range	14-76	
Gender		
Male	24	50.0
Female	24	50.0
KPS		
100	3	6.3
90	18	37.5
80	12	25.0
70	7	14.6
60	2	4.2
50	3	6.3
40	3	6.3
Tumor involvement of SVZ		
+	19	39.6
-	29	60.4
Ventricular opening during surgey		
+	34	70.8
-	14	29.2
MGMT methylation status		
methylated	15	31.3
unmethylated	29	60.4
R132H mutant IDH1 expression		
positive	8	16.7
negative	39	81.3
Radiation modality		
CRT	31	64.6
PBT	17	35.4
Concomitant temozolomide		
+	42	87.5
-	6	12.5
Biodegradable carmustine wafer		
+	3	6.3
-	45	93.8
Bevacizumab upon recurrence		
+	9	18.8
-	39	81.3

SD: standard deviation, KPS: Karnofsky performance status, SVZ: subventricular zone, MGMT: O6-methylguanine-DNA-methyltransferase, IDH1: Isocitrate dehydrogenase-1, CRT: conventional radiotherapy, PBT: proton beam therapy.

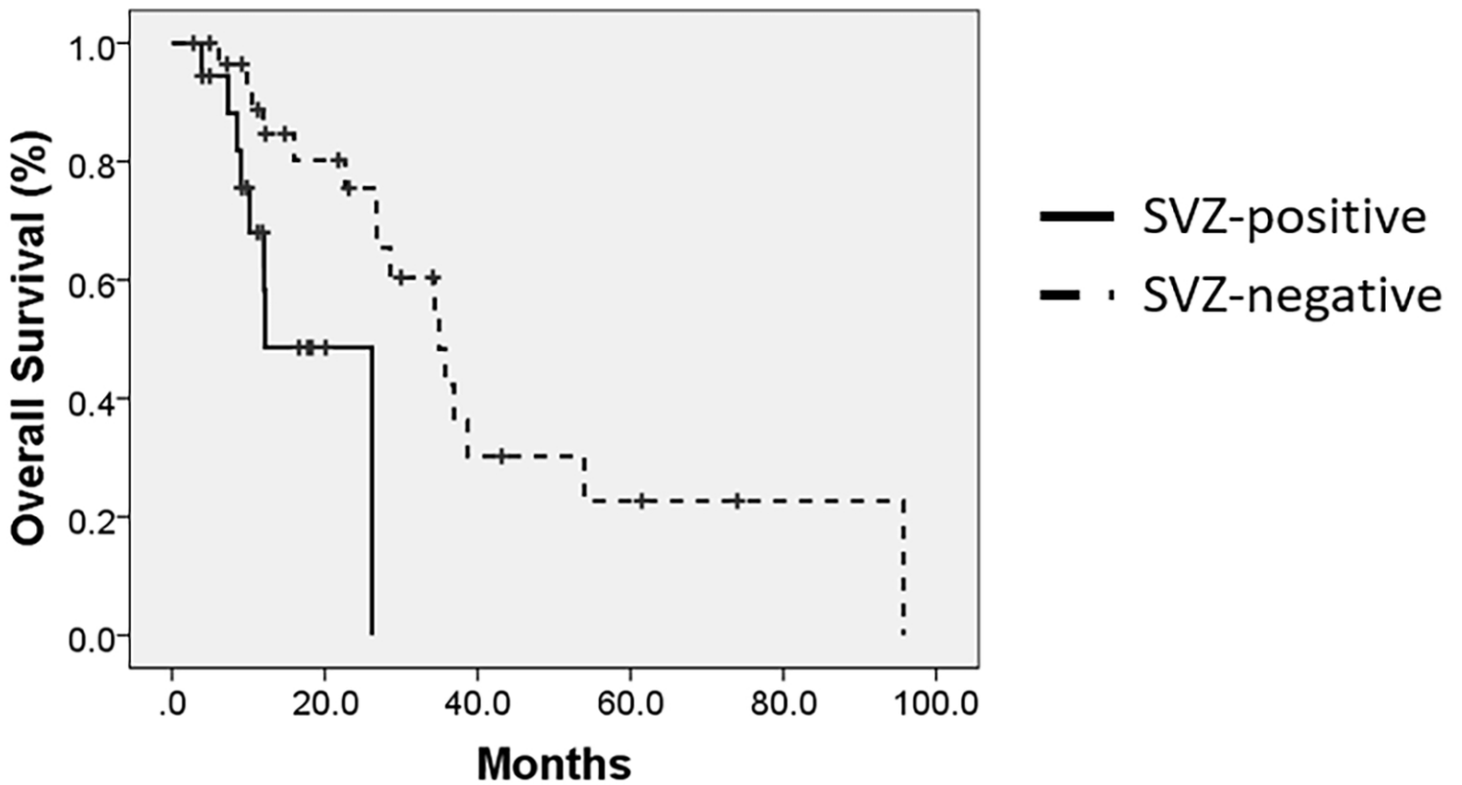
Table 2
Overall survival analysis

Variable	Median Survival (mos)	p Value (log-rank)
Age		<0.001
≥70 yrs	10.1	
<70 yrs	34.9	
Gender		0.837
male	26.8	
female	34.4	
KPS		0.422
≥80	28.6	
<80	26.8	
Tumor involvement of SVZ		0.007
SVZ-positive	12.2	
SVZ-negative	34.9	
Ventricular opening during surgery		0.804
+	26.8	
-	34.9	
MGMT methylation status		0.150
methylated	36.9	
unmethylated	26.2	
R132H mutant IDH1 expression		0.169
positive	36.9	
negative	26.8	
Radiation modality		0.015
CRT	26.2	
PBT	36.9	
Concomitant temozolomide		0.785
+	28.6	
-	10.5	
Biodegradable carmustine wafer		0.689
+	10.1	
-	28.6	
Bevacizumab upon recurrence		0.418
+	35.7	
-	26.8	

