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ORIGINAL ARTICLE

# Adult brainstem glioma: a multicentre retrospective analysis of 47 Italian patients

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## Abstract

**Background and purpose** Adult brainstem gliomas are rare primary brain tumours with heterogeneous clinical course. The low frequency of these tumours makes it difficult to achieve high-quality evidence regarding prognostic factors, adequate therapeutic approach and outcome in such patients.

**Methods** In this retrospective study, we analysed clinical, radiological, molecular, prognostic and therapeutic factors in a series of 47 histologically proven adult brainstem gliomas recruited over a 20-year period (1998–2018).

**Results** Twenty-two patients were male, 25 female with median age of 39 years. The tumour involved one brainstem segment in 20 cases and 2 or more segments in 27. Contrast enhancement was reported in 28 cases. Surgical procedures included biopsy in 26 cases and partial/total resection in the remaining 21. Histological diagnosis was of low-grade glioma in 23 patients, high-grade glioma in 22 and non-diagnostic in 2 cases. Data regarding molecular biology were available for 22 patients. Median overall survival was 35 months, in particular 16 months in high-grade glioma and 84 months in low-grade glioma. At univariate analysis, tumour grade was the only factor with a statistically significant impact on survival time ($p$ = 0,003), whereas younger age, better performance status and total/subtotal resection showed a trend to more prolonged survival. This study also confirms safety of biopsy/surgery in adult brainstem glioma patients and shows a clear trend to a more frequent assessment of molecular biology data.

**Conclusions** Further prospective multicentre efforts, and hopefully clinical trials, are necessary to improve outcome in this neglected glioma patient population.

**Keywords** Brainstem gliomas · Adult · Prognosis · Survival · Management

## Introduction

While brainstem gliomas (BSG) are frequent in children, they are rare in adults, contributing to less than 2% of gliomas [1] A seminal work by Guillamo has identified three major types of adult BSG, namely, high-grade gliomas, diffuse infiltrating low-grade gliomas and tectal gliomas, with marked differences in life expectancy [2]. The low frequency of these

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tumours in adults, together with the major risks inherent to surgical procedures in a highly eloquent area, makes it difficult to achieve high-quality evidence concerning the risk/benefit ratio of surgery as well as of post-surgical treatments. Emergence of molecular markers as diagnostic/prognostic tools in neurooncology in the last 15 years has led to a more aggressive attitude by neurosurgeons even in these tumours, also in consideration of the recent identification of H3 K327M mutation in midline gliomas with low rate of MGMT promoter methylation and overall dismal outcome [3] [4]; this aggressive attitude is also related to improvements in surgical/intraoperative monitoring techniques and to identification of so-called safe entry zones and has the aim to optimize extent of resection, in the aim of improving patients' survival. Despite these increases in knowledge, only about 20% of adult patients with high-grade brainstem glioma underwent surgery as reported in a recent paper by Doyle and Colleagues [5]; in their work, the authors were able to document the outcome in 103 patients out of 502 (i.e. approximately 20% of their patients, from the SEER database and over a time period spanning 4 decades from 1973 to 2015, with a clinic-radiological diagnosis of high-grade glioma (HGG) in the brainstem underwent surgical procedures); they did not report whether the proportion of patients with surgical procedures was increasing over time, however, nor did they provide data on the outcome of non-operated patients. In a previous retrospective analysis of 34 adults from 2 centres in Italy, median overall survival was 59 months [6]; however, histology was obtained only in two thirds of the patients, and no data were available concerning molecular biology. The objective of this study was to investigate clinical features, treatment options and outcome in a cohort of adult patients with histologically verified BSG, collected retrospectively from 8 Italian institutions; the study was promoted by the Neurooncology Group of the Italian Hospital Neuroscience Society in collaboration with AINO (Italian Association of Neuro-oncology) and the Neurooncology Group of SIN (Italian Neurological Society).

