



Gliomatosis cerebri (GC) or GC-like? A picture to be reconsidered in neuro-oncology based on large retrospective analysis of GC series

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Abstract

Introduction Gliomatosis cerebri (GC), defined until 2016 as a distinct astrocytic glioma entity, has been removed from the 2016 World Health Organization classification of tumors of the central nervous system. However, its identity is still debated.

Materials and methods We retrospectively present 122 patients, including a subgroup with histology confirmation ($n = 75$, cohort b).

Results Radiological features showed extension limited to 3 lobes in 31%; bilateral, midline, and basal ganglia and subtentorial involvement in 95%, 52%, 84%, and 60%, respectively; and contrast enhancement in 59.5%. Perioperative mortality occurred in 4%. Histology concluded for grades II, III, and IV, respectively, in 31%, 35%, and 22% (not specified in 12%). Thirty-one percent had isocitrate dehydrogenase (IDH) 1 mutation. Treatments included radiotherapy in 51.2% and chemotherapy in 74.5%. Median overall survival was 17 months. Negative prognostic factors for survival were older age, poorer Karnofsky Performance Scale (KPS), subtentorial, midline and disseminated disease, and lack of chemotherapy, at univariate analysis. At multivariate analysis, $KPS \geq 80$, chemotherapy, and subtentorial and disseminated disease remained prognostic ($p < 0.0001$). For cohort b, same prognostic factors were confirmed, except for midline location, at univariate analysis; at multivariate analysis, only $KPS \geq 80$ and chemotherapy remained prognostic ($p < 0.0001$).

Conclusion We described clinical, neuroimaging, management, and histomolecular features of one of the largest GC series. We identified $KPS \geq 80$, radiological pattern as subtentorial localization and dissemination, and chemotherapy as prognostic factors, at multivariate analysis. Planning prospective study, associated to focused genetic assays, could help to clarify if GC has specific features that may result in the identification as a separate entity from other gliomas.

Keywords Gliomatosis cerebri · Prognostic factors · Subtentorial involvement · Chemotherapy · Disseminated disease

Introduction

Gliomatosis cerebri (GC) was initially defined as a rare brain tumor characterized by diffuse infiltration of neoplastic glial

cells with preservation of neural architecture and minimal mass effect, and it was stated as a distinct disease entity within central nervous tumors involving at least 3 lobes, with diffuse enlargement of anatomic structures in the 2007 World Health

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Organization (WHO) classification edition recognized. Recently WHO reviewed the definition, and GC does not represent a separate entity anymore, but it is considered as a very extensively infiltrating example of another diffuse glioma entity [1].

However, such a matter is still largely debated, as demonstrated by other papers that were published focusing on GC [2, 3]; the International GC Group Meeting recently held [4] and the National Cancer Institute still dedicating a specific section on its website (<https://www.cancer.gov/nci/rare-brain-spine-tumor/tumors/gliomatosis-cerebri>). If GC entity exists, there are no neuroimaging findings (other than extension) nor histologic or molecular markers that are generally accepted as specific for diagnosis of GC. The reasons are probably also due to the underpower of the published studies.

Besides, some authors tried to identify prognostic factors, with inconsistent results. Tumor histological grades have been related to survival in some studies [3, 5, 6] but not confirmed [7, 8]. It is also likely that patients with oligodendroglial phenotype, 1p19q codeletion, O[6]-methylguanine-DNA methyltransferase (MGMT) promoter methylation, and isocitrate dehydrogenase (IDH) 1 mutation have a better survival and better response to chemotherapy (CT) [3, 5, 7–10], but no prospective data are available except for one work, whose results need to be interpreted with caution due to the small sample of patients ($n = 25$) [7].

Due to its rare presentation and the lack of consistent data, GC can still represent a challenging diagnosis, and differential diagnosis needs to be considered [11, 12]; no consensus on the treatment approaches has been reached yet [13].

With these premises, we considered interesting to conduct a large retrospective analysis of mono-institutional GC cases. Specifically, we aimed to address (i) the clinical presentation, (ii) the brain magnetic resonance imaging (MRI) features, (iii) the histopathological and molecular characteristics of the tumors, and (iv) the identification of prognostic factors and eventually relation with early post-surgery death. The analysis was performed on the entire cohort and additionally on the exclusively histologically confirmed series (cohort b).

Material and methods

Clinico-radiological database

We present a retrospective database of 122 patients collected from January 2000 to December 2015 in our Institute Fondazione Irccs Istituto Neurologico Carlo Besta.

Following institutional review board approval, we retrospectively reviewed demographics, clinical presentation [including Karnofsky Performance Scale (KPS)], MRI findings, histopathological diagnosis, and management [including CT and radiotherapy (RT)] of all patients with newly diagnosed

primary GC [1]. Cases of secondary GC following progression of a preexisting tumor were excluded.

