Treatment of Glioblastoma Multiforme –
the Experience of the Radiotherapy Department of Sibiu

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Background: Primary brain tumours are uncommon and comprise only 1.6 per cent of cancers. Malignant gliomas include a spectrum of primary brain tumors that represent some of the most lethal and debilitating neoplasms known. Despite more than 30 years of extensive clinical trials, progress has been made only recently in the treatment of these neoplasms. Material and methods: We performed a retrospective analysis of 273 brain tumors from which 49 patients with histological proven glioblastoma multiforme were treated with radiotherapy and chemotherapy in the Radiotherapy Department of the Emergency County Hospital of Sibiu from 2000 – 2008. Results: Forty-nine patients with glioblastoma multiforme were treated in our Department of Radiotherapy. The initial therapeutic approach was surgery in all 49 patients. Chemoradiotherapy was administered in 29 patients. Concomitant chemoradiotherapy was administered in 6 patients. Conclusions: Concomitant Temozolomide/radiotherapy followed by adjuvant Temozolomide increases survival in patients with glioblastoma multiforme and it is also necessary to improve the treatment planning technique. Radiotherapy should be fully conformal.

Key words: Glioblastoma multiforme, Radiotherapy, Temozolomide.

Introduction

Primary brain tumours are uncommon and comprise only 1.6 per cent of cancers. Malignant gliomas include a spectrum of primary brain tumors that represent some of the most lethal and debilitating neoplasms known. Malignant glioma comprises glioblastoma, anaplastic astrocytoma, mixed anaplastic oligoastrocytoma and anaplastic oligodendroglioma. High-grade gliomas constitute 77% of malignant brain tumors. Eighty – two percent of cases are glioblastoma multiforme (1).

Despite more than 30 years of extensive clinical trials, progress has been made only recently in the treatment of these neoplasms. Both surgery and radiation therapy (RT) have benefited from improvements in tumor imaging, allowing more accurate RT and more complete, safer tumor resections (2-4). The introduction of temozolomide chemotherapy has demonstrated a positive survival impact in patients with newly diagnosed glioblastoma multiforme (5-7).

The aim of this article is to describe the experience of the Sibiu Radiotherapy Department in the treatment of glioblastoma multiforme (GBM).

Material and methods

We performed a retrospective analysis of 273 brain tumors from which 49 patients with histological proven glioblastoma multiforme were treated with radiotherapy and chemotherapy in the Radiotherapy Department of the Emergency County Hospital of Sibiu from 2000–2008.

The following data were collected from the medical records of the patients: age at diagnosis, gender, site of the disease, imaging of the brain before and after surgery, histology, type of surgery; if radiotherapy was given with the intent to cure or to palliate, the type of chemotherapy and number of cycles of chemotherapy.

Regarding the treatment approach, surgery was given in all 49 patients. Radiotherapy was curative in 26 patients concomitant or in adjuvant setting with monochemothery with temozolomide. Radiotherapy was given with palliative intent in 11 patients. In 12 patients radiotherapy was delivered exclusively with curative intent. Fractionated focal radiotherapy (60 Gy, 30 fractions of 2 Gy) was the standard treatment after tumor resection or biopsy. The same treatment sched-
ule was applied in patients treated exclusively with radiotherapy with curative intent. Radiotherapy with palliative intent was delivered at a total dose of 30Gy, 10 fractions of 3Gy.

Chemotherapy with Temozolomide was administered in 9 patients after the recurrence of the tumor; in 11 patients Temozolomide was administered in the adjuvant setting and 6 patients received Temozolomide concomitent with radiotherapy. In the adjuvant setting Temozolomide was administered on a daily dose of 200mg/m² x 5 every 28 days. In the concomitant setting, Temozolomide was administered at a dose of 75mg/m² daily (7 days/week) 1-1.5 hours before radiotherapy from the first to the last day of radiotherapy.

The follow-up data included disease outcome by overall survival (defined as time from the first treatment day to death) and progression – free survival (defined as the time from first therapeutic act to the first evidence of tumor progression clinically or imagistically on CT or MRI).

Results

Forty-nine patients with glioblastoma multiforme were treated in our Department of Radiotherapy. These patients represented 17.94% of all patients with brain tumors.

The distribution of the patients over the 8 years (from 2000 to 2008) is shown in table I.

The most common location of the glioblastoma multiforme was in the frontal lobe. The distribution of the tumors in the brain are shown in the figure 1.

