Management of Patients with Primary Intramedullary Spinal Cord Glioblastoma

Bedjan Behmanesh[1], Matthias Setzer[1], Juergen Konczalla[1], Patrick Harter[2], Johanna Quick-Weller[1], Lioba Imoehl[1], Kea Franz[1], Florian Gessler[1], Volker Seifert[1], Gerhard Marquardt[1]

BACKGROUND: **Primary intramedullary spinal cord glioblastomas are very rare tumors of the spinal cord. They imply a very poor prognosis because complete surgical resection is not possible as the result of the infiltrative growth of these tumors. The aim of this study is to present our data achieved with an aggressive multimodality treatment.**

METHODS: **We retrospectively reviewed our clinical database. All patients with histologically proven intramedullary spinal cord glioblastoma treated in our department were included in this study.**

RESULTS: **Four patients with intramedullary spinal cord glioblastoma were identified between 2006 and 2015, all of whom were female. Mean age at the time of surgery was 33.5 years (range 14–50 years). Tumors were located in the cervical region in 2 patients and in the thoracic region in 2 patients. All 4 patients underwent microsurgical biopsy of the tumor. After surgery, all patients received radiation and temozolomide treatment. One patient underwent additional therapy with Bevacizumab, another patient received Rapamycin and Sunitinib, and the third patient received Chlorethyl-cyclohexyl-nitroso-urea and Etoposide as additional therapy after tumor regrowth. Tumor progression occurred in a mean time of 18.2 months (6–32 months). In this series, all patients died as the result of progression of the malignancy; median survival after diagnosis was 32.5 months.**

CONCLUSIONS: **The surgical outcome of intramedullary spinal cord glioblastoma still remains poor. Severe disability and amelioration of the neurologic status lead to reduced quality of life; however, an aggressive multimodal and interdisciplinary treatment for the disease may be associated with longer survival.**

INTRODUCTION

Primary spinal cord (SC) tumors are rare entities, accounting for 2%–4% of all central nervous system tumors.[1,2] Among these, astrocytoma represent only 6%–8% of all intramedullary tumors, with 75%–90% of them being low-grade gliomas. Therefore, SC glioblastoma multiforme (GBM) is extremely rare, accounting for only 1.5% of all SC tumors.[3-6] These highly malignant lesions occur mainly in the cervicothoracic segments and have a slight tendency to occur in the first decades of life. A short clinical history before diagnosis is mainly associated with the natural history of intramedullary spinal cord glioblastoma (ISCGBM).[7,8] The overall survival (OS) of patients with ISCGBM is approximately 10–12 months, in contrast to a better prognosis of 14 months for its intracranial counterpart.[9] ISCGBM results in death resulting from complications related to progressive SC involvement, respiratory impairment, and cerebral metastases.[7,10] Only few data exist reporting current experience about survival and progression after the introduction of temozolomide (TMZ) and novel therapeutic strategies. The aim of this paper also is to highlight the effect of new drugs on survival and tumor control.

METHODS

The study was approved by the local ethics committee at the authors' institution. We retrospectively reviewed the medical history

Key words
- Intramedullary glioblastoma
- Multimodal therapy
- Radiation
- Spinal cord
- Surgery

Abbreviations and Acronyms
GBM: Glioblastoma
MRI: Magnetic resonance imaging
OS: Overall survival
PFS: Progression-free survival
SC: Spinal cord
ISCGBM: Intramedullary spinal cord glioblastoma
TMZ: Temozolomide

From the Departments of [1]Neurosurgery and [2]Neuropathology, University Hospital Frankfurt, Goethe-University, Frankfurt, Germany

To whom correspondence should be addressed: Bedjan Behmanesh, M.D. [E-mail: bedjan.behmanesh@gmail.com]

Citation: World Neurosurg. (2017) 98:198-202.
http://dx.doi.org/10.1016/j.wneu.2016.10.075

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

of all patients with intramedullary SC tumors treated at our institution during a period of 36 years. Between 2006 and 2015, 4 patients with the diagnosis of ISCGBM were identified. The medical charts were reviewed, including surgical and histologic data, treatment parameters, neurologic outcome, progression-free survival (PFS), and OS. Histologic grading of all tumors was done according to the World Health Organization criteria. Pre- and postoperative neurologic status during follow-up was performed by the staff neurosurgeons using the McCormick Classification scheme (Table 1).[3,11-17] All patients underwent preoperative, postoperative, and follow-up magnetic resonance imaging (MRI) scans. Surgical therapy consisted of a standard posterior approach via a laminectomy or laminoplasty in cases of multilevel tumor involvement in all patients. All operations were performed with an intraoperative microscope and neuromonitoring.