Following the probably GC diagnosis at brain MRI [3], the cases were selected by a neuro-oncologist (A.E.) and then independently reviewed by a neuro-radiologist (C.V.).

Radiological inclusion criteria were presurgical MRI including at least T2-weighted or fluid-attenuated inversion recovery (FLAIR) sequence suggestive for GC (i.e., showing diffuse infiltrative hyper-intensity involving at least three lobes with diffuse enlargement of anatomic structures) and contrast-enhanced T1 sequence.

GC was categorized as either having no discrete tumor mass (type 1, i.e., the classical form) or having a discrete mass in addition to extensive central nervous system (CNS) involvement (type 2) [14, 15].

Radiological information was gathered about primary tumor location, presence of mass effect, contrast enhancement (CE) presence and pattern (ring, nodular, patchy/smooth), dissemination, leptomeningeal spread, and hydrocephalus.

MR proton spectroscopy using Point RESolved Spectroscopy (PRESS) multivoxel technique was performed to enforce radiological diagnosis of glioma (as exemplified in Supplementary Fig. S1) [16], particularly in patients not scheduled for surgery.

In addition, we separately analyzed the group of patients with histological diagnosis of glioma ($n = 75$), which we named cohort b.

Histopathological and molecular studies

Histological diagnosis was reviewed and confirmed by a senior neuropathologist (P.B.) according to the 2016 WHO classification [1].

In those cases with an adequate amount of tissue, immunohistochemical analyses were performed using antibodies to ATRX, p53, IDH1(R132H), as well as to histone H3-K27M mutation (H3K27M), and histone H3-trimethyl-K27 (H3K27me3) in the tumors involving midline.

Immunohistochemical analyses were performed using a Dako Autostainer Link 48-automated immunostainer using EnVision FLEX visualization system kit (Dako-Agilent Technologies) as detection system, with diaminobenzidine as a chromogen (Liquid DAB Substrate Chromogen System, Dako-Agilent Technologies). Heat-induced epitope retrieval was performed in high or low pH buffer, as required.

Molecular analysis was performed in tumor samples obtained at diagnosis for patients where tissue was available.

DNA was extracted from Carnoy-fixed, paraffin-embedded (CFPE) tissue according to a standard phenol-chloroform protocol. Only tumor areas previously identified as neoplastic by hematoxylin and eosin staining were selected and drawn from paraffin blocks by a lancet.

Exon 4 of the *IDH1* gene was amplified with the use of a polymerase chain reaction (PCR), and the used primers were IDH1-For CAAGGATGCTGCAGAAGCTA and IDH1-Rev CATGCAAAATCACATTATTGCC. In all gliomas without an R132 *IDH1* mutation, exon 4 of the *IDH2* gene (which contains the *IDH2* residue R172 equivalent to R132 of *IDH1*) was sequenced and analyzed for somatic mutations, and the used primers were IDH2-For ATTTTAGGACCCCC GTCTGG and IDH2-Rev TGTGGCCTTGACTGCAGAG [17]. The sequences were separated by capillary electrophoresis using 3130 Genetic Analyzer (Applied Biosystems) and analyzed with Chromas Lite program (Technelysium DNA Sequencing Software 2.1.1).

Statistical analyses

Descriptive statistical analyses were used to summarize the demographic and clinico-radiological characteristics of the patients.

Overall survival (OS) was defined as the interval between the date of the radiological diagnosis and death. Perioperative mortality was defined as death within the first 30 days after surgery [17]. Patients who were alive were censored at the time of the last contact. To assess for associations with OS, two-sided log-rank tests were used for categorical variables. The associations between molecular markers and clinical-radiological variables were determined using the chi-squared test or Fisher test. The resulting *p* values were adjusted for multiple comparisons using Benjamini-Hochberg (B-H) procedure with false discovery rates (FDRs) of 0.05.

Results

Clinico-radiological data

We enrolled 122 patients; a subset of 75 underwent surgical resection and got histological diagnosis.

Median age was 53 years old (range 16–81). Mean follow-up was 22 months (1–147 months) (Table 1).

Clinical onset features were the following: headache (23.5%), seizures (35.6%), papilledema (4.3%), cortico-spinal signs (53%), cranial nerves (27.8%), alteration of level of consciousness (28.7%) and of cognitive function (40%), cerebellar signs (18.7%), and spinal signs (2.5%) (Fig. 1). More than one system could be involved at the onset.

