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ORIGINAL COMMUNICATION

Natural history and management of brainstem gliomas in adults

A retrospective Italian study

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Abstract Brainstem gliomas in adults are rare tumors, with heterogeneous clinical course; only a few studies in the MRI era describe the features in consistent groups of patients. In this retrospective study, we report clinical features at onset, imaging characteristics and subsequent course in a group of 34 adult patients with either histologically proven or clinico-radiologically diagnosed brainstem gliomas followed at two centers in Northern Italy. Of the patients 18 were male, 14 female, with a median age of 31. In 21 of the patients histology was obtained and in 20 it was informative (2 pilocytic astrocytoma, 9 low-grade astrocytoma, 8 anaplastic astrocytoma and 1 glioblastoma). Contrast enhancement at MRI was present in 14 patients. In all of the 9 patients who were investigated with MR spectroscopy, the Cho/NAA ratio was elevated at diagnosis. In 8 of the patients, an initial watch and wait policy was adopted, while 24 were treated shortly after diagnosis with either radiotherapy alone [4] or radiotherapy and chemotherapy [20] (mostly temozolomide). Only minor radiological responses were observed after treatments; in a significant proportion of patients (9 out of 15) clinical improvement during therapy occurred in the context of radiologically (MRI) stable disease. Grade III or IV myelotoxicity was observed in 6 patients.

After a follow-up ranging from 9 to 180 months, all but 2 patients have progressed and 14 have died (12 for disease progression, 2 for pulmonary embolism). Median overall survival time was of 59 months. Investigation of putative prognostically relevant parameters showed that a short time between disease onset and diagnosis was related to a shorter survival. Compared with literature data, our study confirms the clinical and radiological heterogeneity of adult brainstem gliomas and underscores the need for multicenter trials in order to assess the efficacy of treatments in these tumors.

Key words brainstem glioma · adults · history · management

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Introduction

Brainstem gliomas (BSG) in adults are rare tumors, as they account for about 1.5 % of the total number of brain tumors [1]. A recent paper by Guillamo et al. [2] has underscored the heterogeneity in clinical course of adult BSG (defined by clinico-radiological and/or histological criteria) with median survival ranging from 7 years in diffuse intrinsic tumors to 1 year in malignant ones, being focal tectal gliomas a subgroup with a good prognosis.

The same study [2] also identified several prognostic factors, such as age < 40 at onset, duration of symptoms before diagnosis longer than 3 months, KPS ≥ 70, low-grade histology, absence of contrast enhancement and "necrosis" on MRI.

As for the therapeutic strategy, high-grade or "aggressive" (on MRI) tumors are commonly treated by radiotherapy, whereas low grade tumors, when unresectable and slowly progressive, are managed either with early radiotherapy or initial observation with MRI, deferring radiotherapy to true clinical and/or radiological progression [3]. The role of chemotherapy is not established, being generally employed at relapse after radiotherapy.

In this paper we retrospectively reviewed and analyzed the natural history, treatment and prognostic factors of a series of 34 adult patients with brainstem glioma, diagnosed and treated at 2 major Centers in Northern Italy.

Patients and methods

The clinical records of 34 patients with clinico-radiological features suggestive for brainstem glioma and treated at the Neuro-oncology and Radiotherapy Units of the Istituto Nazionale Neurologico Besta, Milan and at the Division of Neuro-oncology of the University/S. Giovanni Battista Hospital, Turin, from 1991 to 2003, were reviewed. Two patients were excluded from the study because they were lost to follow-up after the diagnosis.

Clinical data

Among the 32 evaluable patients, 18 were males and 14 females, with an age ranging from 14 to 78 years (median 31). Twenty-one of the 32 patients had an histological diagnosis, obtained in 11 by stereotactic biopsy and in 10 by partial resection. Histological diagnosis was as follows: pilocytic astrocytoma [2], low grade astrocytoma [9], anaplastic astrocytoma [8], glioblastoma [1], unrevealing material [1].

Symptoms at onset included: diplopia in 13 patients, ataxia in 9, hemiparesis in 9, facial paresis in 4, headache in 4, nystagmus in 3, vertigo in 3, facial spasm in 3, hypoacusia in 2, hiccup speech in 2, sensory deficit in 2, dysarthria in 2, bulimia in 1, dysphagia in 1.

