Clinical outcome of gliosarcoma compared with glioblastoma multiforme: North Central Cancer Treatment Group results

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Object. Gliosarcoma, a rare malignancy of the central nervous system, consists of gliomatous and sarcomatous elements. There are conflicting reports regarding its aggressiveness and cell line of origin compared with those of glioblastoma multiforme (GBM). The goal of this study was to compare clinicopathological features such as disease-free survival time and actual survival time in patients with gliosarcoma with a matched group of patients with GBM as well as with the entire group of patients with GBM.

Methods. The authors report on 18 cases of gliosarcoma derived from a series of 748 Grade 4 astrocytoma cases that were part of four consecutive randomized Phase III trials conducted between 1979 and 1996. In this series the gliosarcoma group represented only 2.4% of all GBMs and included 11 men and seven women with a median age of 61.5 years (range 31–81 years). The median tumor size was 5 cm (range 2–8 cm). The locations, all supratentorial, included temporal in 44%, parietal in 28%, frontal in 17%, and occipital in 11%. The 18 patients with gliosarcomas, all Grade 4 (World Health Organization classification), were compared with the entire group of 730 patients with GBM and a control group of 18 patients with GBM matched for known prognostic factors including patient age, randomization date, performance status, extent of resection, and protocol number. Patients in all treatment groups received radiation and nitrosourea-based chemotherapy.

The median time to progression and the median survival times for the patients with gliosarcoma were 28.0 and 35.1 weeks as compared with 24.7 and 41.6 weeks for the entire group of patients with GBM (log rank test, p = 0.94 and 0.27, respectively) and 16.7 and 34.4 weeks in the control group (p = 0.20 and 0.84, respectively). In previous molecular cytogenetic analyses of gliosarcoma these authors have shown similar genetic changes in the gliomatous and sarcomatous components.

Conclusions. The data obtained in this study support the conclusion that gliosarcoma shares significant clinical and genetic similarities with GBM and that the same principles should be applied for patient enrollment in research protocols and treatment for these two kinds of tumor.

Key Words • gliosarcoma • glioblastoma multiforme • brain neoplasm

Gliosarcomas are bimorphic neoplasms composed of malignant glial and sarcomatous elements. Although the glial component is, in most cases, a Grade 4 fibrillary astrocytoma, the sarcomatous element usually has histological features of fibrous or malignant fibrous histiocytoma and, less frequently, osteosarcoma, chondrosarcoma, or rhabdomyosarcoma. The histogenesis of the sarcomatous component has been a matter of controversy, with potential candidates including the capillary endothelium, vascular smooth muscle, astrocytic elements, and multipotent stem cells. The reported incidence of gliosarcoma varies between 2% and 8% of all malignant gliomas. Although some authors have found that the tendency of gliosarcoma to metastasize is much greater than that of glioblastoma multiforme (GBM) or other malignant brain tumors, others report no difference between gliosarcoma and GBM. The incidence of extraneural metastases is reported to be as high as 15% in some studies, with liver and lungs mainly involved.

We report on 18 cases of gliosarcoma derived from a series of 748 patients with Grade 4 glioma. The goal of...
FIG. 1. Photomicrographs showing histological sections of gliosarcoma. The basic features, illustrated by tissue obtained in one of the patients in the study, include variations in cytological composition, cell density, and stroma production in the two tumor elements on H & E staining (upper); the finding of collagen in the sarcomatous component but not in the glioma with reticulin staining (center); and staining for GFAP in the gliomatous element (lower). G = glioma. Original magnification X 100.

Clinical Material and Methods

Between 1979 and 1996, four consecutive randomized Phase III malignant glioma protocols were initiated by the North Central Cancer Treatment Group. Patient inclusion criteria included biopsy-proven malignant supratentorial high-grade glioma, randomization within 4 weeks of surgery, age older than 18 years, and adequate hematological, liver, and renal function. The inclusion criteria were universal for all patients with high-grade gliomas, therefore excluding any selection bias. A total of 748 patients with previously untreated Grade 4 astrocytoma were recruited from these four studies.

The disease diagnosis was confirmed in all patients by centralized pathological review performed by one of the authors (B.W.S.). Among the patients with Grade 4 astrocytoma, 18 cases of gliosarcoma were identified using the World Health Organization criteria.

To be classified as a gliosarcoma, a tumor was required to be bimorphic and to consist of two histologically distinct malignant cell populations. Of these one was astrocytic in nature, with endothelial proliferation and necrosis, thus fulfilling the World Health Organization criteria for a GBM; the other was mesenchymal. Reticulin staining and immunostaining for glial fibrillary acidic protein (GFAP) were performed to confirm the glial nature of the malignant spindle cells, particularly within and around blood vessels and in patients with leptomeningeal or dural invasion. In most cases the sarcomatous element consisted of a large confluent growth of spindle (fibroblastic) to more pleomorphic (fibrohistiocytic) cells that were distinctly different on hematoxylin and eosin staining from the various astrocytic cells comprising the GBM component, being reticulin rich and lacking GFAP staining. A minimum of one medium-power (X 100) field composed of sarcomatous cells was required to make an unequivocal diagnosis of gliosarcoma (Figs. 1 and 2 upper).