## Patients and methods

Overall, 47 patients were recruited over a time range of 20 years (1998–2018) from the following Italian institutions: Fondazione IRCCS Istituto Neurologico Besta in Milan, City of Health and Science and University of Turin, IRCCS Regina Elena National Cancer Institute in Rome, Fondazione IRCCS Istituto Mondino in Pavia, Siena Hospital Neuroradiology Unit, PGXXIII Hospital in Bergamo, Legnano Hospital , Lecco Hospital. Twenty-two patients were male, 25 female; age range was 18-76 years (median 39). Clinical features at onset, neuroradiological features and histological grade were assessed, correlating these features to overall survival. Descriptive statistics, Fisher's exact test and logrank test were used for analysis

## Results

### Signs and symptoms

Symptoms at onset included headache (10/47), cranial nerve involvement (20/47), ataxia (24/47), paresis/hypoesthesia (8/47) and acute intracranial hypertension (12/47). One case of isolated clinically peripheral facial paresis was detected. (Tables 1 and 2).

### Imaging

All patients underwent magnetic resonance imaging (MRI) without and with gadolinium; the tumour involved one brainstem segment in 20 cases and 2 or more segments in 27. Contrast enhancement was reported in in 28/47 patients, 16 high-grade glioma (HGG) and 12 low-grade glioma (LGG); however, there was no statistically significant difference in the proportion of patients with or without CE in the 2 subgroups of LGG and HGG by Fisher's test. PET was performed in 7/47 cases with abnormal results in 6 (i.e. hypercaptation of the tracer, methionine in 5 cases and FET in 1)

### Surgical procedures

Biopsy was performed in 26 patients, partial resection in 10, subtotal resection in 9 and grossly total resection in 2. Perioperative deficits occurred in 4/47 patients; the deficits were transient in 2 cases

### Histology and molecular biology/immunohistochemistry study

Histological diagnosis was of low-grade glioma in 23 patients and high-grade glioma in 22; in 2 cases, biopsy was non-diagnostic (these 2 cases were judged to be HGG on the basis of clinical and imaging features and were treated accordingly). In the LGG subgroup, 9 were pilocytic astrocytomas, 12 grade II astrocytomas and 2 Grade II oligodendrogliomas. In the HGG subgroup, 12 were grade III astrocytomas, 1 grade III oligodendroglioma and 9 glioblastomas.

MGMT methylation status was assessed by polymerase chain reaction method, LOH for 1p and 19q by FISH (fluorescent in situ hybridization), while testing of p53, IDH1 and H3 K27M mutation was by immunohistochemistry.

Over time, the proportion of patients undergoing molecular profiling on top of standard histology increased, as shown in Fig. 1. The results of molecular biology/immunohistochemistry studies are reported patient-by-patient in Tables 1 and 2.

**Table 1** Data regarding high grade glioma patients

| Sex | Age | Extension | Surgery | Histology | Contrast enhancement | Molecular biology |
|---|---|---|---|---|---|---|
| Female | 26 | Ponto-mesencephalic | Biopsy | Astrocytoma grade III | + | No |
| Male | 56 | Ponto-mesencephalic | Partial | Oligodendroglioma grade III | + | No |
| Male | 41 | Ponto-bulbar | Subtotal | Astrocytoma grade III | + | IDH1 wild type |
| Female | 29 | Mesencephalic | Subtotal | Astrocytoma grade III | + | No |
| Male | 20 | Ponto-mesencephalic | Partial | Astrocytoma grade III | + | No |
| Female | 25 | Pons | Biopsy | Astrocytoma grade III | + | p53 neg<br>H3 K27M + |
| Male | 54 | Peduncle and pontine | Biopsy | Astrocytoma grade III | + | No |
| Male | 40 | Bulbar | Partial | Glioblastoma | + | IDH1 wild type<br>p53 neg<br>EGFR neg |
| Female | 24 | Bulbo-pontine | Biopsy | Astrocytoma grade III | - | IDH1 wild type |
| Female | 35 | Bulbo-pontine | Biopsy | Astrocytoma grade III | - | IDH1 wild type<br>p53 neg |
| Male | 68 | Mesencephalic | Biopsy | Glioblastoma | + | H3 K27M +<br>IDH1 wild type |
| Male | 49 | Mesencephalic | Biopsy | Glioblastoma | + | p53 neg<br>IDH1 mutated |
| Female | 74 | Ponto-peduncolo-left cerebellar | Biopsy | Glioblastoma | + | IDH1 wild type |
| Female | 76 | Ponto-peduncolo-left cerebellar | Biopsy | Glioblastoma | + | IDH1 wild type |
| Male | 53 | Bulbo-ponto-peduncolo-right cerebellar | Biopsy | HGG* | - | No |
| Female | 47 | Bulbo-medullar | Partial | Glioblastoma | + | No |
| Male | 24 | Mesencephalic | Biopsy | Astrocytoma anaplastic | - | No |
| Female | 40 | Bulbo-pontine, left cerebellar peduncle | Total | Glioblastoma | - | EGFR + |
| Female | 45 | Mesencephalic | Subtotal | Glioblastoma | - | EGFR + |
| Male | 38 | Bulbo-pontine | Biopsy | Glioblastoma | - | No |
| Female | 49 | Bulbo-pontine | Biopsy | Astrocytoma grade III | + | 1p/19 codeleted<br>MGMT methylated<br>IDH1 mutated |
| Female | 33 | Mesencephalic | Partial | Astrocytoma grade III | - | No |
| Female | 23 | Bulbo-pontine | Biopsy | Astrocytoma grade III | + | No |
| Male | 53 | Bulbo-pontine | Biopsy | HGG* | + | No |