Radiological features were studied by brain MRI with contrast medium. Detailed radiological characteristics were reported in Fig. 1. Besides others, CE was present in 63.3%, showing the following pattern: ring in 43.1%, nodular in 15.5%, and patchy/smooth in 41.4% of the cases. Examples of brain MRI are reported in Fig. 2.

Therapy included RT in 51.2% of patients [conformational RT 47.5% (38/80) and whole brain RT (WBRT) 3.75% (3/80) (*n* = 80)] and CT in 74.5% (79/106) (Table 1).

Outcome

Median OS was 17 months (CI 95%: 14–21 months), using Kaplan Meier analysis.

Median follow-up was 16 months (range 1–147).

Univariate analysis of clinical prognostic factors showed the older age and low KPS as significantly related to shorter OS. As for the age interval, we considered the traditional cutoff prognostic factor of age > 40 years old and > 65 years old, used respectively for lower-grade gliomas (LGG) and grade IV glioma [19]: Patients older than 40 years old and older than 65 years old had poorer outcome. In both cases, patients had a poorer outcome when compared to young olds: Patients older than 40 years old showed median OS of 16 months (95% CI: 11 to 19 months) versus 32 months (95% CI: 17–44 months) (*p* = 0.033); patients older than 65 years old showed median OS of 11 months (95% CI: 9 to 17 months) versus 18 months (95% CI: 15–27 months) (*p* = 0.0204). Related to performance status, both KPS ≥ 80 and KPS ≥ 70 were significantly related to better OS (median OS = 25 months versus 10 months, *p* = 0.0018; median 18 months versus OS = 9 months, *p* = 0.024, respectively).

Among radiological features, subtentorial localization was significantly related to worse prognosis (15 versus 21 months, *p* = 0.036), as well as midline location (15 versus 21 months, *p* = 0.036) and presence of dissemination (6 versus 17 months, *p* = 0.0010) (Fig. 3). Bilateral involvement, disease extension to 3 lobes or more, mass effect, cerebellar location, presence of contrast enhancement, and hydrocephalus at onset did not impact on OS at Kaplan Meier analysis.

Age ≥ 65 years old was associated with KPS < 80 (*p* = 0.0029, chi-squared test, after B-H adjustment *p* = 0.0041) and midline location with subtentorial (*p* = 0.0073, chi-squared test, after B-H adjustment *p* = 0.0041).

At multivariate analysis (cox proportional hazard regression) KPS ≥ 80, subtentorial location, dissemination, and CT remained significantly prognostic, showing relative risk 3.608 (95% CI, 1.991–6.538; *p* < 0.0001), 0.4893 (95% CI, 0.2769–0.8644; *p* = 0.0138), 0.3463 (95% CI, 0.1405–0.8540; *p* = 0.0213), and 3.499 (95% CI, 1.3106–9.3434; *p* = 0.0124), respectively. In contrast, no independent positive association with class of age (both age ≥ 65 years old and age ≥ 40) and midline was identified.

Cohort b (histological-proven GC cohort)

Among the 122 patients, 75 patients underwent surgical resection or biopsy and got histological diagnosis. Patient

Table 1 Demographic, clinical, and therapeutic features of gliomatosis cerebri (GC) patients (entire cohort)

Demographic and clinical variables	N (%)
Sex (N = 122)	
Male	91 (74.6)
Female	31 (47.4)
Median age at diagnosis, years (N = 122)	53 (95% CI, 46–57)
Age group (years)	
0–39	32 (26.2)
40–64	62 (50.8)
> 65	28 (22.9)
Mean follow-up, months (N = 122)	
Median Karnofsky Performance Score (KPS) at diagnosis (N = 74)	80 (95% CI: 70–80)
KPS < 70	15 (12.9)
KPS = 70	16 (13.1)
KPS > 70	44 (36.1)
Adjuvant therapy	
Radiotherapy (N = 80)	41 (51.2)
Chemotherapy (N = 106)	79 (74.5)
Median overall survival (months) (N = 122)	17 (95% CI: 14–21 months)

