

# Gliosarcomas in the elderly: analysis of 7 cases and clinico-pathological remarks

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## ABSTRACT

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**Aims and background.** Gliosarcomas are rare malignant primary brain tumors that usually affect the fifth or sixth decades of life. The purpose of this study was to describe our experience with such lesions in elderly patients and to establish their prognosis factors.

**Methods.** Between 1993 and 2001, 7 patients over 60 years of age were treated at our institute for cerebral gliosarcomas. All patients underwent surgery for total or at least sub-total removal of a neoplastic mass.

**Results.** Owing to poor clinical conditions (Karnofsky performance score = 40), one patient was not treated postoperatively. Remaining patients were treated with whole-brain radiotherapy, whereas concomitant chemotherapy (temozolomide) was administered only to 4 patients. Histological examination showed the prevalence of sarcomatous aspects in 3 patients; the gliomatous aspect prevailed in 4 patients.

**Conclusions.** Sarcomatous aspects and multimodality treatment (surgery, radiotherapy and chemotherapy) were associated with a better prognosis and showed in these elderly patients a trend similar to that of young people.

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## Introduction

Gliosarcomas are primary cerebral tumors characterized by a biphasic tissue pattern with areas of glial and mesenchymal differentiation<sup>1</sup>. Recently, genetic studies demonstrated a monoclonal origin for gliosarcoma cells and a mesenchymal phenotype acquisition from malignant astrocytes<sup>2,3</sup>.

The incidence of malignant brain tumors has increased, especially among the elderly population (between 65 and 85 years of age)<sup>4</sup>. Nevertheless, elderly patients are often treated suboptimally, because of the wide-spread opinion that these patients do not endure surgery and radiotherapy as well as younger people. Mangiola *et al.*<sup>5</sup> showed how age itself should not be considered a prognostic factor for under-treatment in the management of cerebral glial neoplasms, because the overall median survival after surgery in elderly people is similar to that of other patients.

We present a series of 7 elderly patients affected by gliosarcomas and treated in a multimodality way: surgical, therapeutic and prognostic considerations are made.

## Materials and methods

Between 1993 and 2001, 7 patients over 60 years of age were treated at our institute for cerebral gliosarcomas (Table 1). Their ages ranged from 61 to 81 years (mean, 74), and the Karnofsky Performance Scale (KPS) ranged from 40 to 90 (mean, 74). Histological diagnosis was made following the criteria of Meis *et al.*<sup>6</sup>: the tumor should be

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**Table 1 - Composition of the study group**

Case no.	Age/Sex	KPS	Location - size (cm)	Surgical resection	Histological prevalence	RT	CHT	Concomitant RT/CHT	Recurrence (wk)	Reoperation	Survival (wk)
1	65/M	90	F - 4.5	ST	G	Yes	Yes	Yes	Progression	No	67
2	74/M	80	T - 3.2	ST	G	Yes	Yes	Yes	Progression	No	66
3	61/F	80	T - 4	T	S	Yes	Yes	Yes	Yes (71)	Yes	83
4	80/F	80	P - 3.7	T	S	Yes	No	No	Yes (59)	No	62
5	77/M	90	F - 5.5	T	G	Yes	Yes	Yes	No	No	65
6	79/M	80	T - 3	T	S	Yes	No	No	Yes (52)	Yes	64
7	81/M	40	O - 5.5	ST	G	No	No	No	Progression	No	12

KPS, Karnofsky performance scale; RT, radiotherapy; CHT, chemotherapy; F, frontal; T, temporal; P, parietal; O, occipital; ST, subtotal; T, total; G, gliomatous; S, sarcomatous.

bimorphic, composed of an astrocytic malignant cell population with areas of necrosis and secondary concomitant sarcomatous spindle cells elements, and confluent in at least one medium power field.

Preoperative study was managed with magnetic resonance imaging (MRI). In all patients, early postoperative MRI was performed to establish the tumor resection degree: total removal was estimated when residual tumor was <10%.