Postoperatively, frozen section analysis and final histologic preparation confirmed the diagnosis of ISCGBM in all cases. After surgery, all patients underwent radiotherapy, with an average dose of 50 Gy in 5 weeks. Chemotherapy with TMZ was administered in all patients concomitantly during radiotherapy. MRI was performed within 72 hours after surgery and subsequently every 3 months thereafter. Tumor regrowth and progression were defined as clinical and/or radiographic progression on follow-up MRI. Additional chemotherapy was administered according to the decision of the neuro-oncological conference.

OS was defined as the period from the initial surgery to the date of death. Survival and PFS were analyzed with Kaplan-Meier curves. A matched pair analysis with 4 patients with intracranial GBM treated in our department was performed for comparison and detection of differences focusing on PFS and survival. This analysis included patients with identical demographic characteristics, such as age, sex, radiation therapy, and TMZ. In addition, a review of the literature was performed to compare the OS, patient's characteristics, and treatment modality.

RESULTS

All patients were female, and their ages ranged from 14 to 50 years at the time of surgery (mean 33.5 years). The follow-up period ranged from 10 to 46 months (mean 32.5 months). The presenting symptoms and signs were pain, hypesthesia, or paresthesia in all cases. Two patients revealed motor weakness preoperatively and only 1 patient an improvement of the neurologic status after surgery and postoperative therapy. The preoperative functional assessment, which was made in all patients, showed 1 patient with McCormick Grade I, 1 with McCormick Grade II, another with McCormick Grade III, and 1 patient with McCormick Grade IV. After surgery, 2 patients had a McCormick Grade II and 2 patients McCormick Grade III. In the follow-up period, 3 patients had McCormick Grade IV and one patient had neurologic improvement from McCormick Grade IV to McCormick Grade III. Lesions were located in the cervical SC in 2 patients and in the thoracic region in another 2 patients (Table 2).

Table 1. Modified McCormick Score

Grade	Clinical Definition
I	Neurologically normal
II	Moderate deficit, limitation of function, independent without external aid
III	Severe motor or sensory deficit, limited function, dependent in external aid
IV	Severe deficit, paraplegia or quadriplegia, dependent

The O6-methylguanine-DNA methyltransferase promoter was methylated in 2 of 4 cases, and a TP53 mutation was detected in 2 patients. Molecular examination did not reveal IDH1 or ATRX mutations.

None of the patients with ISCGBM underwent total resection. All patients showed progression of the tumor. In none of the patients, the tumor had disseminated to a different location in the SC. In one case, tumor dissemination within the brain was observed. Mean PFS was 18.2 months (range, 6–32 months) (Figure 1). Mean OS was 32.5 months (range, 10–46 months) (Figure 2).

Conventional radiation therapy (40–50 Gy in 20–25 fractions) was performed in all patients and was combined with concomitant chemotherapy consisting of TMZ. In case of tumor progression, an additional chemotherapy or radiation was recommended. One patient underwent additional Bevacizumab therapy and survived 46 months after surgery. The second patient displayed a tumor regrowth after 6 months and died after 10 months without further therapy after tumor progression. Patient 3 had a PFS of 11 months and received additional Rapamycin and Sunitinib after tumor progression. She died after 24 months. Patient 4 had a PFS of 32 months and underwent additional chlorethyl-cyclohexyl-nitrosourea and Etoposide treatment. She underwent a second radiation therapy and died 41 months after the initial presentation. The cause of death was respiratory paralysis in 2 cases and severe pneumonia in another 2 cases. No patient was lost in the follow-up (Table 2).

An additional matched pair analysis with patients with intracranial GBM revealed no significant difference in regard to OS and PFS (median survival 35 months in intracranial GBM group, 32.5 months in the ISCGBM group; $P > 0.05$).

DISCUSSION

As a result of the extremely rare occurrence of ISCGBM the current literature is scarce. A review of the pertaining literature suggests that this entity shows a predilection in the earlier decades of life.[4,18-20] In our series, mean age was 33.5 years with one patient being younger than 18 years. Apparently, the most affected spinal areas are the cervical and thoracic region in line with the data presented here.[6,21,22] Because complete resection of these tumors is not possible because of their infiltrative growth pattern, surgery commonly is limited to biopsy or subtotal resection. Particularly the benefit of a more aggressive surgical procedure is unproven. All measures have produced disappointing results inasmuch as mean survival amounts 10–12 months after diagnosis.[11,14-18,23]

The introduction of adjuvant TMZ therapy, in addition and radiation therapy, has produced a considerable improvement in survival and clinical outcomes of patients with intracranial GBM,[24] but its role in the management of ISCGBM remains