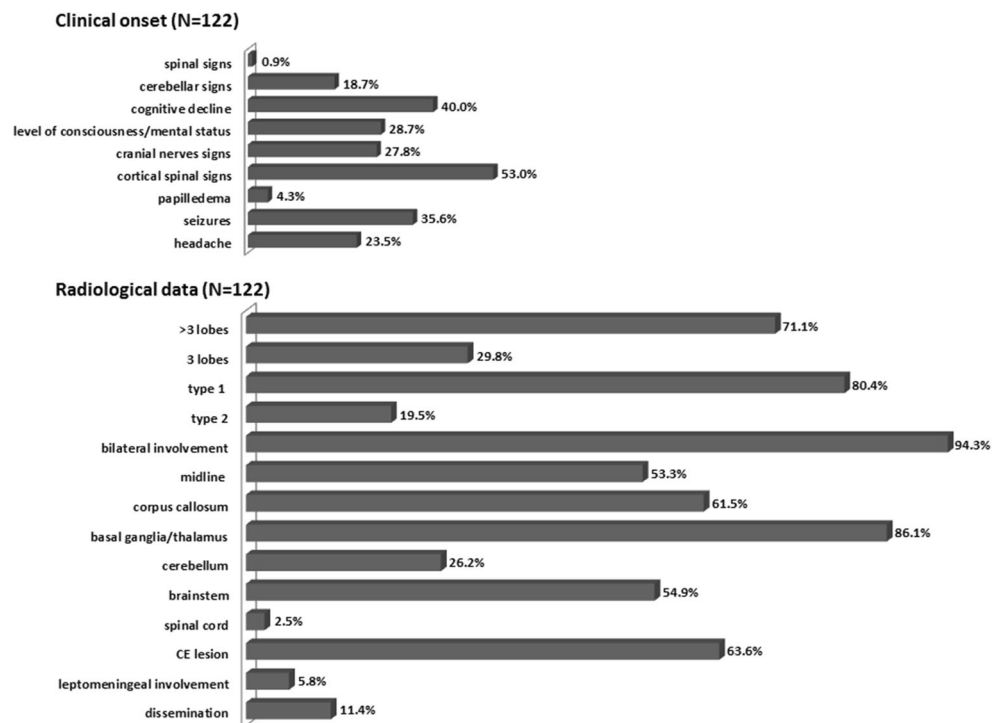
characteristics of cohort b, including histological and molecular data, are shown in Table 2.

Clinico-radiological data

Median age was 48 years old (range 42–54). Mean follow-up was 23.51 months (1–144 months).

Clinical onset features were the following: headache (19.4%), seizures (38.8%), papilledema (6%), cortico-spinal signs (45.0%), cranial nerves (25.0%), alteration of level of consciousness (21%) and of cognitive function (36.0%), cerebellar signs (13.0%), and spinal signs (0%) (Supplementary Fig. S2). More than one system could be involved at the onset.

Radiological features were studied by brain MRI with CE. Detailed radiological characteristics were reported in

Fig. 1 Detailed clinical onset (top) and radiological (bottom) data are reported

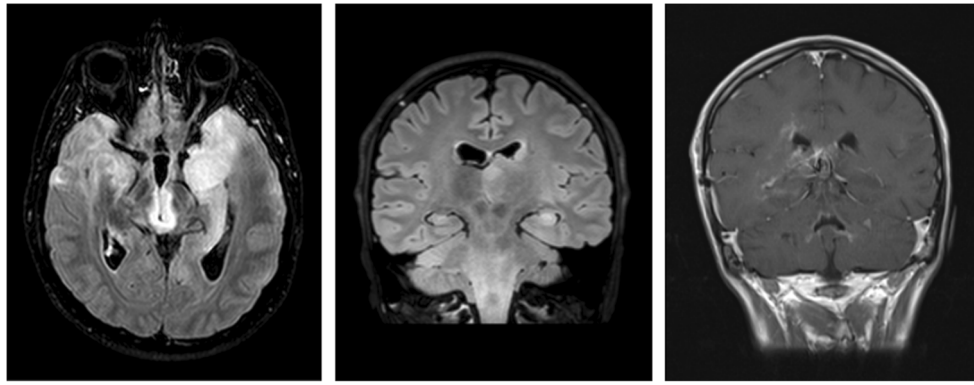


Fig. 2 MRI showing examples of GC extension. (Left to right) (i) Subtentorial localization (tumoral lesion extended from bulb and pons to left cerebellar peduncle, left hippocampus, and left striatum and thalamus at coronal FLAIR showing), (ii) midline involvement (parenchymal lesion hyperintense in axial T2-weighted in midline and subtentorial, right temporal and left fronto-temporal-insular, with no mass effect),

and (iii) signs of dissemination and leptomeningeal enhancement at post-contrast enhancement T1 axial imaging included ring areas in the left frontal within an extended parenchymal lesion involving bilateral midline lesion and bilateral frontal and midline. Features associated to outcome are reported (left-right): midline involvement and subtentorial localization (FLAIR) and dissemination (contrast-enhanced T1 w.i.)

Supplementary Fig. S2. Besides others, CE was present in 74.55%, showing the following pattern: It was ring in

36.36%, nodular in 14.55%, and patchy/smooth in 23.64% of the cases.