All patients in this study were treated with external-beam radiation and chemotherapy. The external-beam radiation was delivered by conventional fractionation up to a total dose of 6000 to 6500 cGy. Chemotherapeutic agents included nitrosoureas, that is, carmustine, 1-(2-chloroethyl)-3-(2,6-dioxo-3-piperidyl)-I-nitrosourea (PCNU), and dibromodulcitol. These agents were given every 5 to 7 weeks for periods varying from 6 months to 2 years in standard doses: 200 mg/m² for carmustine, 100 mg/m² for PCNU, and 200 mg/m² for dibromodulcitol. Anatomical sites and sizes of tumors were determined by computerized tomography scanning or magnetic resonance imaging. The location of recurrence and the presence of extraneural metastasis were determined by reviewing the patients’ charts. With few exceptions, information on age, gender, extent of resection, performance score, survival time, and disease-free survival time was available for all patients through the National Central Cancer Treatment Group database.

Statistical Analysis

The distributions of the aforementioned clinical variables between the group of 18 patients with gliosarcoma and the 730 with GBM were compared using chi-square and Wilcoxon rank tests. Both the survival and disease-free survival (time to progression) times were measured in this study was to describe clinicopathological features, including the propensity of the tumor to metastasize, actual survival time, and disease-free survival time in patients with gliosarcoma and to compare them with a matched control group of patients with GBM as well as with the entire group of patients with GBM.
Gliosarcoma compared with GBM

from the time of randomization. Survival curves were estimated using the Kaplan–Meier method. Log rank tests were used to compare the survival distributions of the 18 patients with gliosarcoma with those of all the GBM patients as well as with a control group of 18 patients with GBM who were matched for age, date of randomization, performance score, extent of surgery, and protocol number. Prognostic variables for survival in the entire group of 748 patients with Grade 4 astrocytomas were examined using classification and regression tree models

with the following baseline variables: age, gender, histological diagnosis of gliosarcoma, performance score, year of randomization, and protocol numbers.

### Results

The incidence of gliosarcoma among the entire group of 748 patients was 2.4%, similar to previous reports. Patient characteristics are described in Table 1. The sarcomatous elements were in large part fibrous or fibrohistiocytic in appearance, with osteosarcomatous and chondromatous components identified in one tumor each. Of all patients with disease recurrence, the recurrent tumors were found in the central nervous system and in the vicinity of the initial tumor in most patients. No clinically confirmed recurrences at the incision site or metastases in extraneural sites were observed; however, autopsy data were not available.

The 18 patients with gliosarcoma were compared with the 730 with GBM and with a control group of 18 patients with GBM who were matched for age, date of randomization, performance score, extent of resection, and protocol number. The control for the patient with gliosarcoma whose baseline performance score was coded as unknown (Table 2) was matched on the basis of the other four variables. The distribution of different prognostic variables

### TABLE 1
Clinical characteristics of the 18 patients in the gliosarcoma group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>tumor incidence (%)</td>
<td>18 of 748 GBM patients (2.4)</td>
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<tr>
<td>sex</td>
<td>male 11, female 7</td>
</tr>
<tr>
<td>median age (yrs)</td>
<td>61.5 (range 31–81)</td>
</tr>
<tr>
<td>median tumor size (cm)</td>
<td>5 (range 2–8)</td>
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<tr>
<td>location (%)</td>
<td>temporal 44, parietal 28, frontal 17, occipital 11</td>
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### TABLE 2
Comparison of prognostic variables between gliosarcoma, matched control group, and the entire GBM group

<table>
<thead>
<tr>
<th>Comparison Criteria</th>
<th>GS Group (18 patients)</th>
<th>Control GBM Group (18 patients)</th>
<th>Entire GBM Group (730 patients)</th>
<th>P Value†</th>
<th>No. %</th>
<th>P Value†</th>
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<tr>
<td>sex</td>
<td>male</td>
<td>11</td>
<td>13</td>
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<td>420</td>
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<tr>
<td>female</td>
<td>7</td>
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<tr>
<td>age (yrs)</td>
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<td></td>
<td>40–60</td>
<td>7</td>
<td>39</td>
<td>7</td>
<td>39</td>
<td>295</td>
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<tr>
<td></td>
<td>≥60</td>
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<td>56</td>
<td>10</td>
<td>56</td>
<td>373</td>
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<tr>
<td>baseline PS</td>
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<td>78</td>
<td>12</td>
<td>67</td>
<td>502</td>
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<td></td>
<td>2–3</td>
<td>3</td>
<td>17</td>
<td>6</td>
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<tr>
<td>extent of resection</td>
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<td>11</td>
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<td>168</td>
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<tr>
<td></td>
<td>subtotal</td>
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<td>56</td>
<td>13</td>
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<tr>
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<td>88–72–52</td>
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<td>14</td>
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<td>93–72–52</td>
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* GS ~ gliosarcoma; PS ~ performance score according to the criteria of the Eastern Cooperative Oncology Group.
† Calculations based on totals excluding those with missing values.
‡ Treatment group according to the North Central Cancer Treatment Group protocols.
§ One patient with GBM was enrolled in another protocol for which he or she was ineligible.
FIG. 3. Graphs showing Kaplan-Meier estimate of the time to progression (upper) and survival time (lower) in patients with gliosarcoma as compared with the entire GBM group.

between the groups is shown in Table 2. There was no statistically significant difference between the groups, except for the protocol distribution between gliosarcoma and the entire GBM group \( (p = 0.0293) \). However, given the fact that all four consecutive protocols yielded comparable results regarding survival and time to progression, this difference in distribution does not affect time to progression and survival.