All patients underwent a brain and spinal MRI at diagnosis. At that time, in 6 patients the tumor was limited to one of the three levels of the brainstem, being in 4 the midbrain, in 1 the pons and in 1 the medulla. In the remaining 26 patients the tumor had already involved more than one level of the brainstem in 7, the spinal cervical cord in 9, the cerebellum in 6 and the thalamus/basal ganglia in 4. Hyperintensity in T2-weighted and Flair images was seen in all patients.

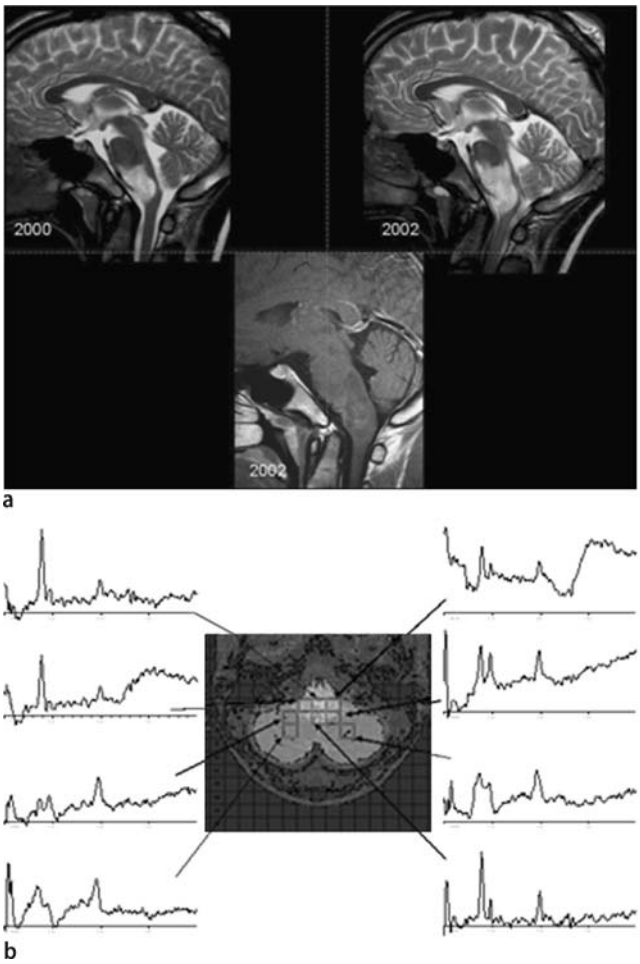

Fig. 1 **a** Top: sagittal T2-weighted images at diagnosis (2000) and 2-year follow-up in a 22-year old male patient with clinical progression. Bottom: post-contrast T1-weighted sagittal section at follow-up (2002), showing tenuous diffuse contrast enhancement. **b** Spectro-MRI showing an increase in the choline peak in 3 out of 8 investigated voxels of interest (VOI)

Contrast enhancement was present in 14 patients, being slight and diffuse in 5, and absent in 18 (Fig. 1). Detailed MRI features at diagnosis are reported in Table 1.

MR spectroscopy was performed in 11 patients before radiotherapy (Fig. 1). Single voxel H-MR spectroscopy (PRESS: TR/TE = 1500/136 ms; VOI = $20 \times 20 \times 20$ mm^3 with water suppression) was obtained placing the volume of interest (VOI) within the mass, trying to avoid partial volume effects with adjacent brain with normal MRI signal. Data from 2 patients were excluded because of technical failure. In the other 9 patients the quality of the spectra was good. The choline/NAA ratio was elevated in all 9 patients and varied from 3.32 to 1.08, 0.6–0.8 being the normal range in the brainstem and cerebellum. The Cho/Cr ratio was also elevated (range 1.89–1.01) in all except one patient. The lactate signal was detected in 3 patients. The Cr/NAA ratio was abnormal in all patients due to loss of the NAA signal.

Four patients, in whom MRS was performed, had a histological diagnosis, consisting of an anaplastic astrocytoma in 2 cases, fibrillary astrocytoma in 1 and glioblastoma in 1.

