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CLINICAL STUDY - PATIENT STUDY

Clinical and epidemiological characteristics of pediatric gliosarcomas

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Abstract Gliosarcoma (GS) is a glioblastoma with a sarcomatous component that is presumed to be a metaplastic differentiation of glioma cells. We studied the clinical relevance of this histological glioblastoma subentity within the pediatric population. We obtained patient data from the German HIT-GBM database, which contains clinical data for more than 600 pediatric patients with centrally reviewed high-grade gliomas. By applying defined inclusion criteria (diagnosis of GS proven by central neuropathological review; patient age 0 to 21 years), four patients were identified. In addition, after a review of the English medical scientific literature, 19 additional cases were found. The relative frequency of GS in the German HIT-GBM database was only 1.9%. In the whole series of 23 pediatric GS patients, including previously reported cases, the male-to-female-ratio was 1.2:1. GS was found in all pediatric age groups with a median age of 11 years, but there was an unexpectedly high accumulation in infants (6 of 23 <3 years of age, 26%). GS showed a strong predilection of the cerebral hemispheres (22 out of 23 cases). Increased intracranial pressure was the leading symptom of a short clinical history with a median duration of 0.7 month. Interestingly, six patients (26%) were reported with a history of cranial radiotherapy prior to GS diagnosis. In 60% of the GS patients in our series, gross total resection was achieved. Median overall (OS) and event-free survivals (EFS) of the total cohort were 12.1 and 9.8 months, respectively. In conclusion, GS is a very rare tumor entity in children. Literature review suggests a relatively higher incidence in infants and in patients with a previous history of radiotherapy.

Keywords Gliosarcoma · Glioblastoma multiforme · Children · Infants · Case report · HIT-GBM trial · Clinical course · Review

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Introduction

Gliosarcoma (GS; ICD-O code 9442/3) is a rare brain tumor characterized by histomorphologic heterogeneity, with alternating areas of glial and mesenchymal differentiation (Fig. 1) [1]. According to the most recent World Health Organization (WHO) classification of central nervous system tumors [2], GS is regarded as a distinct variant of glioblastoma multiforme (GBM). The mesenchymal component in GSs appears to harbor cytogenetic and molecular abnormalities similar to those found in GSs' glial component. GSs are genetically similar to primary GBMs in that 20–40% of both tumor entities harbor *TP53* mutations, *PTEN* deletions, and *CDKN2A* deletions. The exception to this genetic similarity is the relative infrequency of *EGFR* amplification in GSs [3–5]. GSs represent less than 5% of all glioblastomas and are similar to GBM in having a slight male predominance and affecting patients in all age groups, with an increasing incidence in the elderly [6]. In most cases, GSs are located supratentorially, with a predilection for the temporal lobe, followed by the frontal, parietal, and occipital lobes [1, 7]. As in GBM, the prognosis in GS is poor [1, 6, 8].

Very few reports on pediatric GS are available in the literature. To the best of our knowledge, only 19 pediatric cases of GS with individual data have been published in the English literature to date [9–24]. In the current report, we retrospectively reviewed the data for four pediatric patients with GS who had been enrolled in the HIT-GBM trials in Germany, Austria, and Switzerland since 1994 and summarized data for the 19 cases from the published literature. The 23 pediatric GS cases reviewed herein represent the largest series of this rare tumor in children to date.

Patients and methods

Patient characteristics and inclusion criteria

We searched the HIT-GBM database of the Society of Pediatric Oncology and Hematology in Germany, Austria, and Switzerland (Gesellschaft fuer Paediatrische Onkologie und Haematologie; GPOH) to identify pediatric cases of GS. In accordance with the Declaration of Helsinki, all patients whose information is in this database and/or their parents had given informed consent for statistical analyses and data storage at the time of enrollment in the various HIT-GBM trials. Inclusion criteria for this retrospective review were: (1) a histopathologic diagnosis of GS confirmed by central neuropathologic review (performed by pathologists in the German Brain Tumor Reference Center, Department of Neuropathology, Bonn, Germany) and (2) a patient age of 0–21 years at the time of initial diagnosis.

Statistical analysis

The identified cases from the HIT-GBM database and from the literature were all used for the statistical analysis. Statistical analysis was performed using the statistical package for social studies (SPSS® Inc, Chicago, IL). Overall survival (OS) and event-free survival (EFS) were determined by Kaplan–Meier analysis and log-rank testing.

