International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

# Glioblastoma Recurrence Patterns After Radiation Therapy With Regard to the Subventricular Zone

**Sebastian Adeberg, MD,* Laila König, MD,* Tilman Bostel, MD,* Semi Harrabi, MD,* Thomas Welzel, MD,* Jürgen Debus, MD, PhD,*,†,** and Stephanie E. Combs, MD*,†**

**Department of Radiation Oncology, University Hospital of Heidelberg; †Heidelberg Ion Therapy Center, Heidelberg, Germany; and **DKFZ Clinical Cooperation Unit Radiation Oncology, German Cancer Research Center Heidelberg, Germany*

Received Feb 1, 2014, and in revised form Jul 17, 2014. Accepted for publication Jul 19, 2014.

**Summary**

Glioblastoma is the most common and aggressive primary brain tumor, with one of the worst survival rates. Karnofsky performance status and age are the most important prognostic factors. Our data show evidence that tumor location with regard to the SVZ is another prognostic factor for survival.

**Purpose:** We evaluated the influence of tumor location and tumor spread in primary glioblastoma (GBM), with respect to the subventricular zone (SVZ), on recurrence behavior, progression-free survival (PFS), and overall survival (OS).

**Methods and Materials:** 607 patients (376 male and 231 female) with a median age of 61.3 years (range, 3.0-87.9 years) and primary GBM treated with radiation therapy (RT) from 2004 to 2012 at a single institution were included in this retrospective study. Preoperative images and follow-up examination results were assessed to evaluate tumor location. Tumors were classified according to the tumor location in relation to the SVZ.

**Results:** The median PFS of the study population was 5.2 months (range, 1-91 months), and the median OS was 13.8 months (range, 1-102 months). Kaplan-Meier analysis showed that tumor location in close proximity to the SVZ was associated with a significant decline in PFS and OS (4.8 and 12.3 months, respectively; each $P<.001$). Furthermore, in cases where tumors were involved with the SVZ, distant cerebral progression (43.8%; $P=.005$) and multifocal progression (39.8%; $P=.008$) were more common. Interestingly, opening of the ventricle during the previous surgery showed no impact on PFS and OS.

**Conclusion:** GBM in close proximity to the SVZ was associated with decreased survival and had a higher risk of multifocal or distant progression. Ventricle opening during surgery had no effect on survival rates. 

Reprint requests to: Sebastian Adeberg, MD, Department of Radiation Oncology, University Hospital of Heidelberg, Im Neuenheimer Feld 400, 69120 Heidelberg, Germany. Tel: (0049)-6221-5635654; E-mail: Sebastian.adeberg@med.uni-heidelberg

Presented in part at the Annual Meeting of the German Society of Radiation Oncology (DEGRO), 9th - 12th May 2013, Berlin, Germany.

Conflict of interest: none.


0360-3016/$ - see front matter 
http://dx.doi.org/10.1016/j.ijrobp.2014.07.027

## Introduction

Glioblastoma (GBM) is the most frequent primary malignant central nervous system tumors in adults (1). The median survival rates remain poor, with a median survival of 14.6 months after surgical treatment followed by chemoradiation therapy (1). Even though therapeutic strategies have improved over the past decade, death occurs inevitably from either recurrent or progressive disease (2). High percentages of all patients experience in-field relapses after initial radiation therapy (RT) combined with temozolomide (TMZ) (3), whereas distant relapses occur in only 2% to 13% of cases (4-6). Earlier data suggested that the heterogeneity in patient survival and recurrence patterns of patients with GBM might be related to neuronal stem cells in the SVZ (7, 8). GBM stemlike cells representing a minority of cells in the tumor may be responsible for the aggressive characteristics, self-renewal, and radioresistance of the tumor (7, 9). The SVZ, which is close to the lateral wall of the lateral ventricle, and the subgranular layer of the dentate gyrus are capable of generating glial cells and neurons throughout adult life. Furthermore, it has been shown in animal experiments that glioma may arise from stem cell populations in the SVZ (10). Accordingly, the SVZ seems to be more susceptible to tumorigenesis than are the cortical areas (11, 12).