FDG-PET was performed in 8 patients before radiotherapy: it was

Table 1 MRI features at presentation

MRI characteristics (%)	
T1-weighted images	
Hyposignal	68%
Isosignal	32%
T1-weighted images with gadolinium infusion	
Contrast enhancement	28%
Contrast enhancement with "necrosis"	12%
T2-weighted images	
Hypersignal	100%
Heterogeneous	50%
Homogeneous	50%
General patterns	
Non-enhancing, diffusely infiltrative	50%
Enhancing localized mass	25%
Isolated tectal tumor	3%
Others	
Posterior exophytic	12%
Diffusely infiltrative with enhanced nodule	10%
Associated features	
Mass effect	66%
Hydrocephalus	23%
Cystic component	12%
Haemorrhage	0%

clearly abnormal, due to an increased uptake of the tracer, in 3, slightly abnormal in 2 and normal in 3.

Two patients in whom FDG-PET was performed had an histological diagnosis, consisting of anaplastic astrocytoma.

During the follow-up MRI was performed every 3 months.

Management at diagnosis

In 8 patients, an initial "watch and wait" policy was adopted, due to the paucity of symptoms/signs and the low grade appearance on MRI, whereas the other 24 patients underwent an antineoplastic treatment, due to either the need for palliation of disabling symptoms/signs or the existence of an "enhancing aggressive" disease on MRI.

Radiotherapy concomitant with and followed by chemotherapy was used in 20 patients, whereas radiotherapy alone, deferring chemotherapy at tumor progression, was used in 4 patients. Conformal radiotherapy was performed with total doses ranging from 48 to 54 Gy with 1.8 Gy per fraction. The planned target volume was calculated basing on T2 findings on MRI.

As for chemotherapy, temozolomide was administered in 18 patients concomitantly with radiotherapy at a dose of 75 mg/sqm/day and adjuvantly at the dose of 200 mg/sqm/day for 5 days every 28 days, up to a maximum of 9 cycles.

Sulphamethoxazole/trimethoprim (800 mg/160 mg) was administered every other day during radiotherapy. Two patients received PCV (CCNU 110 mg/sqm day 1, procarbazine 75 mg/sqm/day days 8 to 21, vincristine 1 mg/sqm days 8 and 28), starting on day 1 of radiotherapy, up to a maximum of 5 cycles.

Management at progression

Six patients progressed after the initial watch and wait policy, and the treatment included conformal radiotherapy, which was administered concomitantly with temozolomide at a dose of 75 mg/sqm/day, and was followed by adjuvant temozolomide in 4 cases, while no chemotherapy was delivered in 2. Two patients are still free from progression.

Among patients progressing after first-line treatment, 7 received second-line chemotherapy that consisted of an association of cis-platin and temozolomide in 3 patients, PCV in 2 cases, temozolomide in 1 case, ACNU and procarbazine in 1 case. Two patients received first-line chemotherapy with nitrosureas after previous radiation alone.

Response and outcome

Response after treatments was evaluated according to MacDonald's criteria (CR, PR, SD, PD) [4], based on changes in T1-weighted images with contrast for enhancing tumors and in T2 or Flair images for non-enhancing tumors. We also used the category of MR (minor response) to define a decrease of at least 25% but less than 50% of the tumor area. The response was evaluated while the patients were receiving a stable or decreasing dose of corticosteroids.

Survival was estimated by the Kaplan-Meier method and survival curves were compared with the log rank test. Univariate and multivariate analysis (using the Cox regression model) were performed on the following parameters: age, duration of symptoms before diagnosis, contrast enhancement/necrosis on MRI, biopsy proven diagnosis and type of histology. A subdivision of patients into the different subgroups, as described by Guillamo et al. [2], was performed.

Results

Response to treatments

We did not observe any partial or complete response after radiotherapy alone or plus chemotherapy. A clinical response was reported in 15 patients, whereas 10 patients showed a stable disease and 6 displayed tumor progression.

Nine patients displayed clinical improvement concurrent with a radiologically stable disease: this included a reduction of gait ataxia, spasticity, vertigo or eye movement abnormalities, while 6 patients showed both clinical and radiological response (minor response in all cases).

At tumor progression, 2 of 9 patients displayed temporary clinical and radiological stabilization after second-line chemotherapy (in one case PCV, in the other cis-platin and temozolomide).

Outcome

After a follow-up ranging from 9 to 180 months, all but 2 patients have progressed and 14 patients have died (12 for disease progression, 2 for pulmonary embolism).

The disease progression was either clinical [4] or radiological [2] or both [25].