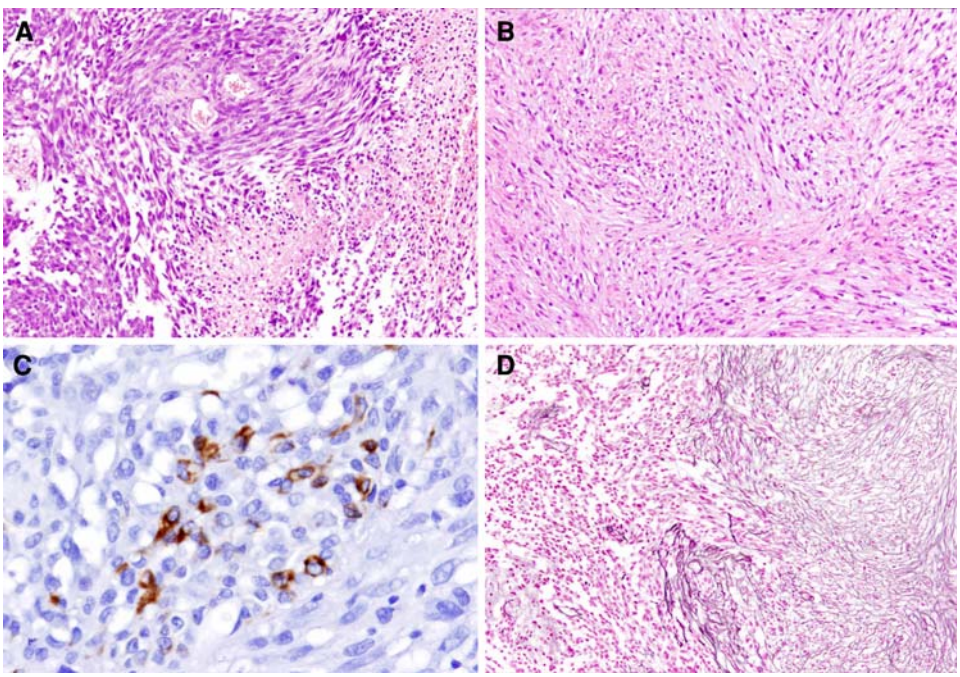

Fig. 1 Histology of patient no. 2. **a** Astroglial component with increased mitotic activity and necrosis, hematoxylin and eosin staining; **b** sarcomatous component with spindle cells, hematoxylin, and eosin staining; **c** expression of glial fibrillary acidic protein (GFAP) in subpopulations of the astroglial tumor component, immunohistochemistry; **d** reticulin fibers are restricted to vessels in the astroglial component (*left*), but very dense in the sarcomatous component (*right*), silver staining. By immunohistochemistry, no nuclear accumulation of p53 was demonstrated

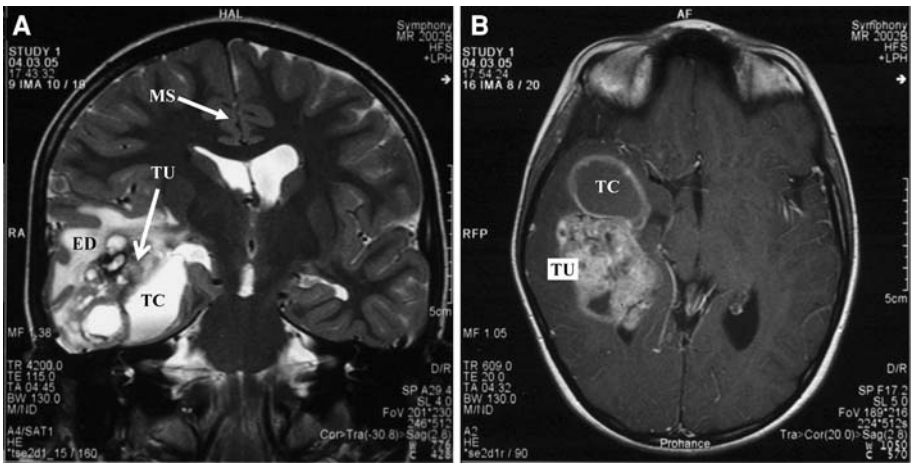

Fig. 2 Brain MRI of patient no. 2 at first presentation. T2 coronal (**a**) and T1 axial sections (**b**, with contrast) show a contrast-enhancing solid tumor (TU) with a cystic component (TC) and an extensive peritumoral edema (ED). Both tumor and edema cause a marked midline shift (MS) as a correlate of significantly increased intracranial pressure