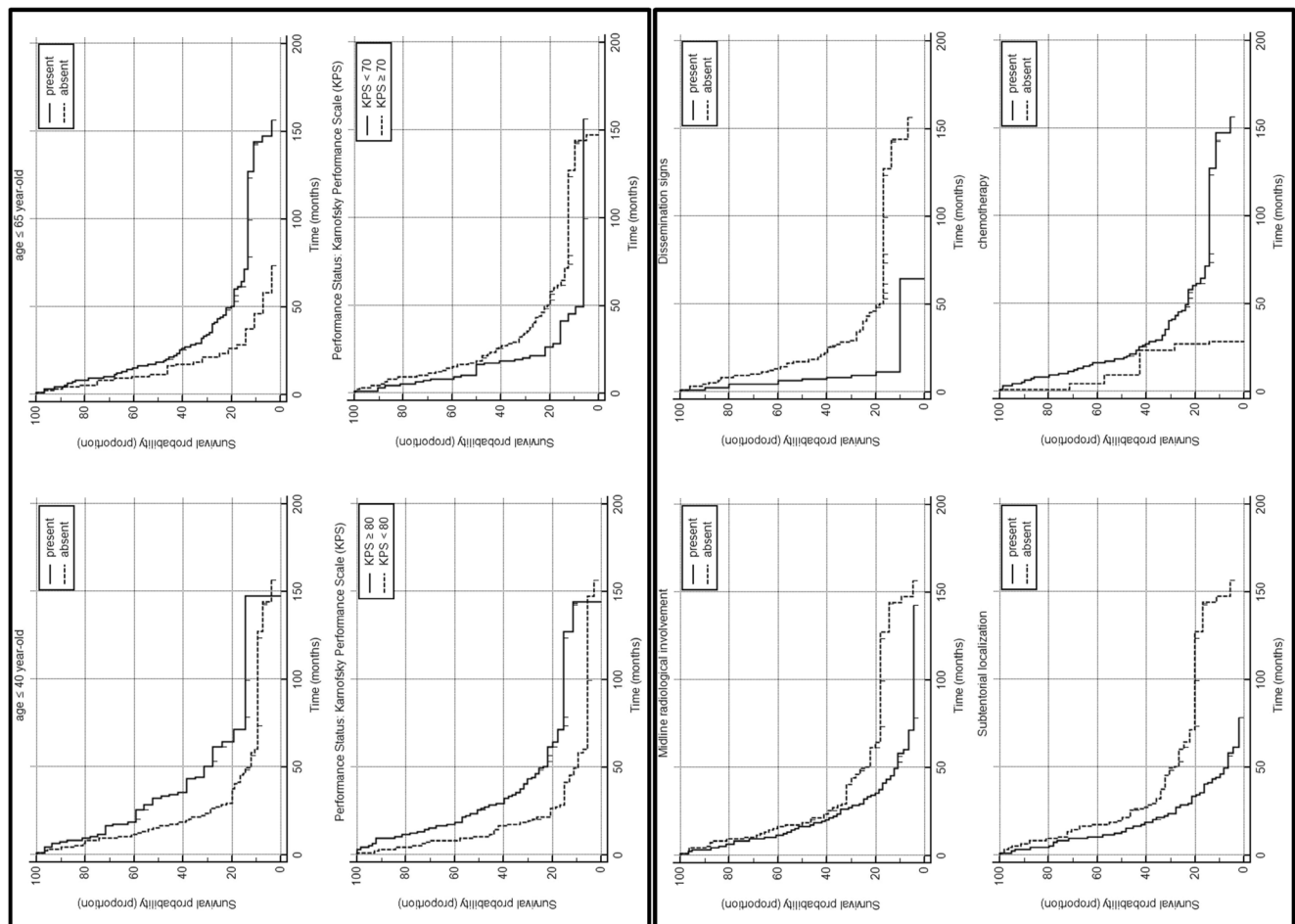


Fig.3 Kaplan Meier curves that resulted statistically significant are reported for the entire cohort. The top frame includes clinical features and the bottom frame incorporates radiological and therapeutic prognostic factors

Table 2 Demographic, clinical, and histomolecular features of gliomatosis cerebri (GC) patients (cohort b)