* Non-diagnostic biopsy

## Clinical outcome

After a follow-up ranging from 2 to 240 months, 24 patients have died (15 HGG, 9 LGG). First-line treatments delivered after histology included radiotherapy in 18 HGG patients and chemotherapy in 20; in 2 patients, no post-surgical treatment was delivered due to early tumour progression/poor general conditions. In 2 patients, upfront chemotherapy with temozolomide was delivered. In the 18 patients undergoing radiation treatment and chemotherapy, this latter consisted of temozolomide in 17 and PVC in 1; in 6 of the 18 patients receiving both RT and CT, the Stupp schedule was adopted (all with glioblastoma). At disease progression, 1 patient was treated with repeat surgery and chemotherapy, 4 received chemotherapy and 1 radiotherapy. In the LGG group, 9 patients were followed with a watch and wait approach, 3 received first-line radiation therapy, 2 upfront temozolomide and 9 received radiation therapy and adjuvant temozolomide. At progression, 2 patients underwent repeat surgery, 3 radiation therapy, 2 temozolomide chemotherapy and 1 radiation therapy followed by temozolomide. CSF spread was detected during follow-up in 7/47 patients; 5 of these occurred in HGG patients (1 grade III astrocytoma and 1 GBM having undergone biopsy, 1 grade III astrocytoma and 1 GBM having undergone subtotal resection and 1 grade III oligodendroglioma having undergone partial resection) and 2 in LGG patients (both with grade II astrocytoma and biopsy and partial resection, respectively). Median overall survival (OS) in the whole cohort was 35 months (in HGG 16 months, in LGG estimated projected survival 84 months). Progression free survival (PFS) was 7 months in