An event was defined as tumor relapse or progression, occurrence of a secondary malignancy, or death from any cause. Patients were grouped according to these parameters: sex (male/female), age (<3 years/≥3 years), preceding radiotherapy of the brain (yes/no), and extent of tumor resection (gross total tumor resection defined as 100% macroscopic removal of tumor mass versus non-total tumor resection). We compared these parameters for prognostic relevance to EFS and OS. For all statistical analyses, significance was set at $P < 0.05$.

Case reports and summaries

Our search of the HIT-GBM database identified four GS patients who met our criteria and whose data we retrospectively reviewed. The literature search identified 19 GS cases whose data we summarized.

Patient no. 1

In June 2000, the 8-year-old girl was admitted to hospital with generalized seizures and a 2-month history of headache. The MRI showed a brain tumor localized in the right temporal lobe, and the patient underwent a craniotomy with partial resection of the tumor. The histological diagnosis of GS was based on the heterogeneous picture with components of pleomorphic glial cells and a high amount of collagen fibers besides a pleomorphic component with reticulin fibers and leukocyte infiltration. Both histological components expressed p53 and MIB-1 (5–10%) and less intense S100 and GFAP. Since a pleomorphic xanthoastrocytoma was taken into consideration as the underlying diagnosis, no adjuvant therapy was given until the tumor showed further progression 2 months later. At this time gross total resection was achieved. The patient received combined radiochemotherapy according to the HIT-GBM C protocol [25], but the tumor was again progressive 5 months after initial diagnosis with intracranial and spinal cord metastases. Chemotherapy was modified to carboplatin/etoposide. After one cycle the patient died from pneumonia.

Patient no. 2

The 10-year-old boy was admitted to hospital in March 2005 with generalized seizures and a 4-month history of headache and vomiting. Cranial MRI showed a polycystic tumor (6 × 8 × 6 cm) in the right temporal lobe with contrast enhancement of the solid areas (Fig. 2). The patient underwent a craniotomy with gross total tumor resection. On histology a biphasic histopathological pattern with a sarcomatous as well as a glial component led to the diagnosis of GS. Both tumor parts showed an increased proliferation (MIB-1 index 5%) and no nuclear accumulation of p53. The patient received a combined radiochemotherapy according to the HIT-GBM D protocol beginning with pre-irradiation high-dose methotrexate and continuing with simultaneous radiochemotherapy and consolidation chemotherapy until March 2006 [26]. Due to side effects, some chemotherapy cycles had to be modified. In April 2006, the patient reported paresthesia of the lower limbs, and a spinal MRI showed multiple metastases in the spinal canal. In the following month two different chemotherapy regimens were applied. Initially, chemotherapy with carboplatin/etoposide led to a temporary reduction of pain medication, but chemotherapy was accompanied by a neutropenic fever episode as well as the need for platelet transfusions. Since overall mobility was not improved, and weight loss continued, patient and parents asked for cessation of this chemotherapy and temozolomide was started but was accompanied by distinct nausea, increasing insomnia and marked thrombopenia. After acceptance of the palliative situation by the patient and parents, the

decision was made to continue with pure palliative symptom control without further chemotherapy. The patient died at home 18 months after the initial diagnosis.

Patient no. 3

In April 2005 the 6-year-old boy was admitted to the hospital since he had become unconscious after a head trauma. His mother reported on vomiting for 4 months. The CT showed a large hemorrhage in the right frontal lobe leading to a herniation of the brain stem. Thus, an immediate decompressive craniotomy was performed in which a tumor of the right frontal lobe (6 × 5 × 4 cm) was found and partially resected. The histopathologic diagnosis of GS was based on the biphasic pattern with glial tumor cells showing numerous atypical mitoses and a sarcomatous component. Ki67 staining (MIB-1 index) demonstrated up to 30% positive tumor cells. The patient received combined radiochemotherapy according to the HIT-GBM D protocol with pre-irradiation high-dose methotrexate [26]. Nevertheless, a further local progression and leptomeningeal spread to the spinal cord was found. Since his general condition worsened rapidly, chemotherapy was discontinued, and the patient was discharged for home palliative care.