We did not observe a CSF spreading in any patient; all relapses were local. However, no systematic spinal MRI follow-up studies were performed. The median time to tumor progression (TTP) was 10 months (Fig. 2). The median TTP was 6 months in patients undergoing early

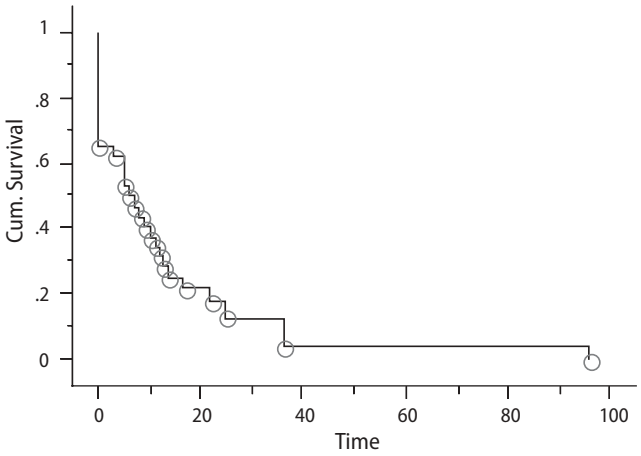

Fig. 2 Time to tumor progression (TTP) in months in the whole group of patients

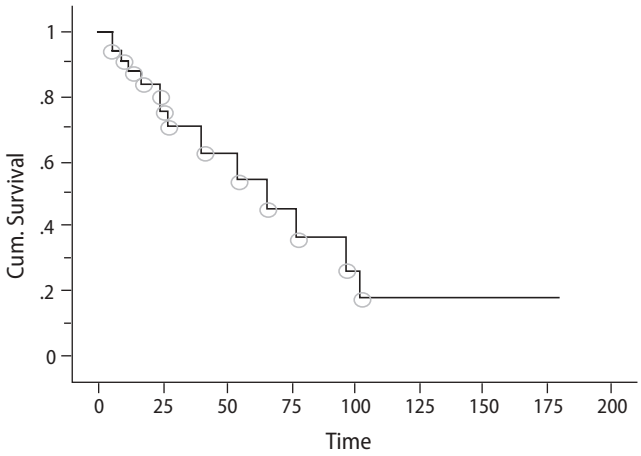

Fig. 3 Survival time (ST) in months in the whole group of patients

treatment and 35 months in patients with initial watch and wait. The median overall survival time (ST) was 59 months (Fig. 3). The median ST was 52 months in patients undergoing early treatment and 95 months in patients with initial watch and wait.

Toxicity

Grade IV myelotoxicity after 1 or 2 cycles of adjuvant temozolomide, leading to a discontinuation of the drug, was observed in 3 patients (in one patient affecting both platelets and leukocytes, in 2 patients affecting platelets). Grade III myelotoxicity occurred in 3 patients after 3 to 4 cycles of either temozolomide (1 case) or PVC (2 cases). Non-hematological toxicity was seen in one patient developing trigeminal herpes Zoster infection after 5 cycles of temozolomide.

Prognostic factors

The results of uni- and multi-variate analysis for prognostic factors are reported in Table 2. The time elapsed between disease onset and diagnosis was the sole parameter with a significant prognostic value both in univariate and multivariate analysis.

A time interval between onset and diagnosis shorter than 4 months was significantly predictive ($p = 0.0075$) of a shorter ST (Fig. 4).

No significant differences in ST emerged between patients with or without an histological diagnosis (Fig. 5). Also, the presence/absence of enhancement and "necrosis" on MRI were not significantly associated with a shorter ST, despite a trend to a shorter ST in patients displaying necrotic lesion(s). According to Guillamo subdivision, 16 (50%) patients were considered as diffuse intrinsic low grade gliomas, 12 (39%) patients as malignant gliomas and 1 (3%) as focal tectal gliomas, and their median survival was 75 and 25 months, re-

Table 2 Risk ratio (death) according to Cox analysis

Variables	n	Univariate results			Multivariate results*		
		Risk ratio	95% C.I.	p value	Risk ratio	95% C.I.	p value
Age							
<40	21	1	Reference		1		
≥40	11	1.87	0.49–7.02	0.35	0.84	0.21–3.41	0.81
Interval onset-diagnosis							
≤4 months	12	1	Reference		1		
>4 months	13	0.18	0.04–0.72	0.01	0.14	0.03–0.65	0.01
Enhancement							
absent	18	1	Reference		1		
present	14	1.4	0.45–4.31	0.45	2.0	0.58–7.10	0.27
Histology							
low-grade	9	1	Reference				
high-grade	9	4.10	0.35–47.19	0.25			

