Clinical Neurology and Neurosurgery xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Demographic, radiographic, molecular and clinical characteristics of primary gliosarcoma and differences to glioblastoma

Daniela Pierscianek [a,e,*], Yahya Ahmadipour [a,e], Anna Michel [a,e], Laurèl Rauschenbach [a,e], Marvin Darkwah Oppong [a,e], Cornelius Deuschl [d,e], Sied Kebir [b,e], Karsten H. Wrede [a,e], Martin Glas [b,e], Martin Stuschke [c,e], Ulrich Sure [a,e], Ramazan Jabbarli [a,e]

[a] Department of Neurosurgery and Spine Surgery, University Hospital Essen, University of Duisburg-Essen, Essen, Germany
[b] Division of Clinical Neurooncology, Department of Neurology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany
[c] Department of Radiotherapy, University Hospital Essen, University of Duisburg-Essen, Essen, Germany
[d] Institute for Diagnostic and Interventional Radiology and Neuroradiology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany
[e] German Cancer Consortium, Partner Site University Hospital Essen, Essen, Germany

ARTICLE INFO

Keywords:
Gliosarcoma
Glioblastoma
Temporal lobe
Tumor cysts
Survival

ABSTRACT

Objective: Gliosarcoma (GSC) is a rare histological variant of glioblastoma (GBM). Due to limited evidence regarding clinical, genetic and radiographic characteristics of GSC, this study aimed to analyze independent outcome predictors of GSC, and to address the differences between GSC and GBM concerning the baseline characteristics and patients' survival.

Methods: Patients treated between 2001 and 2018 for the diagnosis of GBM and GSC were included in this study. Patients' records were reviewed for demographic, clinical, genetic and radiographic characteristics. Univariate, multivariate and propensity score matched analyses were performed.

Results: In the GSC sub-cohort (N = 56), patients' age, preoperative clinical status, midline tumor location and tumor size were found to be independently associated with overall survival. As compared to GBM individuals (N = 1249), a temporal location (p = 0.002), presence of eccentric tumor cysts (p < 0.001), a higher ratio of TP53 staining (p = 0.002) and a lower ratio of GFAP staining (p = 0.005) were characteristic for GSC. The diagnosis of GSC was associated with a poorer survival (p = 0.002) independently of the patients' age, sex, clinical status and extent of resection, However, this association was no more significant, when enhancing the multivariate analysis with molecular-genetic characteristics (IDH1 mutation and MGMT promotor methylation status).

Discussion: Certain radiographic and molecular-genetic patterns present the distinct characteristics of GSC. There is an association between the diagnosis of GSC and a poorer outcome. This difference might be linked to different genetic alterations in GBM and GSC. Prospective studies are needed to further elucidate the characteristics of GSC and develop targeted treatment approaches for this rare variant.

1. Introduction

Primary gliosarcoma (GSC) is a rare histopathological variant of glioblastoma (GBM) and accounts for approximately 2% of all GBM [1,2]. As the diagnosis of GSC is scarce, its biological and clinical characteristics, as well as potential differences to GBM are only rarely investigated. Despite two distinct histopathological patterns with mesenchymal and glial differentiation in GSC, genetic studies indicate a monoclonal origin [3]. According to several studies, GSC are frequently harboring telomerase reverse transcriptase promotor mutations [4], whereas O6-Methylguanine DNA Methyltransferase (MGMT) promotor methylation is observed with a lower frequency compared to GBM [4–6]. The treatment strategy for GSC is the same as for GBM and consists of a multimodal approach with initial surgery followed by postoperative radio- and chemotherapy (RTX, CTX) [1].

Regarding the prognosis of GSC, there is ambiguous evidence. Whereas some studies did not detect significant differences in survival between GBM and GSC [6,7], others described a worse prognosis for GSC

* Corresponding author at: Department of Neurosurgery, University Hospital Essen, D-45147 Essen, Germany.
E-mail address: daniela.pierscianek@uk-essen.de (D. Pierscianek).

https://doi.org/10.1016/j.clineuro.2020.106348
Received 9 June 2020; Received in revised form 12 October 2020; Accepted 27 October 2020
Available online 1 November 2020

[8–10]. In this context, specific tumor characteristics contributing to distinct survival patterns of GSC and GBM patients require further elucidation.

This study aimed to assess the demographic, radiographic, molecular and clinical characteristics of GSC, with special emphasis on potential differences to GBM in a large institutional observational cohort.

2. Patients and Methods

2.1. Study population

In this retrospective longitudinal cohort study, all consecutive patients that were treated for primary GSC and GBM between 2001 and 2018 were eligible for inclusion. GBM cases with later transformation to secondary GSC (n = 10) were excluded from the study. Patients were treated with microsurgical tumor resection or biopsy followed by postoperative RTX and CTX. The study was approved by Institutional Ethics Committee.