**Table 2** Data regarding low grade glioma patients

| Sex | Age | Extension | Surgery | Histology | Contrast enhancement | Molecular biology |
|---|---|---|---|---|---|---|
| Female | 31 | Pontine, left cerebellar | Partial | Oligodendroglioma grade II | - | IDH1 wild type<br>1p/19 codeleted |
| Male | 39 | Ponto-mesencephalic | Biopsy | Astrocytoma grade II | - | No |
| Male | 47 | Ponto-mesencephalic | Biopsy | Astrocytoma pylocytic grade I | - | No |
| Male | 35 | Bulbar | Subtotal | Astrocytoma pylocytic | - | p53 neg |
| Female | 51 | Pons, peduncle | Total | Astrocytoma pylocytic | + | No |
| Female | 38 | Pontine | Biopsy | Astrocytoma grade II | - | No |
| Female | 47 | Right bulbar | Biopsy | Astrocytoma pylocytic | + | No |
| Male | 35 | Bulbar | Subtotal | Astrocytoma pylocytic | + | p53 neg |
| Male | 61 | Bulbar | Biopsy | Astrocytoma pylocytic | + | p53 neg<br>IDH1 wild type |
| Female | 38 | Bulbo-pontine | Subtotal | Astrocytoma pylocytic | + | No |
| Male | 18 | Mesencephalic | Subtotal | Astrocytoma pylocytic | + | No |
| Male | 49 | Pontine | Partial | Astrocytoma grade II | - | 1p/19 q non codeleted |
| Female | 43 | Mesencephalic | Subtotal | Astrocytoma diffuse | - | IDH1-2 wild type |
| Female | 45 | Bulbo-pontine | Biopsy | Astrocytoma grade II | + | No |
| Female | 78 | Bulbar | Biopsy | astrocytoma | - | No |
| Female | 39 | Ponto-mesencephalic | Biopsy | oligodendroglioma | - | 1p/19 q codeleted |
| Female | 35 | Mesencephalic | Partial | astrocytoma | - | No |
| Male | 47 | Pontine | Biopsy | Astrocytoma grade II | + | No |
| Female | 15 | Bulbo-ponto-cerebellar | Subtotal | Astrocytoma grade I | + | No |
| Female | 31 | Bulbo-pontine | Partial | Astrocytoma grade II | - | No |
| Male | 19 | Cerebellopontine | Partial | Astrocytoma grade II | + | MGMT unmethylathed |
| Male | 30 | Mesencephalic | Biopsy | Astrocytoma | + | MGMT methylated<br>1p/19q no codeleted |
| Male | 42 | Bulbo-pontine | Biopsy | Astrocytoma grade II | + | IDH1 mutated |

HGG and 39 months in LGG. Figures 2, 3, 4 and 5 report OS according to tumour grade, extent of resection, age and KPS. Overall, the only factor with a statistically significant impact on survival time was tumour grade. A trend to more prolonged survival in patients undergoing total/subtotal resection as compared with all other patients was detected, as well as a trend to more prolonged survival in patients with younger age at onset and with a better performance status.

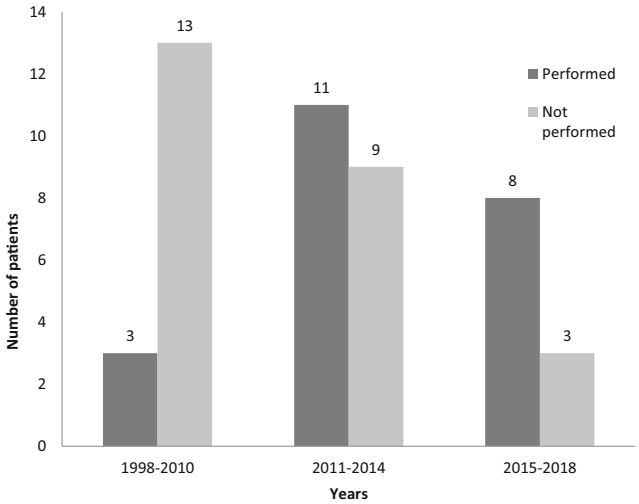


**Fig. 1** Distribution of patients undergoing molecular profiling according to different periods of time (i.e. 1998–2010, 2011–2014, 2015–2018)

## Discussion

Brainstem gliomas are not rare in children, in whom diffuse intrinsic pontine glioma (DIPG) is the most frequent variety and carries a grim prognosis; despite multiple clinical trials and international cooperative efforts [7], median life expectancy in these children does not exceed 1 year after diagnosis [8]; on the other hand, pilocytic astrocytomas (more frequent in the cerebellum) are associated with a better prognosis. In adults, glial tumours arising in the brainstem are more heterogeneous; as a matter of fact, they include high-grade gliomas, diffuse infiltrating low-grade gliomas, tectal gliomas and exophytic gliomas of the cervicomedullary junction [9]; these subgroups have been related to differences in median survival [2]. Due to the rarity of these tumours, no standard therapeutic approach exists; in the last years, both the emergence of