Demographic and clinical variables	N (%)
Sex (N = 75)	
Male	46 (61.3)
Female	29 (38.7)
Median age at diagnosis, years (N = 75)	48 (95% CI: 42–54)
Age group (years)	
0–39	22 (29.3)
40–64	42 (56.0)
> 65	10 (13.3)
Mean follow-up, months (N = 55)	15.1 (27.5)
Median Karnofsky Performance Score (KPS) at diagnosis (N = 75)	80 (95% CI: 70–80)
KPS < 70	15 (20.0)
KPS = 70	16 (21.3)
KPS > 70	44 (58.7)
Adjuvant therapy	
Radiotherapy (N = 47)	26 (55.3)
Chemotherapy (N = 70)	43 (61.4)
Surgery (N = 75)	
Partial exeresis	24 (32.0)
Open biopsy	21 (28.4)
Stereotactic biopsy	29 (39.2)
Histological diagnosis (N = 75)	
Grade	
II	23 (27.8)
III	26 (34.6)
IV	16 (21.3)
High grade	2 (2.7)
Not other specified	8 (10.6)
Subtype	
Oligodendroglial	5 (6.7)
Astrocytic	54 (72.0)
Glioblastoma	13 (17.3)
Glioblastoma with giant cell component	3 (4.0)
Molecular data	
IDH1 mutation (N = 36)	11 (30.5)
p53 IHC (N = 41)	19 (46.3)
ATRX staining (N = 25)	15 (60.0)
trimH3 IHC (N = 13)	13 (100.0)
H3K27M IHC (N = 13)	0 (0)
Median overall survival (months) (N = 75)	17 (95% CI: 13–27 months)

Radiological features confirmed to be not significantly different in cohort b compared to the largest cohort including also the radiologically diagnosed lesions.

Perioperative mortality

Thirty-days postsurgical mortality [17] occurred in 4% (3/75); for all of them, open biopsy approaches had been used. These patients exhibited GC involving basal ganglia/thalamus in 2/3 cases and subtentorial regions in 2 cases (one with involvement of both brainstem and cerebellum, the other only brainstem). Reasons for death were brain edema ($n = 2$), including one with development of fatal sepsis and unknown ($n = 1$, occurred after discharge). Factors significantly related to peri-surgical death were hydrocephalus ($p = 0.0297$, chi-squared test) and KPS < 80 ($p = 0.0354$, chi-squared test). After the B-H adjustment, the associations resulted not significant.

Histopathological and molecular data

Histology was available in all of the 75 cases who underwent surgery for partial exeresis (32%, $n = 24$ cases), open biopsy (28%, $n = 21$ cases), or stereotactic biopsy (38.6%, $n = 29$ cases). Grade II glioma was diagnosed in 27.8% ($n = 23$) cases, grade III in 34.6% ($n = 26$) cases, grade IV in 21.3% ($n = 16$) cases, and not-otherwise-specified high grade in 2.7% ($n = 2$) cases (Supplementary Figure S3); the remaining cases ($n = 8$) were ill-defined. An oligodendroglial component was described in 5 cases. In relation to disease extension and grade, we reported that 18% ($n = 3/16$) of grade IV GC had cerebellar involvement.

Immunohistochemical analysis for IDH1(R132H) mutation was performed in 36 cases and found present in 11 (30.5%): six grade II, four grade III, and one grade IV gliomas. IDHwt gliomas were mainly grade III and IV.

Nuclear expression of p53 at immunohistochemistry was detected in 19 out of 41 cases.

ATRX immunostaining was tested in 25 cases, and loss of expression was observed in 10 cases.

Thirteen midline cases were also investigated for H3-K27M and H3K27me3: They respectively resulted negative and positive in all the cases; three of them showed IDH1 mutation. H3-K27M mutation is mutually exclusive of IDH1 mutation. No GC with midline extension showed H3-K27M mutation.

Therapy included RT [(conformational 53%, 25/47 ($n = 47$), WBRT 2.1% (1/47)] and CT 61.4% (43/70).

Outcome

Median OS was 17 months (CI 95%, 12.5–25.5 months), using Kaplan Meier analysis.

Median follow-up was 16 months (range 1–144).

Univariate analysis of clinical prognostic factors showed the older age and low KPS as significantly related to shorter OS. Patients older than 65 years old had poorer outcome,

showing median OS of 8 months (95% CI: 4 to 17 months) versus 18 months (95% CI: 15–29 months) ($p = 0.036$). Related to performance status, both $KPS \geq 80$ and $KPS \geq 70$ were significantly related to better OS (median OS = 28 months versus 9 months, $p = 0.0049$; median OS = 19 months versus OS = 9 months, $p = 0.0158$, respectively).

Among radiological features, subtentorial localization was significantly related to worse prognosis (13 versus 17 months, $p = 0.047$) and presence of dissemination (6 versus 17 months, $p = 0.0082$) (Supplementary Fig. S3). Bilateral involvement, disease extension to 3 lobes or more, mass effect, midline, cerebellar location, presence of contrast enhancement, and hydrocephalus at onset did not impact on OS at Kaplan Meier analysis.