Patient no. 4

The 9-year-old boy was admitted to the hospital in February 2007 with vomiting, diplopia and vertigo following a suspected head trauma. The cranial MRI showed a tumor of the diencephalon and the right cerebral peduncle. A craniotomy was performed, but the tumor could only be resected partially. On histology a biphasic pattern with sarcomatous and glial components was found, and the diagnosis of GS was made. On immunohistochemistry 30% of the tumor cells overexpressed p53-protein, and up to 10% expressed MIB-1. The patient was enrolled in the HIT-GBM D trial [26] and was treated with simultaneous radiochemotherapy followed by consolidation chemotherapy. After 8 months, the patient showed tumor progression. Temozolomide chemotherapy was started. After 12 months, the patient was admitted to the hospital because clinical deterioration due to tumor progression with extension into both thalamic regions. At the last reported follow-up 14 months after the initial diagnosis, the patient had been discharged home in a still significantly reduced condition. To the best of our knowledge, this is the first pediatric patient with a GS located in the mesencephalon published to date.

A further gliosarcoma patient was identified in the HIT-GBM database in whom the diagnosis was made by both the local neuropathologist and the central review by the German Brain Tumor Reference Center. During the work on this paper, the tumor was reevaluated by an international board of pediatric neuropathologists, and the diagnosis was revised to desmoplastic infantile astrocytoma with pronounced anaplastic features. Although we excluded this patient from the following analysis, we are still reporting this case, since it demonstrates the difficulty of the histological classification of rare pediatric brain tumors and the need for a central review with wide experience.

In this patient, in December 2003, routine cerebral ultrasound scan screening showed a large polycystic structure in the right temporo-parietal lobe of the newborn. During the following weeks the lesion grew rapidly, causing hydrocephalus. A craniotomy and partial resection of the tumor were performed. On histology a biphasic tissue pattern with mainly sarcomatous components but also small glial parts with necrosis were seen. GFAP staining was positive within the glial parts, and the MIB-1 index was as high as 20% in both components. After the diagnosis of GS, the patient was treated according to the HIT SKK protocol [27] with intensive multiagent chemotherapy. After 5 months of chemotherapy, the residual tumor presented with a sharp demarcation on MRI; therefore, a second craniotomy was performed resulting in gross total tumor resection. At the last reported follow-up 25 months after the initial diagnosis, the patient was in good clinical condition with no signs of tumor progression.

Patients nos. 5 to 23

In addition, we identified 19 cases of pediatric GS previously reported in the English literature [9–24]. These cases are summarized in Table 1.

Results

The 23 cases comprised 12 males and 10 females; gender was not reported in one case. The median patient age was 11 years (range 0–21) (Table 1). Figure 3 presents a comparison of age distribution for GS and GBM cases. There was a peak accumulation of GS cases in infants: 6 (26%) of the 23 patients were under 3 years of age at diagnosis (Fig. 3).

Duration of clinical history was short with a median of 0.7 month (range 0–4.0 months). Signs of raised intracranial pressure were the leading initial symptoms with vomiting and/or headache (14/21 cases, 67%) and macrocephaly (mainly infants, 5/21 cases, 24%). Other less frequent symptoms were psychomotoric slowing and/or reduced consciousness in five patients (24%), hemiparesis in four patients (19%) and seizures in three patients (14%).

Secondary gliosarcomas were found in five patients after a previous history of cranial radiotherapy for the following

Table 1 Summary by case of 23 pediatric patients with gliosarcoma from the German HIT-GBM trial database (nos. 1 to 4) and from the published literature (nos. 5 to 23)