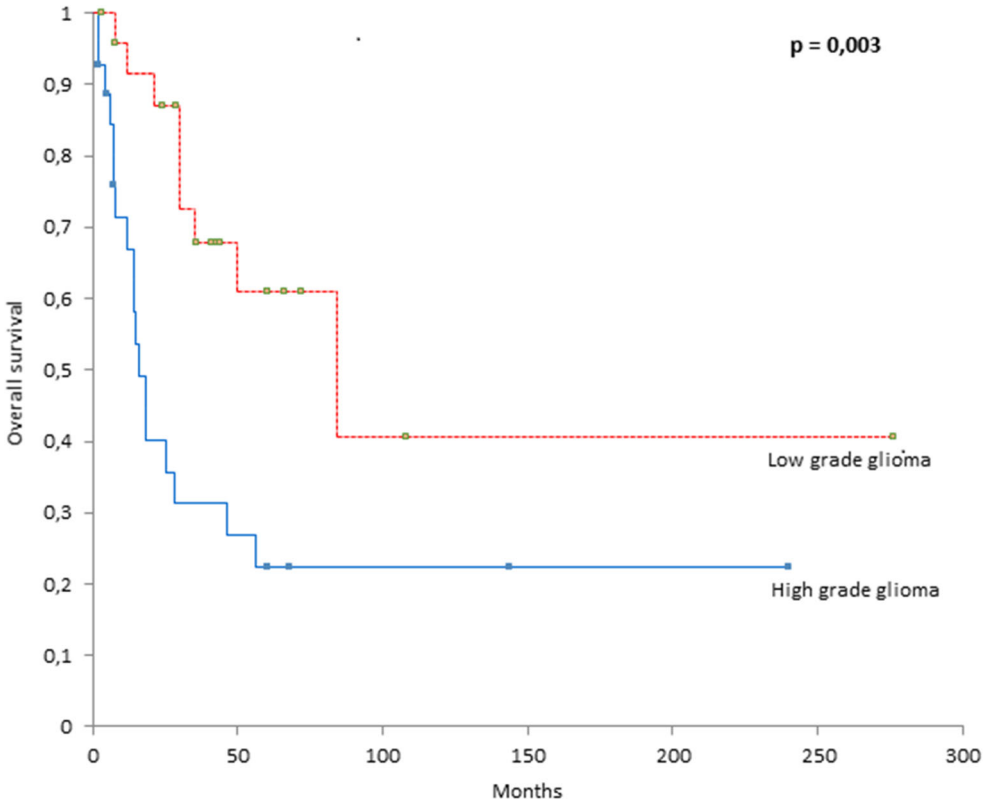


**Fig. 2** Kaplan-Meier curves comparing overall survival (OS) in patients with low-grade glioma versus patients with high-grade glioma

molecular markers with prognostic/predictive value and the more widespread utilization of intraoperative monitoring have led to a more aggressive approach; however, still a minority of patients undergo histological assessment in non-selected