Postoperative radiotherapy (60 Gy with LINAC extended 2 cm beyond the edema margins for 6 weeks) was administrated (alone or concomitant with chemotherapy) on the average at 20 days from surgery in all patients except one, who had poor clinical conditions (KPS <40) so that no adjuvant postoperative treatment was administered.

Chemotherapy was given to 4 patients: temozolomide, 75 mg/m<sup>2</sup>/d concomitantly to radiotherapy, subsequently 200 mg/m<sup>2</sup>/d for 5 days every 28 days until disease progression.

Three patients of our group did not receive chemotherapy: one had a very low KPS, and the other 2 had severe thrombocytopenia (45,000 and 50,000 per mm<sup>3</sup>). After discussion with relatives and the patients themselves about the risks of chemotherapy in such conditions, they refused the temozolomide administration.

## Results

The study group was composed by 5 males and 2 females (M/F ratio: 5/2), ranging in age from 61 to 81 years (median, 74). The preoperative KPS was 90 for 2 patients, 80 for 4 and 40 for 1. MRI showed non-homogeneous lesions (average size, 4.2 cm) with marked enhancement after gadolinium administration and perilesional edema; a broad-dural-based involvement was evident in 3 cases. Cerebral localization was frontal in 2 cases (29%), parietal in 1 (14%), temporal in 3 (43%) and occipital in 1 (14%).

The surgical procedure showed two types of lesions: one with well-demarcated margins and dural involve-

ment similar to an aspect of meningioma (in 3 cases), and the other, necrotic and infiltrating like glioblastoma (in 4 cases). Postoperative MRI demonstrated the amount of tumor resection, showing total removal for 4 and sub-total for 3 patients. Histological examination confirmed that the 3 lesions with a prevalence of sarcomatous components were those with radiological and intra-operative aspects resembling meningiomas (group S). The other 4 had more gliomatous aspects resembling glioblastomas at MRI and at surgery (group G).

Mean survival in group S was 69.7 weeks and in group G was 52.5 weeks (Table 1). However, survival differed also with respect to type of treatment: one patient (group G, case 7), because of poor clinical conditions, had no additional therapy after surgery and had the worst prognosis with only 12 weeks of survival. Two patients (group S, cases 4 and 6) were treated postoperatively with radiotherapy alone and had a mean survival of 63 ± 1 week. Four patients (group G, cases 1, 2 and 5; group S case 3) underwent concomitant radiotherapy and chemotherapy and showed the best results in terms of survival – mean 70.2 weeks.

The total median recurrence rate was 60.8 weeks: 60.7 in group S and 61 in group G. A second operation was performed in 2 cases of group S who had a total resection at the first surgery and in which a new total removal was possible at the second operation. One patient (case 5) was still alive at the follow-up 65 weeks after surgery, and in 3 patients progression was associated with a prevalent gliomatous aspect.

## Discussion

Gliosarcoma is a rare subtype of glioblastoma multiforme that shows a dimorphic population of glial and mesenchymal elements. First described by Stroebe in 1895<sup>7</sup>, it accounts for 1.8-8% of glioblastomas<sup>8,9</sup>, with an incidence of one new case per million inhabitants<sup>10</sup>. It occurs mostly between 40 and 60 years of age, and preferred sites of localization are temporal lobes, followed by parietal and frontal lobes<sup>8,11</sup>. It is very rare in younger people, whereas it is increasingly more often

diagnosed in the elderly, as are other malignant cerebral tumors<sup>4</sup>. More frequently than gliomas, gliosarcomas may metastasize to extracranial organs (lung, lymph nodes, pleura, bone marrow, liver)<sup>12</sup>, as shown by Maiuri *et al.*<sup>9</sup>, who recorded 15-30% of metastasis in their study group. Gliosarcomas, still in analogy with gliomas, may be radio-induced, as recently demonstrated<sup>13,14</sup>.

Histogenesis hypotheses affirm that gliosarcoma is a malignant transformation of cells in blood vessels of a pre-existing glioblastoma<sup>15</sup>, although recent genetic studies have shown a monoclonal origin of sarcomatous and gliomatous elements<sup>16,17</sup>. Indeed, sarcomatous cells appear to derive from glial cells during tumor progression, thereby sharing the same genetic aberration shown by Biernat *et al.*<sup>2</sup> for p53 mutation and by Reis *et al.*<sup>18</sup> for p16 deletion and PTEN mutation.

