Journal of Clinical Neuroscience xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Case study

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

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ARTICLE INFO

Article history:
Received 16 May 2017
Accepted 5 January 2018
Available online xxxx

Keywords:
Glioblastoma
Gross total resection
Subventricular zone
Proton beam therapy

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.

1. 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

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https://doi.org/10.1016/j.jocn.2018.01.009
0967-5868/

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.

2. 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 h. 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 $p < .05$ was considered statistically significant in all analyses.

3. 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.

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 surgery		
+	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.

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 ($p = .007$) (Fig. 1A). We also observed a statistically significant difference in OS according to radiation modality. The median

Please cite this article in press as: Matsuda M et al. Prognostic analysis of patients who underwent gross total resection of newly diagnosed glioblastoma. J Clin Neurosci (2018), https://doi.org/10.1016/j.jocn.2018.01.009