Case no.	Pt. age (years)	Sex (M/F)	Duration of history	Initial symptoms	Tumor localization	Cranial pre-irradiation	Resection	Radiotherapy status or dose (gray)	Event	Survival duration or status (months)	Comment	Source
1	8	F	2 months	Headache, seizure	Right temporal lobe	No	Total	59.4	Progression (5 months)	6		Current report, Karremann
2	10	M	4 months	Headache, seizure	Right temporal lobe and lateral ventricle	No	Total	59.4	Progression (9 months)	18		Current report, Karremann
3	6	M	4 months	Loss of conciousness, vomiting	Right fronto-parietal lobe, corpus callosum	No	Partial	59.4	Progression (1 month)	4		Current report, Karremann
4	9	M		Macrocephaly	Right mesencephalon	No	Partial	54	Progression (8 months)	Alive (14)		Current report, Karremann
5	15	F	10 days	Vomiting, headache, nausea, loss of consciousness (10 min), papilledema	Right temporal lobe	No	Total	No	Relapse (4 months)	5		Salvati [9]
6	13	F	A few days	Headache, psychomotor slowing	Midline-tumor: parieto-occipital lobes reaching the corpus callosum	No	Subtotal	64	No	Alive (9)		Salvati [9]
7	16	M	2 months	Paresthesia-like episodes in right limb, mild hemiparesis	Parasagittal frontal tumor	Yes	Total	64	No	Alive (24)	Haemangioma 10 years before (radiation 25 gy)	Salvati [9]
8	0	F	0	Macrocephay, seizure	Left temporo-parietal lobes and basal ganglia	No	Total	30	No	Alive (34)		Ono [11]
9	0	M			Right temporal lobe	No				Alive (21)		Radkowski [10]
10	21	F		Headache, vomiting, giddiness, slurred speech, papilledema	Left frontal lobe	Yes	Total	30	Progression (6 months)	Alive (6)	Medulloblastoma 8 years before (radiation)	Malde [13]
11	13	M		Headache, vomiting, neck stiffness, left hemiparesis	Right temporo-parieto-occipital lobes	Yes	Total	32	Relapse (6 months)	13	ALL 12 years before (radiation 24 gy)	Kaschten [14]
12	2	M		Headache, vomiting	Left frontal lobe	No	Total		Relapse (1 month)	3		Okami [12]
13	0		2 months	Macrocephaly, hypotonia	Left temporo-parieto-occipital lobes	No	Total	No	Perioperative death	0		Rizk [16]
14	11	F	2 months	Headache, vomitting	Left posterior temporo-parietal area	No	Total	Yes	Thoracic metastasis (2 weeks)	1		Cerame [15]

Table 1 continued

Case no.	Pt. age (years)	Sex (M/F)	Duration of history	Initial symptoms	Tumor localization	Cranial pre-irradiation	Resection	Radiotherapy status or dose (gray)	Event	Survival duration or status (months)	Comment	Source
15	18	M		Comatose condition	Right frontal lobe	Yes	Decompression		No	Alive (1)	Giant-cell glioblastoma (2. relapse, radiation)	Deb [19]
16	18	M		Left side weakness, headache	Right frontal lobe	Yes	Partial	No		5	Astrocytoma II 10 years before (radiation 50 gy)	Lach [17]
17	12	M	1 week	Nausea, vomiting, headache	Right frontal lobe	No	Total	60	No	Alive (16)	Hodgkin disease 7 years before	Lee [18]
18	17	F		Progressive withdrawal, speech problems	Both frontal lobes, corpus callosum	No	Partial	No	Progression and death 10 days after surgery	0.3		Lee [18]
19	11	M	5 days	Headache, vomiting, nausea, papilledema	Right fronto-parietal lobes	No	Total	60	No	Alive (25)	Hodgkin disease 6 years before	Takaue [20]
20	0	F	0	Macrocephaly, lethargy	All over the left hemisphere	No						Goldstein [22]
21	2	M	1 month	Vomiting, dramatic increase in head size	Most of the right hemicerebrum	No	Partial	No			Heptachlor ingestion by the mother during pregnancy	Chadduck [21]
22	18	F	4 months	Headaches and visual abnormalities	Occipital lobe	No	Subtotal	56	Wide spread along the meningeal routes	12	Transformation in a sarcoma	McKeever [24]
23	19	F			Left parieto-occipital lobe	Yes		No		7	Ependymoma 29 months before (radiaton 54 gy)	Kepes [23]