* The final model did not include histology due to the small number of cases

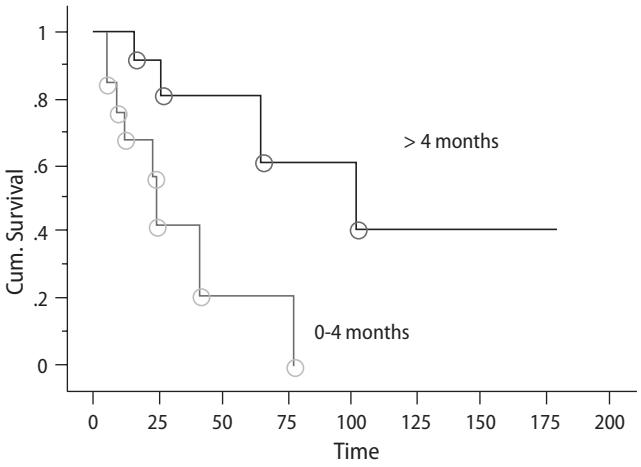

Fig. 4 Survival time (months) by interval between onset of symptoms/signs and diagnosis: ≤ 4 months (median survival 23 months) versus > 4 months (median survival 100 months) (p = 0.0075 logrank)

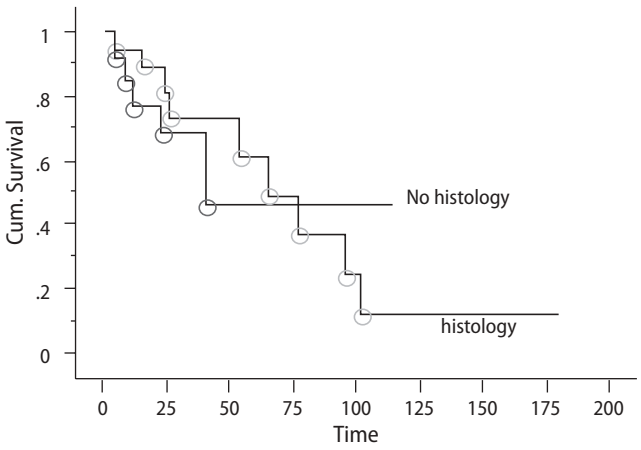

Fig. 5 Survival time (months) by type of diagnosis: biopsy-proven versus radiological. Median survival time of 65 months in biopsy-proven patients and 38 months in patients without histologic assessment (p = 0.75 logrank

spectively (the only patient with focal tectal glioma was still alive after a follow-up of 80 months).

Discussion

The data concerning BSG in pre-MRI era are mostly reported in neurosurgical series [5, 6] where both pediatric and adult patients are grouped together. Despite limitations in radiological diagnosis and follow-up, it is noteworthy that some of the observations raised by these authors have been confirmed by subsequent studies. The study by Tokuriki [5] on 85 cases reported that in 19 patients only histology was obtained, and median survival was 10.5 months: this is probably explained by the high proportion (69 out of 85) of "typical" pontine, high-grade childhood gliomas. Also, the observation was raised by these authors that, in adults, the tumors are more commonly extended to more than one brainstem segment at diagnosis: this is confirmed by our series, in which 6 out of 32 patients only showed an isolated involvement of one brainstem segment at diagnosis.

The series reported by Bricolo and colleagues [6] is rather different, as it includes a high number of patients with a histological diagnosis of either grade I (pilocytic astrocytoma) or grade II glioma. The data of the present series are in line with those reported by Guillamo et al. [2] and Landolfi et al. [7] for adult patients with BSG in the MRI era.

Median age at onset in this series was 31, and a median age of 29, 40 and 37 has been reported in Guillamo's, Landolfi's and Linstadt's [2, 7, 8] series, respectively. Twenty of 32 (65 %) patients in this series had an histological confirmation: this rate is slightly lower than in the French study (71 %). In this series there is a slight prevalence of low grade over high grade tumors (11 versus 9) compared to the French series (15 versus 17).

Regarding symptoms and signs at onset, diplopia, hemiparesis and ataxia were the most common presenting features in our patients. These features are similar to those described by Landolfi et al., although they report a higher incidence of cranial nerve dysfunction. Of note, 3 patients displayed a facial spasm, while Guillamo et al. have reported a facial myokimia in 5 out of 22 patients with diffuse intrinsic BSG. In a recent report, Elgamal and Coakham [9] reviewed the literature and found 9 patients with brainstem tumors in whom the hemifacial spasm was an isolated neurological sign.