In our study group, we were able to identify two subgroups: some patient lesions showed features similar to those of meningiomas at MRI (marked diffused enhancement after gadolinium administration, well-defined peripheral margin), designated as group S, whereas others resembled high-grade gliomas (ring-shaped enhancement, necrotic areas, barely distinguishable margins), designated as group G. These radiological findings were matched with postsurgical histological findings: group S had a prevalence of sarcomatous elements in contrast to group G, in which a predominance of gliomatous cells was observed.

In the literature, the average survival is estimated to be less than one year<sup>8,17</sup>. As already shown in other studies<sup>9,19</sup>, we also found a better prognosis for lesions with a prevalent sarcomatous component and with radiological and surgical aspects of meningioma. All the patients with these features in our study group survived for more than a year and benefited from the multimodality treatment (case 3 obtained the best result and survived for 83 weeks). Indeed, not only a radical cytoreduction seems to be of critical importance for the prognosis of these patients, but also the possibility to perform postoperative radiotherapy and chemotherapy drastically influences the survival rate. In our series, patients of group S who were not treated with postoperative radio-chemotherapy had survival rates similar to those of group G who were received a multimodality treatment. These data suggest the importance of the adjuvant postoperative therapeutic route not only for patients of group G, but also for those of group S for whom, once a multimodal treatment is established, the best results in terms of survival can be reached (case 3).

We thus consider glioblastoma and gliosarcoma in the same way as regards the therapeutic choice: first surgery, supported by functional and spectroscopic MRI pre-operatively and intraoperative neuronavigation with functional mapping, for an as-radical-as-possible cytoreduction; early postoperative (within 24 h) MR in-

vestigation to evaluate residual tumor; 20-40 days later, radiation treatment with conformational techniques using LINAC for a total of 60 Gy, irradiating 2 cm over the borders of the lesion; chemotherapy with temozolomide concomitantly with radiotherapy.

For the latter step, there is some controversy in the literature. It is unknown whether gliosarcomas respond to sarcoma-based chemotherapy<sup>6,8,17</sup>, whereas the role of temozolomide is uncertain<sup>20</sup>. It is used because of the glial origin of these lesions, and only Morantz *et al.*<sup>21</sup> noted a modest increase in terms of survival using this therapeutic protocol compared with a control group treated only by radiation (36 *vs* 33 weeks of survival). In our series, we found positive results using chemotherapy not only for group G but also for group S, which suggests a therapeutic effect also in lesions with a prevalence of sarcomatous components. However, more data are necessary to establish the correlation between survival rates and temozolomide administration in these patients.

We found no difference in survival rate in our elderly group compared to younger study groups when a complete therapeutic strategy could be performed.

According to that observed by Mangiola *et al.*<sup>5</sup> for glioblastomas, we found that age itself was not a prognostic factor, whereas more important for outcome were clinical and neurological pre-operative conditions (KPS score). Indeed, as for younger patients affected by gliosarcomas, higher KPS allow multimodality treatment, and the possibility of postoperative radiotherapy and chemotherapy administration is the most valuable prognostic factor. When the KPS did not allow adjuvant treatment other than surgery, we observed the worst results (case 7), whereas when the KPS permitted multimodality treatment, especially for group S, we obtained the best results (case 3). Of course, in our series too radical a surgery (cytoreduction >90%) dramatically increased the median survival rate, which demonstrated it to be another primary prognostic factor.

## Conclusions

As for other younger patients, in the elderly it is also possible to identify two subtypes of gliosarcomas that correspond to two different prognostic groups of patients: lesions with a predominance of sarcomatous components are associated to a better prognosis, whereas the prognosis worsens when a predominance of gliomatous elements is identified. Moreover, the most important predictive factors are the entity of surgical removal of the neoplastic mass and the possibility to administer postoperative adjuvant therapy (radio- and concomitant chemotherapy). Age itself is not a prognostic factor when the KPS allows total surgical removal and multimodality treatment.

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