Histological grading (grade II versus higher grade or lower grade versus grade IV) did not significantly relate to prognosis at Kaplan Meier analysis: In particular, median OS is 22 months (95% CI: 17 to 54 months) in grade II versus 16 months (95% CI: 9–27 months) in higher grade ($p = 0.1098$), and median OS was 19 months (95% CI: 16 to 29 months) in lower grade versus 9 months (95% CI: 8–18 months) in grade IV ($p = 0.133$); median OS was 22 months (95% CI: 17–54 months) in grade II versus 12 months (95% CI: 9–28 months) in grade IV ($p = 0.1490$). In grade III glioma patients, median OS was 17 months (95% CI: 9–28 months).

Prognostic correlations depending on the treatment modalities including biopsy or partial tumor resection with or without RT or CT were further investigated. Based on limited available data, we found no relation between surgical type approach and OS, neither with RT. CT is the only treatment that positively impact OS ($p = 0.0023$).

Age ≥ 65 years old was associated with $KPS < 80$ ($p = 0.0081$, chi-squared test, after B-H adjustment $p = 0.0047$) and brainstem ($p = 0.0477$, chi-squared test, after B-H adjustment $p = 0.0083$) and midline location with grade II ($p = 0.0046$, chi-squared test after B-H adjustment $p = 0.0083$).

The curves regarding features associated to outcome in cohort b are displayed in Supplementary Fig. S4.

No specific molecular signature resulted related to longer OS by linear regression analysis (including IDH1 mutation, ATRX, p53).

At multivariate analysis (cox proportional hazard regression), $KPS \geq 80$ and CT remained still significantly prognostic ($p < 0.0001$), showing relative risk 3.172 (95% CI, 1.483–6.787; $p = 0.0029$), 5.2586 (95% CI, 1.6753–16.506; $p = 0.0045$), respectively. By contrast, there is no independent positive association with age ≥ 65 years old neither radiological features.

Discussion

The incidence of GC is very low, ranging around 4 ‰ [13], overall age-adjusted incidence rates (AIR) increased to 0.15 cases/million individuals [18].

We retrospectively described a very large patient cohort affected by GC, based on radiological features (entire cohort). Previous data [18] did not show difference in OS between GC diagnoses by histopathology versus clinical/radiological assessment. Besides that, to outmost exclude any bias due to differential diagnosis, we also sub-analyzed the cohort of patients with histological confirmation of GC (cohort b).

Our demographic and clinical features grossly confirmed what previously reported [6, 7]. The median age at diagnosis was 53 years; common clinical signs included cortico-spinal tract, sensory-motor deficits, spinocerebellar, headache, seizures, cranial neuropathies, and papilledema [19].

Overall survival was 17 months [12, 15] with no significant difference based on histological grade subgroups; anyway, if we compared with appropriate restriction median OS of grade II GC (22 months, ranging from 17 to 54 months) and grade III GC (17 months, ranging from 9 to 28 months), it resulted shorter than less extended gliomas [ranging from 2.2 to more than 12.5 years (median 11.3 years) for grade II [20] and from 30 months to 92 months for grade III, respectively [21]].

About radiological characteristics, the categorization in type 1 and 2 GC resulted into 80.45% and 19.55%, respectively. We detected higher frequency of subtentorial involvement and bilateral extension than others [2]. We also included specific parameters such as the midline location and the dissemination pattern, never specifically addressed in the previous papers.

In our series, 18% ($n = 3/16$) of grade IV GC had cerebellar involvement, much more frequent than prevalence of cerebellar glioblastoma (GBM) [22]; probably due to the small sample, no prognostic role of cerebellar localization was described in our GC setting, at variance to cerebellar GBM [23].

Due to differential diagnosis and to preliminary data about improved outcome after surgical resection, surgical approach can be indicated [8]. In particular, when patients are symptomatic due to edema and mass effect, partial resection can be done with an aim of tumor debulking [24]. Surgery was not performed in high-risk patients (older age, poor clinical condition, significant comorbidity, deep-seated/eloquent tumor locations) or if the patient refuses the procedure. Perioperative morbidity of microsurgical glioma resection has been reported to be highly variable, currently lying in the range of 5–20% or even higher [25]. Biopsy procedures can be considered in high-risk patients, traditionally reporting much lower risk in glioma setting, especially in experienced hands [25]. However, in our series, surgical procedure resulted in 30-day death in 4%, due to intracranial hypertension and sepsis. Such proportion is higher than what is reported for glioma surgery [17, 26], even if in a subtentorial localization [27, 28], and should be considered before surgical decision. Histological data confirmed as previously the range from traditionally grade II to IV glioma at morphological analysis [29]. Other molecular markers as IDH1, ATRX, and H3K27

were addressed but limited to a small number of samples (due to low availability), with no conclusive results on specific molecular pattern neither prognostic role. To notice, the midline samples analyzed for H3K27M showed no mutation, diverging from midline glioma [30].