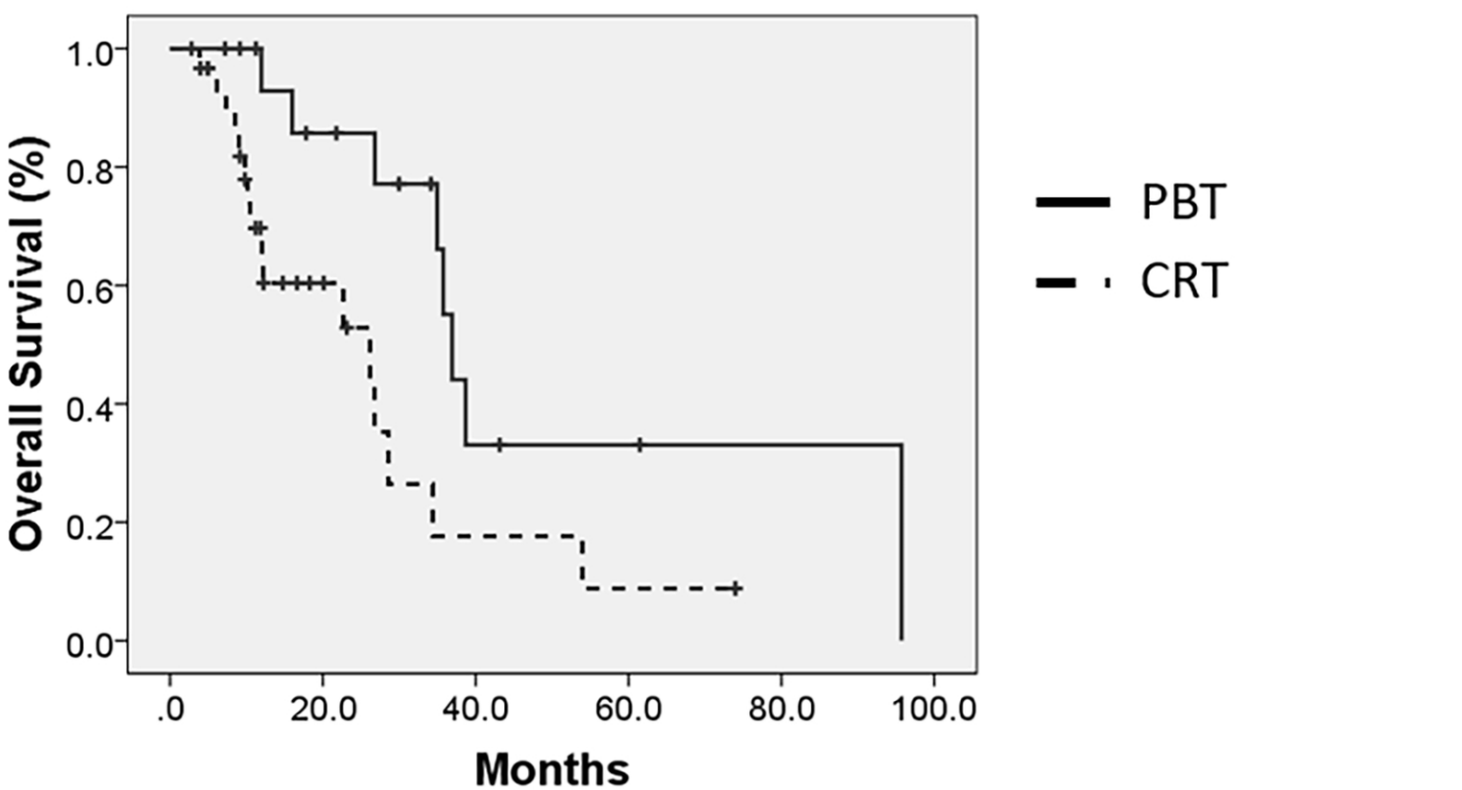
KPS: Karnofsky performance status, SVZ: subventricular zone,
MGMT: O6-methylguanine-DNA-methyltransferase, IDH1: Isocitrate dehydrogenase-1,
CRT: conventional radiotherapy, PBT: proton beam therapy.

Fig.1

a


Tumor involvement of the SVZ
Overall Survival (%)
1.0
0.8
0.6
0.4
0.2
0.0
.0
20.0
40.0
60.0
80.0
100.0
Months
SVZ-positive
SVZ-negative

b


Radiation modality
Overall Survival (%)
1.0
0.8
0.6
0.4
0.2
0.0
.0
20.0
40.0
60.0
80.0
100.0
Months
PBT
CRT