At the time of this analysis, 17 patients with GBM and one with gliosarcoma were too recently treated to be evaluated for survival. The numbers of documented disease recurrences and deaths were, respectively, 11 and 16 in the 17 patients with gliosarcoma; 16 and 18 in the 18 matched GBM controls; and 598 and 669 in the 713 patients with GBM for whom follow-up data were available. The median time to progression and median survival for the patients with gliosarcoma were 28.0 and 35.1 weeks, respectively, as compared with 16.7 and 34.4 weeks in the matched control group \( (\log \text{rank test } p = 0.20 \text{ and } 0.84, \text{ respectively; } \text{Fig. 2}) \) and 24.7 and 41.6 weeks in the entire GBM group \( (p = 0.94 \text{ and } 0.27, \text{ respectively; } \text{Fig. 3}) \). As the probability values indicate, the differences are not statistically significant. Multivariate analysis in which the classification and regression tree model was used in all 748 patients with Grade 4 astrocytomas for whom follow-up survival data were available also showed that the pathological diagnosis of gliosarcoma was not of additional prognostic importance.

Discussion

Our study demonstrates that gliosarcoma behaves similarly to GBM. When similar treatments are administered (combined radiation therapy and chemotherapy), there is no significant difference in time to progression and overall survival time between patients with GBM and gliosarcoma. In our series, the median time to progression was 6 months for patients with GBM and 7 months for patients with gliosarcoma, whereas the median survival time was 10 months for patients with GBM and 9 months for those with gliosarcoma. Neither difference is statistically significant. Our results are consistent with the reported survival times of patients with GBM when combined modality treatment is used.

In addition, our results indirectly support laboratory observations that have led to the suggestion that the gliomatous and sarcomatous elements of gliosarcoma have a common origin. Loss or mutation of chromosome 17p, where the \( p53 \) gene is located, occurs in low-grade astrocytomas, anaplastic astrocytomas, and GBMs, indicating that such a loss is an early event in the evolution of the glial malignancy. Using single-strand conformation analysis, Biernat, et al., showed that gliosarcomas containing a \( p53 \) alteration had the identical mutation (exon 5, codons 151 and 173) in both the gliomatous and sarcomatous components.

Using comparative genomic hybridization along with cytogenetic analysis, fluorescence in situ hybridization (FISH) analysis, polymerase chain reaction, and analysis of microsatellite allelic imbalance, Boerman, et al., showed that the sarcomatous and gliomatous portions of all five gliosarcomas that they investigated were similar regarding the presence and absence of specific genetic alterations: trisomy 7, monosomy 10, and deletion of 9p were the most frequent alterations. Three patients from our series were included in that study. Cytogenetic analysis in these three patients showed similar genetic changes in the sarcomatous and gliomatous elements as had been previously described. Figure 4 demonstrates the results of FISH analysis in which centromere probes for chromosomes 7 and 10 were used in one of the patients in our study. Both the gliomatous and the sarcomatous component (isolated by microdissection) exhibited trisomy 7 and monosomy 10. Similarly, by using interphase cytogenetics, Paulus, et al., showed that both the glioma and the sarcoma portion in two of the three gliosarcomas studied showed the same genetic alterations (monosomy 10 and monosomy 17). These genetic observations support the hypothesis that the gliomatous and sarcomatous elements of gliosarcomas share a common precursor cell.

Conclusions

Patients with gliosarcoma and GBM treated in a similar fashion have essentially identical outcomes. The bimorphic appearance of the cells most likely results from epigenetic phenomena that are currently incompletely understood. Because the term gliosarcoma best describes a morphological entity (gliosarcoma multiforme variant), it should be used as such. In clinical trials, patients with gliosarcoma should be treated identically to those with GBM.
Gliosarcoma compared with GBM

FIG. 4. A FISH analysis was performed using centromere probes (CEP) for chromosomes 7 and 10, after microdissection of the gliomatous and sarcomatous elements of tumor tissue obtained in one of the patients in our study. Orange dots represent the chromosome centrosomes in the cell nucleus. When the chromosome 7 centromere probe was used, most cells in both the sarcomatous and gliomatous elements were found to have three copies of chromosome 7 (trisomy 7). In contrast, when a centromere probe for chromosome 10 was used, most cells in both the sarcomatous and gliomatous elements were seen to have one copy of chromosome 10 (monosomy 10).

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References


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