Besides descriptive analysis, the goal of the work was to identify factors that may help to predict outcome and treatment.

Our data confirmed that more advanced age and KPS < 80 are associated to short OS, in both entire and histological (cohort b) cohorts. This finding holds true even in a multivariate analysis, including radiological covariates as mentioned above [8].

Histological grade showed no impact on OS, as reported by some authors [8, 10]. Such data could also be the expression of the large heterogeneity of glioma type tumor as well as the influence of the sampling site [31, 32].

About radiological parameters, midline location and the dissemination pattern resulted negative prognostic factors (at univariate and multivariate analysis), as well as the subtentorial localization, which was previously contrastingly reported as not relevant or negatively impacting on the outcome [8]. Restricting the analysis on cohort b, midline location lost prognostic significance, probably due to the sample numerosness. Dissemination in GBM is reported in 8% [33], but at lower frequency in lower-grade glioma and typically in pediatric population [34]. The knowledge of biological features that favor leptomeningeal dissemination is minimal, including some molecular risk factors including PTEN [35] and ANXA 2 [36] and the contribution of surgical ventricular entry or tracts [37, 38]. The observations of poorer outcome in GC extended to specific brain areas can further be the expression of subtypes, as recently characterized for midline gliomas and cerebellar GBM [24, 30], and these data suggest to address this pattern with specific interest.

Main limits of the study are the following: first, the retrospective analysis, in a long interval; second, the inclusion of both radiological and histological cases and the lack of suitable tissue for more detailed molecular analysis in many samples; and third, the inclusion of patients treated with different modalities, than can have different impact on OS (based on that, we consider not reliable to assess the effect of the different CT/RT treatment options and combinations on outcome).

GC has historically been treated heterogeneously, making it difficult to draw conclusions regarding its optimal management. Given the diffuse involvement of the brain, surgery plays only a limited role. There is no standard guideline for surgery and the extent of surgical resection in GC. A previous study has reported that any survival benefit is not provided between partial resection and biopsy in 30 GC patients [39]. Thus, RT and CT have emerged as the primary treatment modalities of patients with GC. Except for Glas et al. (2011) [9], all other GC studies are retrospective series. In the last years,

adjuvant CT has been used to delay radiation-related neurotoxicity [12, 15]: in our Institute, we use as standard of care first line CT in younger and good-performer patients. ANOCEF reported no significant difference between PCV (Procarbazine CCNU Vincristine)-treated and temozolomide (TMZ)-treated patients in either progression-free survival (PFS) (15.8 versus 16 months) or OS (25.6 versus 26.4 months) [8].

We documented longer outcome in patients treated with CT versus RT or no therapy. However, such data are only descriptive and retrospective and includes different drugs, and it cannot be translated as mandatory indication. Anyway, it is consistent with a recent systematic review that reported an outcome benefit after CT and surgical resection and not higher response after RT, whether monotherapy or combined with CT, compared to CT alone [2]. Others did not confirm such data [3].

However, we cannot exclude the possibility that improved survival in patients with GC-receiving CT is secondary to patient selection bias or that the effect is driven by improvements in overall treatment and not to CT.

There is no standard treatment for GC [2], and the therapeutic choice should be tailored to the patient characteristics. To our knowledge, very few ongoing trials specifically include adult GC as disease to treat (NCT03173950; NCT03243461; NCT02758366).

Despite the described limitations with the present work, our effort was to identify valuable characteristics of a rare tumor such as GC, moving toward a deeper comprehension of such entity and potentially targeted therapy. If GC will be identified as something different from a “straightforward” radiological pattern of glioma but an entity characterized by infiltrative spread and aggressive clinical course, we should consider the definition of GC instead of the current “GC-like” term.

Going forward, firstly, a more complete understanding of GC will benefit from large molecular assay (i.e., whole exome or perhaps epigenetic analyses) rather than targeted sequencing. Centralization of data due to its rarity and distribution of information regarding GC is key to making progress and promoting awareness with the goal of early diagnosis.

Second, considering the lack of large prospective studies and the inconsistency of correlative molecular data so far, next step will be a prospective study to analyze the efficacy of primary chemotherapy in patients with GC and to define clinical, imaging by specific criteria, and molecular factors influencing outcome.

Conclusions

This study suggests that the question as to whether GC is a distinct disease entity or a distinctive phenotype of diffuse glioma remains subject of debate, as well as the question if

specific GC subtypes (as subtentorial and midline) do exist. Additional molecular investigations are needed, and cooperation among institutes is strongly requested, due to extreme rarity of the disease.

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Data accessibility The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval None.

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