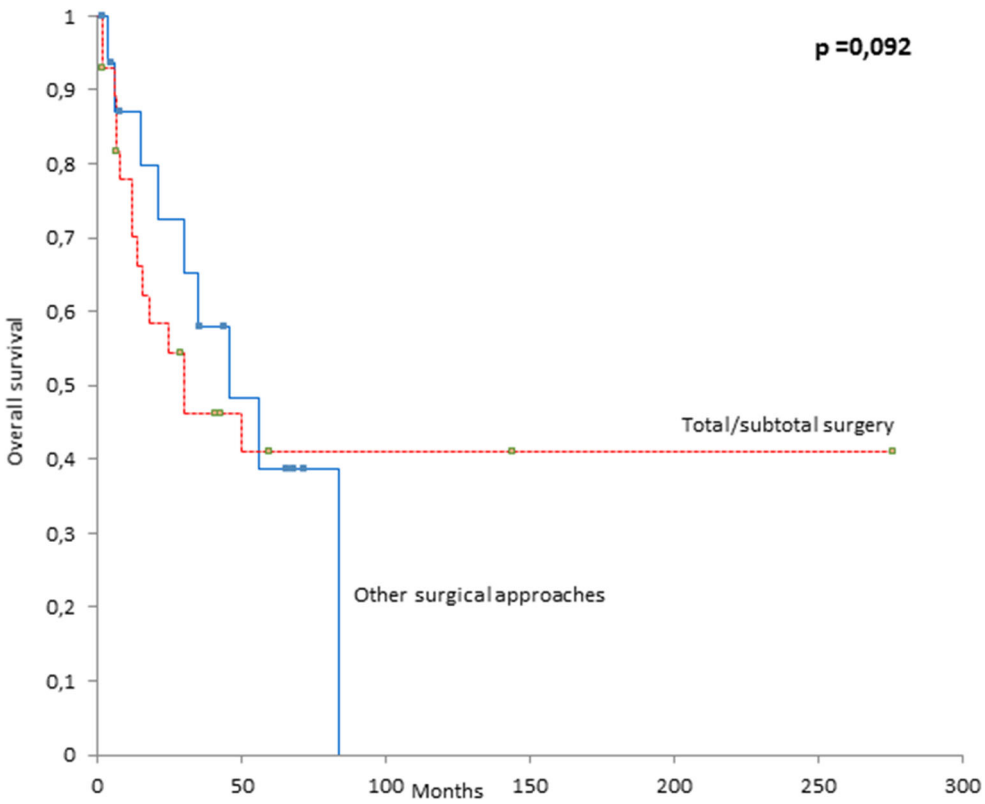


**Fig. 3** Kaplan-Meier curves comparing overall survival (OS) in patients who underwent total/subtotal surgery versus patients who underwent other surgical approaches

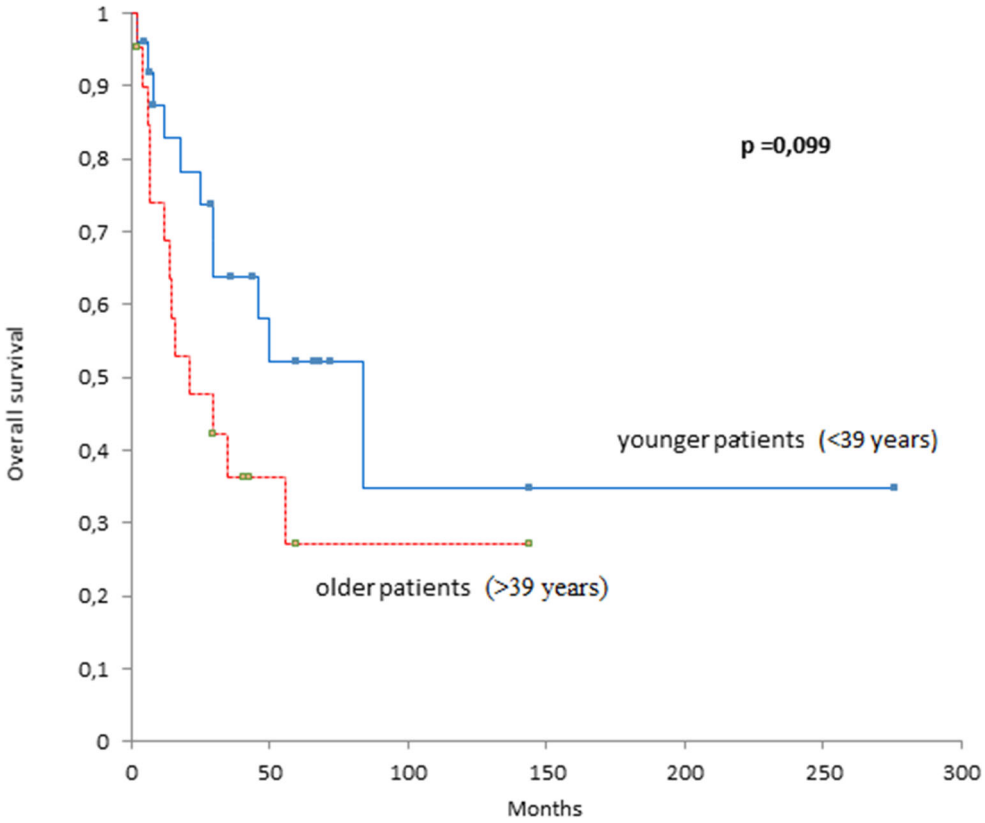


**Fig. 4** Kaplan-Meier curves comparing overall survival (OS) in younger patients (< 39 years) versus older patients

populations. Lack of histological diagnosis increases the risks of inaccurate diagnosis and consequent inappropriate treatment; this risk is estimated to be higher in contrast-enhancing lesions of the brainstem [10]. In a previous study, we included 34 patients with either histology-proven or clinic-radiological diagnoses adult brainstem glioma from 2 Italian