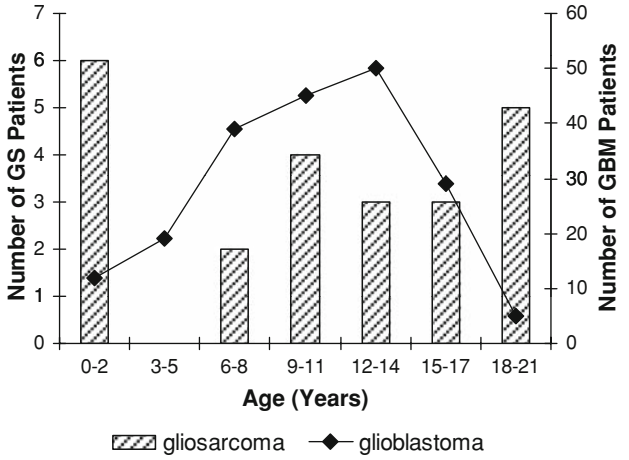

Fig. 3 Comparison of age distribution for gliosarcoma (GS) and glioblastoma multiforme (GBM) cases. Most of the patients with GBM were adolescents (*black line*, data from the HIT-GBM database). In contrast, the age distribution of GS patients showed two peaks: in addition to a peak in the teenage years, an additional peak was noted in infants. Of the 23 patients reviewed in our series, 6 were under 3 years of age

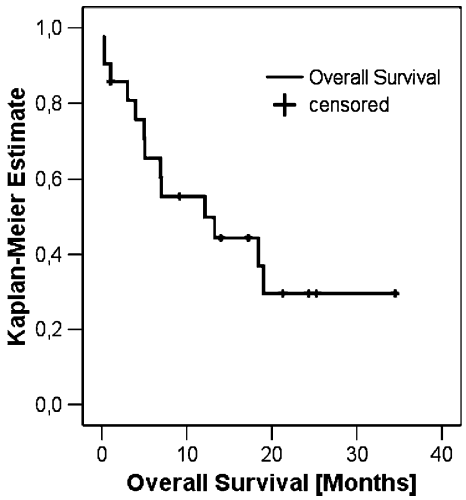

Fig. 4 Overall survival in 23 pediatric patients with gliosarcoma

malignancies: low grade glioma, medulloblastoma, acute lymphoblastic leukemia, meningioma and giant cell glioblastoma (Table 1). In addition, one patient had received radiotherapy of the scalp due to an angioma. Thus, in total, 26% (6 out of 23) of all pediatric GS patients had received irradiation of the brain between 29 months and 12 years before GS diagnosis. However, none of the four patients from the HIT-GBM data base developed a GS after previous cranial radiotherapy.

With one exception (patient no. 4), GS was strictly localized in the cerebral hemispheres (96%, 22 out of 23 cases; Table 1) with a predilection of the frontal lobes (11 cases, 48%) followed by both the parietal and temporal lobes (10 cases each, 43%). The occipital lobe was affected in seven cases (30%). The exception was our case no. 4, with the primary tumor in the mesencephalon. GS in other regions of the CNS were only found in case of metastasis (Tables 1 and 2).

Gross total tumor resection was achieved in 60% of GS patients (12 out of 20 cases, extent of surgery was not reported in 3 cases).

The median OS was 12.1 months and median EFS 9.8 months. One-year OS was 55 ± 11%, and 2-year OS was 30 ± 11% (Fig. 4). One-year EFS was 44 ± 11%, and the 2-year EFS was 30 ± 11% (Table 2). We compared different groups in Kaplan–Meier survival analyses. Patients who underwent gross total tumor resection had a survival of 13.3 months versus 12.1 months if gross total tumor resection was not achieved, but the difference was not significant. The apparent inhomogeneous age distribution did not translate into significant differences in survival, although survival was superior in the four patients under 3 years of age at diagnosis versus older patients: Here, 2-year OS was 50 ± 25% versus 21 ± 12%, and 2-year EFS was 50 ± 25% versus 22 ± 13% in older patients. Gender did not have an impact on survival. Patients who developed a secondary GS after previous radiotherapy did not show an inferior outcome when this analysis was restricted to patients older than 3 years of age. Median OS and EFS of this group were 13.3 and 7.0 months versus 12.1 and 9.8 months for non-infant patients without previous radiation (not significant).

Discussion

In 23 pediatric patients with gliosarcoma, we found an inhomogeneous bipolar age distribution with one peak in the first year of age and a second broader peak in teenage patients. The frequency of previous radiotherapy among GS patients from the literature was high, although similar results were not found in the pediatric GS patients from the HIT-GBM database. Survival was as poor as generally reported for GBM.