All patients displayed on MRI hyperintense areas in T2-weighted/FLAIR sequences; the contrast enhancement was present in 18 of 32 (45 %): this value is close to that reported by Guillamo et al. The use of MRS and FDG-PET has not been reported so far in these tumors. It is noteworthy that an increased Cho/NAA ratio was present in all patients at diagnosis.

A high degree of concordance was detected between MRS and histology: 3 patients showed both abnormal MRS and high-grade histology, while among the 2 patients undergoing both FDG-PET and histological assessment, both had high-grade gliomas but only one had an abnormal PET.

Concerning the response to treatments, the proportion of patients displaying a minor response or stable disease after radiochemotherapy or RT alone was 48 % (15/31) and 32 % (10/31) respectively, while 19 % (6/31) of the patients displayed progressive worsening regardless of treatment. One patient died due to pulmonary embolism at the beginning of radiotherapy, and therefore was not included in those evaluated for response. The proportion of patients with a radiological progression during radiotherapy is close to the 18 % reported by Guillamo et al. It must be stressed that – unlike Guillamo

et al., we did not find partial responses, but minor responses only. This could be in part attributed to the prevalence in our series of slowly growing tumors, which are expected to respond to a lesser extent to radiotherapy. A discordance between clinical and radiological responses in these tumors is not uncommon: 6 out of the 15 patients only, who displayed a clinical improvement, also had some degree of radiological responses. This lack of correlation may be due to the anatomy of the brainstem, where critical nuclei or fiber bundles may suffer an early clinically relevant damage despite negligible increase in size on MRI. Hopefully, functional measures, such as MRS, might provide a more reliable tool in assessing response; this is partly supported by recent data in children with diffuse intrinsic pontine gliomas, in whom a relationship was observed between clinical response to radiotherapy and decrease in the choline/NAA ratio [10]. We have no data in this regard.

Median ST in our cohort was 59 months, compared to 54 months in Landolfi's and 5.4 years in Guillamo's series. As in other series, ST was significantly shorter in patients with a shorter interval between onset and diagnosis. Survival curves were similar for patients with or without histologic assessment. This finding has been previously reported in childhood brainstem tumors, leading some authors [11] to the conclusion that "apart from cystic or exophytic tumors or the placement of a shunt, surgery can only be recommended when it is considered to have a low risk of causing any neurologic sequelae and when performed by an experienced neurosurgeon". On the other hand, the need for histologic assessment by means of stereotactic biopsy is still advocated by some authors [12] in children with brainstem lesions "not exhibiting the classic MR imaging and clinical features of diffuse glioma". More in general, regarding the need of a biopsy to establish an histological diagnosis in the patients who are not candidates to a surgical resection (i. e. those with exophytic and/or cystic tumors), our approach is similar to that of Landolfi et al. and Guillamo et al. Patients exhibiting the "classical" picture of a diffusely infiltrating non-enhancing lesion on MRI do not require a biopsy, as MRI has a high degree of accuracy and the risk of morbidity due to tumor location is quite high. Only 5 patients with diffusely infiltrative tumor pattern underwent biopsy in our series (due to complete absence of mass effect). Among patients with contrast enhancing lesions, a biopsy should be considered more carefully in order to rule out infections or inflammatory lesions. It remains to be clarified if modern neuroimaging techniques, such as MRS and/or PET, could allow a better characterization of brain stem lesions in terms of differential diagnosis.

In our series, a trend for a negative prognostic impact of age higher than 40 and for high-grade histology was evident, but did not reach statistical significance: this may be due to the limited sample size. Two patients died from pulmonary embolism, and 1 suffered from DVT, stressing the high frequency of this complication in this subgroup of glioma patients as well.

In this retrospective study the administration of temozolomide, employing the regimen that has been successful in glioblastomas [13], does not seem to improve outcome. A partial explanation of this finding could be that the combined regimen was not effective in the subgroup of patients who had not a glioblastoma (i. e. a grade III or II glioma). Similarly, a prospective multi-institutional study in diffuse brainstem gliomas in children [14] reported that the administration of temozolomide after RT did not alter the poor prognosis associated with these tumors.

Multicenter trials are required to better define the benefit of different treatment modalities in brain stem tumors, but their rarity and heterogeneity at diagnosis are severe limiting factors [15].

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