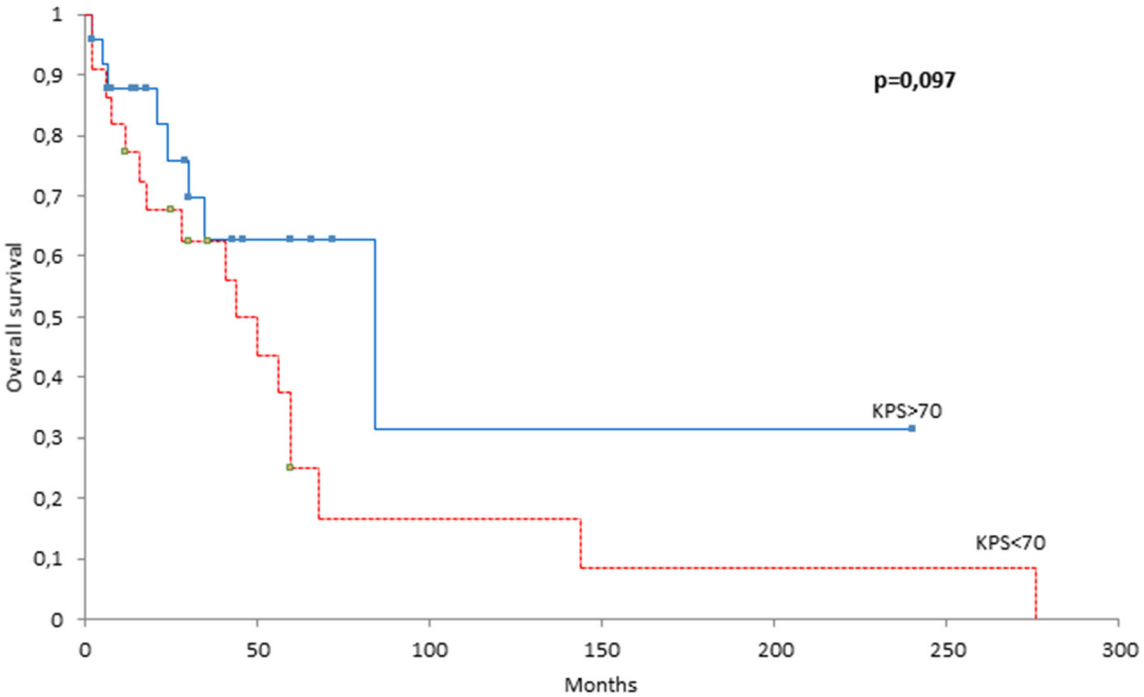


**Fig. 5** Kaplan-Meier curves comparing overall survival (OS) in patients with higher Karnofsky performance status (KPS > 70) at disease onset versus patients with lower Karnofsky performance status (KPS < 70) at disease onset

centres and found no difference in overall survival between these 2 subgroups [6]. More recently, a number of studies have been published, overall confirming a short median survival in high-grade brainstem gliomas and a more prolonged survival in LGG [10–13]. Interestingly, despite heterogeneous treatment schedules adopted in these series after histological assessment, there seems to be little difference in overall survival between supratentorial gliomas and brainstem glioma (BSG) in adults; the role of chemotherapy concomitant with/following radiation therapy is not clear, and the fear of increasing oedema in a critical area still limits the adoption of the Stupp schedule in adult BS glioblastoma, despite no evidence of increased toxicity [6]. In this case series, median overall survival was 35 months; in high-grade gliomas, however, it was of 16 months, whereas in LGG the projected estimate was of at least 84 months. In the HGG subgroup, therefore, OS was not so different from that detected in supratentorial glioblastomas. Of interest, our study provides data on the proportion of non-informative biopsy (i.e. 2/47, approximately 5% in our cohort) and on procedure-related additional neurological deficits (which took place in 4 out of 47, being permanent in 2). Very similar data were reported by Guillamo et al. [2] with 2/48 non-informative histologies in their cohort. Diagnostic work-up was mostly limited to MRI (with and without gadolinium); only in 7 cases did patients undergo amino acid PET (with abnormal results in 6).