The relative incidence in our HIT-GBM database was 1.9% GS among pediatric glioblastomas (4 out of 206 cases), which is less than in adult patients where GS accounts for up to 5% of glioblastomas [1, 4, 6]. The gender distribution [1, 6, 8] and the tumor location appear to be comparable between adult and pediatric patients [8, 28]. Most tumors were supratentorially found with a strong predominance of the temporal lobe in most adult series, while in our cohort the frontal lobe was most frequently affected. Signs of increased intracranial pressure

Table 2 Data summary and distribution for 23 gliosarcoma cases in pediatric patients

Data category	Value	
Male-to-female ratio	1.2:1	
Median age (range), in years	11	(0–21)
Median clinical history (range), in months	0.7	(0–4.0)
Median follow-up (range), in months	6.0	(0–34)
Patient history of previous radiotherapy		
Yes	6	(26%)
No	17	(74%)
Tumor locations[a]		
Frontal lobe	11	(48%)
Parietal lobe	10	(43%)
Temporal lobe	10	(43%)
Occipital lobe	7	(30%)
Mesencephalon	1	(4%)
Extent of resection		
Total	12	(60%)
Non-total	8	(40%)
Unknown	3	
Radiotherapy administered		
Yes	13	(68%)
No	6	(32%)
Unknown	4	
Event-free survival[b] (in months)		
Median	9.8	
1-year	44	±11%
2-years	30	±11%
Overall survival[b] (in months)		
Median	12.1	
1-year	55	±11%
2-years	30	±11%

[a] Eleven patients had multiple lobes involved

[b] Kaplan–Meier estimates

(vomiting, headache and macrocephaly) were the leading symptoms of GS in pediatric patients. Psychomotoric slowing and/or reduced consciousness, hemiparesis and seizures represented other less frequent initial symptoms. These findings are in good concordance with a previously published series of 29 mainly adult patients presenting with weakness (50%), headache (40%) and seizures (10%) [7]. Probably due to the superficial localization, gross total tumor resection was feasible in as many as 60% (12 out of 20 patients; in 3 missing data), but in contrast to a previously published series of adult gliosarcoma patients [6] the survival benefit from gross total resection did not reach significance (data not shown) [29–31].

With all these characteristics so similar between the pediatric and the adult GS population, and between the pediatric GS and pediatric GBM population, the two-peak age distribution is even more surprising. Holt described the first case of an infant with GS in 1917 [32], but since then relatively little has become known about this peculiar entity. Four of the patients in our series were young infants (1–4 months of age at diagnosis), and the oldest of them showed an increased head circumference at birth [22]. These patients may represent congenital GS. The survival of the young patients in our series was surprisingly good, in particular when considering that radiation cannot play the same predominant role in this population as in older patients. This is in keeping with the experience of other reports [33–36], and it supports the hypothesis that infant GS might represent a disease quite distinct from typical GBM. The prognosis of those patients is good, and the tumors should be resected whenever possible.

A second peculiar group of patients was identified in the literature review: six of the pediatric patients developed a secondary GS after previous radiotherapy for another disease: medulloblastoma, giant cell glioblastoma, low grade glioma, meningioma, acute lymphatic leukemia and angioma. This parallels the experience in adult patients reported by others: Perry and coworkers reported on 32 patients with GS, out of whom 7 had previous irradiation for glioblastoma multiforme [37]. However, in Perry's study a counterintuitive better survival was found in those patients with secondary GS, which was not true in our patients: There was no significant difference in OS and EFS in GS with or without previous cranial radiotherapy.

In conclusion, the present study encompassed the largest cohort of pediatric patients with GS to date. It shows that GS represented a rare tumor entity in children with a relative incidence of 1.9% among all GBM, and hence, epidemiologic and prognostic analysis is only feasible by including previously published cases from the literature. Therefore, interpretation of data is limited to its retrospective character. Even this rare group could be separated into three distinct populations. The tumor is relatively frequent in infants and very young children, and has a particularly good prognosis in this group even when treated only with resection and chemotherapy without radiation, so efforts should be undertaken to completely resect these tumors. A second population of patients developed GS as secondary malignancy after cranial radiotherapy. These patients were older, but in contrast to adults, the survival was as poor as in the third population who developed GS de novo. These patients shared the particularly poor prognosis with adult GS patients or other GBM patients. In the future, molecular pathological analyses might corroborate our observations and further elucidate the biology of this rare tumor entity in children.

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