In a study by Lim et al (7), GBM was categorized with regard to the SVZ (Fig. 1). Four subtypes were determined, and the data suggest that GBM in contact with the SVZ tend to show multifocal relapse, earlier recurrence, and decreased OS (7, 8). Interestingly, a subependymal tumor spreading along the borders of the lateral ventricle also seems to be associated with lower survival rates (13).

To assess the influence of GBM location with involvement of the SVZ on survival and progression patterns, we analyzed our data bank of GBM, focusing on the spatial relationship of the tumor to the SVZ, GBM recurrence behavior based on magnetic resonance imaging (MRI), and survival.

## Patients and Methods

Between January 2004 and December 2012, 723 consecutive patients with primary GBM were treated with RT or chemoradiation therapy at the Department of Radiation Oncology/University Hospital Heidelberg, Germany. Treatment decisions were made according to the current treatment standard at the time, respecting individual patient factors such as age or Karnofsky performance score.

We reviewed the clinical course records and preoperative and postoperative MRI (Table 1). Patients were followed up prospectively at the center 6 weeks after treatment and at 3-month intervals in the following period until death. Examinations included contrast-enhancing MRI.

The data for 607 patients (84.0%) were sufficient for survival and tumor location analysis. In all, 376 male and 231 female patients with a median age of 61.3 years (range, 3.0-87.9 years) were counted. At the time of RT, 78.4% of all patients were older than 50 years.

A total of 416 patients (68.5%) underwent surgical resection as initial treatment, which was complete in 178 cases (42.8%) and subtotal in 238 (57.2%) cases. In 177 patients (29.2%), the diagnosis of GBM was confirmed by biopsy without surgical resection being performed. Ventricle opening during previous surgery was detected in 107 patients (18.9%), and surgery without ventricle opening was performed in 457 patients (80.1%). One hundred four patients (17.1%) received RT as reirradiation at the time of progression.

Three hundred ninety-three patients (71.7%) received concomitant chemotherapy with TMZ, 37 (6.1%) patients received combined therapy with a different agent (bevacizumab, cetuximab, cilengitide, imatinib, or temsirolimus), 170 (28.3%) patients received RT alone, and in 6 patients the regimens could not be determined with absolute certainty. A higher percentage (57.9%) of patients with GBM in close proximity to the SVZ received simultaneous TMZ therapy, compared with patients (43.3%) with GBM not involving the SVZ ($P<.001$).

The O6-methylguanin-DNA-methyltransferase (MGMT) promoter status was assessed in 175 patients (28.9%), of whom 70 (40.0%) had a hypermethylated MGMT promoter status, 4 (2.3%) had a partial methylated MGMT promoter status, and 101 (57.7%) did not present with a hypermethylated MGMT promoter status.

### Radiation therapy

For treatment planning, patients were provided with custom-made immobilization masks. Computed tomography and MRI were performed. Over the long time frame of this study and the heterogeneity of the patients, several fractionation schemes were used. Patients received a median dose of 51.7 Gy (range, 10-68 Gy) in 2.16-Gy daily fractions (range, 1.8-3.0 Gy/day). In 15 cases, radiation therapy could not be completed for various reasons, and these patients received a smaller cumulative dose.

The target volume was defined as the region of the primary tumor, including all contrast-enhancing lesions on T1-weighted MRI and the T2-hyperintense region. A safety margin of 2 to 3 cm for potential microscopic spread was added.

### Follow-up

Overall survival (OS) was calculated as the time between the day of proven pathologic diagnosis and the day of death.

Progression-free survival (PFS) was calculated as the time between the first treatment day and appearance of local or distant progression based on contrast enhanced T1-weighted MR sequences on axial and coronal imaging.