Of note, the presence of contrast enhancement at MRI was not significantly related to higher glioma grade in this study, highlighting the need for histological assessment in the aim of avoiding under- or overestimation of tumour grade; for biopsy, only the risk of under-grading is obviously present.

Molecular biology testing/immunohistochemistry analyses were heterogeneous among the various centres, reflecting the long recruitment period; however, these studies were performed in approximately 50% of the patients, reflecting an increased awareness by clinicians and neuropathologists of the clinical relevance of these studies.

The percentage of patients undergoing analysis of molecular markers on top of standard histology, as a matter of fact, increased over time as shown by our data.

Tumour dissemination took place in 7 out of 47 patient over the follow-up; 5 of these were patients with HGG; data on CSF spread by BSG are not frequently reported in the literature; in the cohort studied by Guillamo [2], CSF dissemination occurred in 6 out of 48 patients (13%), a figure very similar to that obtained in the present study. Also in children with the DIPG the frequency of CSF dissemination is reported at about 17% [14]. In the work by Reithmeier [13], 104 patients with histologically proven BSG (nearly 90% diagnosed by stereotactic biopsy) had a median age of 41, and an overall median survival of only 18.8 months for the whole patient population (and 26.2 months in grade 2 tumours); the distribution in histological grade was not very different from that in our series, so we may speculate that the far higher proportion of stereotactic biopsies in their series may partly explain the shorter survival. No molecular data results were reported in this paper, which included patients enrolled between 1997 and 2007. In a smaller series by Hundsberger [12], 21 patients' (15 biopsy, 6 partial or complete resection) median age was again 41, and median overall survival was 30.5 months in grade II gliomas versus 11.5 in grade III/IV; in this report, including patients enrolled from 2004 and 2012, molecular biology data were only available in one-third of the cases. Overall, our work and the previous ones document the favourable impact of younger age, lower glioma grade and better performance status and a trend to a favourable impact for surgery versus biopsy. Too few data are available to test the prognostic/predictive relevance of molecular tests in adult BSG. While external-beam radiation therapy (54 Gy) remains a "standard" approach in high-grade BSG or in symptomatic LGG, it remains to be established if and which chemotherapy approach is the safest and most effective in the setting of adult BSG; one may be tempted to address upfront chemotherapy in diffusely infiltrating, grade II 1p/19q co-deleted gliomas, whereas application of the Stupp schedule in brainstem glioblastoma needs to be carefully weighted in consideration of the risks of radionecrosis.

## Conclusion

Our case series has limits; first of all, it is a retrospective collection of heterogeneous patients from different centres with differences in volume of treated patients and of available facilities; however, this limitation makes our data collection closer to the real-life situation of adult BSG patients, who are usually not included in clinical trials and for whom management cannot rely on firmly established guidelines. Also, the choice of including only patients with histological confirmation (except 2) does not exclude selection bias; from this standpoint, it would be of great interest to analyse available data from patients included in registries (SEER) who were not treated with surgery, in order to detect possible gross differences in outcome. Despite these limitations, the present series confirms safety of biopsy/surgery in adult BSG patients, without detecting major changes in overall median survival in the last 10 years; it also shows a clear trend to a more frequent assessment of molecular biology data in those adult BSG patients in whom a surgical decision is made, without an impact on the severity and frequency of perioperative worsenings.

The future landscape of adult BSG treatment is likely to change in the next years, due to progress in molecular diagnosis at single-cell level, spreading of use of liquid biopsy [15] and molecular neuroradiology.

However, it is unlikely that these tools will lead to avoidance of histological assessment at least in the medium term,

since they will have to be validated in a comparison with histology itself. The introduction of epigenomic analysis (particularly DNA methylation data) is also shedding new light in brainstem glioma, with striking correlations of histone H3 mutation clusters both with survival and even anatomical site of the tumours.

Only prospective multicentre efforts—and hopefully clinical trials—will help improve outcome in this neglected glioma patient population; these should include also functional status evaluation, quality of life assessment in patients and caregivers and a focus on shared decision-making in patients likely to preserve their cognition and judgement ability for a long time of their disease trajectory, at variance with most supratentorial glioma patients.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no potential conflicts of interest.

**Ethical approval** The study was approved by an Internal Insitutional Review Board.

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