The patients’ ages ranged from 27 to 75 years. The distribution of the patients according to their age is shown in figure 2.

The initial therapeutic approach was surgery in all 49 patients. In 18 patients a complete macroscopic resection was obtained, in 25 patients it was a partial resection with an debulking approach and in 6 patients a biopsy was performed only.

The distribution of the type of surgical interventions are shown in figure 3.

Table I: The distribution of patients from 2000-2008.

<table>
<thead>
<tr>
<th>Year</th>
<th>Total number of brain tumors</th>
<th>Meduloblastoma multiforme</th>
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<tbody>
<tr>
<td>2000</td>
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<td>3</td>
</tr>
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<td>2008</td>
<td>29</td>
<td>6</td>
</tr>
</tbody>
</table>

Fig. 1: Distribution of glioblastoma multiforme in the brain.
The pathological reports confirmed a glioblastoma multiforme in all patients.

Surgery was followed by radiotherapy within 4-6 weeks. The irradiation was performed with a Theratron Elite 100 unit.

Radiotherapy with curative intent was delivered in 12 patients. We performed adjuvant radiotherapy 4-6 weeks after surgery. The median survival was 11 months.

Radiotherapy with palliative intent was delivered in 11 patients only with biopsy or partial resection pure performance status and neurological disfunctions. The aim of this therapy was the palliation of symptoms.

Chemoradiotherapy was administered in 29 patients. Temozolomide was administered after the recurrence of the tumor in 9 patients. Four patients died with disease progression before they received 6 cycles of Temozolomide. Two patients died 2 and respectively 3 months after completing 6 cycles of Temozolomide. Three patients had stable disease, but after 5 and respectively 7 months had recurrent disease.

Temozolomide was administered in the adjuvant setting in 11 patients (5 patients with complete macroscopic resection, and 6 patients with partial resection). The median survival was 13.4 months.

Concomitant chemoradiotherapy was administered in 6 patients. In the concomitant setting Temozolomide was administered at a dose of 75mg/m² daily (7 days/week) 1-1.5 hours before radiotherapy from the first to the last day of radiotherapy. One patient is in complete remission after 1.5 year. One patient died one month after completing the treatment with progressive disease. One patient had recurrent disease 4 months after completing the treatment. Three patients are in complete remission and are now on the maintenance phase; Temozolomide 200mg/m² is administered on a daily x 5 schedule every 28 days.

Discussion

Malignant gliomas include a spectrum of primary brain tumors that represent some of the most lethal and debilitating neoplasms known. In contrast with other high-grade malignancies, recurrence of high-grade gliomas is predominantly a local problem (8).
Surgery may consist of a simple biopsy to establish a diagnosis. More often, patients undergo a craniotomy aimed at removing as large a fraction of the tumor as is safely possible, with the goal of establishing a diagnosis and reducing the residual tumor burden. Surgery alone is never curative, and therefore cannot be considered definitive.

Radiation therapy has been used in the treatment of glioblastoma multiforme for over six decades. Radical radiotherapy should only be offered to patients with excellent performance status. Therefore, radical radiotherapy should be restricted to younger patients (9). Many centers use 70 as an age cut-off; above this age patients are not offered radical radiotherapy (10). This age restriction is designed to avoid acute side effects and long courses of treatment in patients with a poor prognosis resulting from an older age. In our study, for the same reason, we treated 11 patients with palliative radiotherapy.

Temozolomide is a lipophilic second-generation alkylating agent developed especially for the treatment of malignant gliomas. Temozolomide was studied as a single agent in recurrent glioma patients, where it first gained FDA approval.

Concomitant chemoradiotherapy is now the gold standard of care. Temozolomide at a low dose of 75mg/m² is administered daily (7 days/week) 1-1.5 hours before radiotherapy plus six cycles of adjuvant Temozolomide (150 or 200 mg/m² for 5 days per 28 days cycle), which improves the 2-year survival versus radiotherapy alone from 10.4% to 26.5%. In our study we had only 6 patients with concomitant chemoradiotherapy because of budget problems in the first years.

The current study is a starting point for the radiotherapy technique improvement and for the multidisciplinary approach of more patients with concomitant chemoradiotherapy.

Conclusions

Despite aggressive treatment, high-grade malignant gliomas have a poor prognosis with current methods. Concomitant Temozolomide/radiotherapy followed by adjuvant Temozolomide increases survival in patients with glioblastoma multiforme. To improve survival it is also necessary to improve the treatment planning technique. Radiotherapy should be fully conformal.

References:


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