2.2. Data management

Medical records were reviewed for patients' age at diagnosis, sex, pre- and postoperative clinical condition (Karnofsky Performance Scale, KPS), treatment modalities (microsurgical tumor resection, biopsy, RTX, CTX) and outcome variables (overall survival (OS), 1-year survival (1-YS), 2-years survival (2-YS)). Histological evaluation included the identification of genetic alterations (methylation status of the MGMT gene promotor and mutational status of the isocitrate dehydrogenase gene 1 (IDH1)), Ki67 protein (Ki67) proliferation index, tumor protein 53 (TP53) and glial fibrillary acidic protein (GFAP) staining, as reported previously [11]. The preoperative magnetic resonance imaging (MRI) was reviewed by the senior author (RJ) with regard to the following radiographic variables: anatomic location, presence of eccentric cysts, the presence of intralesional necrosis, maximal tumor diameter, presence of multiple contrast-enhancing foci, and contact to skull base dura. The quantitative measurement of tumor diameter was performed upon the largest extension of the lesion in the axial, sagittal and coronary planes, using the Centricity Enterprise Web software (Version 3.0, GE Medical Systems, Chicago, IL, USA).

The study goals were: a) identification of outcome predictors of GSC; b) analysis of the differences between GSC and GBM patients concerning the baseline characteristics; c) survival comparison with elucidation of tumor features contributing to distinct survival patterns.

2.3. Statistical analysis

All assessed variables were investigated in univariate and multivariate analyses. Categorical data were analyzed using two-sided fisher's exact test. Continuous variables were investigated using the Mann-Whitney U test and Kruskal-Wallis test (for not normal distributed data) or students' t-test (for normally distributed data). For analysis of a linear dependence, the Pearson correlation coefficient was applied. Patients' and tumor characteristics that reached a *P*-value of $\leq$ 0.1 in univariate analysis, were included in multivariate analysis. Missing data were replaced using multiple imputation. For comparison of radiographic characteristics between GSC and GBM, propensity score matched analyses were performed with a 1:2 matching upon age, sex and tumor location. Statistical analysis was performed using SPSS (version 26, SPSS Inc., IBM, Chicago IL, USA) and PRISM (version 5.0, GraphPad Software Inc., San Diego, CA, USA). Differences with a *P* value $\leq$ 0.05 were considered statistically significant.

3. Results

3.1. GSC cohort: population characteristics

The GSC cohort comprised 56 patients. The median age was 61.6 years (range 19.2 – 84.7). GSC showed a male predominance (N = 40; 71.4%). In this cohort, 9 (27.3%) patients demonstrated MGMT promotor methylation and all patients were wild-type for the IDH1 gene. Analysis of the radiographic characteristics of GCS revealed a median tumor diameter of 44 mm (range 8 – 88). There was no cystic formation in 33 tumors (63.4%) and no necrosis in only 5 tumors (9.6%). Multifocal tumors were detected in 29.6% of patients. 15 tumors presented with contact to the dura of the skull base (28.3%). The clinical and radiographic characteristics of GSC are summarized in Table 1.

3.2. GSC cohort: outcome predictors

There was a linear correlation between patients' age and OS in our cohort of GSC patients ($p < 0.001$; Pearson r coefficient -0.5695). Patients with a poor preoperative condition (KPS $\leq$ 70%) had a significantly shorter median OS (3.9 months [range 0.1 – 13.5] vs. 8.2 months [range 1.0 – 25.7], $p = 0.003$). The remaining results of univariate analysis, that did not reach statistical significance are shown in Supplemental Table S1.

In the multivariate analysis, OS of GSC individuals was independently associated with patients' age (unstandardized coefficient [UC]: -0.228 [95% CI: -0.328– -0.128], $p < 0.001$), preoperative KPS $\leq$ 70% (UC: -3.545 [95% CI: -6.112 – -0.978], $p = 0.007$), midline tumor location (UC: -5.516 [95% CI: -10.593 – -0.44], $p = 0.033$) and tumor size (UC: -0.125 [95% CI: -0.205 – -0.044], $p = 0.002$). Multifocality and adjuvant treatment (combined RTX + CTX vs. RTX) were not predictive for OS in GSC individuals.

3.3. Comparison of clinical characteristics between GSC and GBM cohorts

Baseline characteristics of 56 GSC patients and 1249 GBM patients were addressed in the univariate analysis (Table 2). Regarding the patients' age, we did not find a significant difference (61.6 years [range 19.2 – 84.7] vs. 63.8 years [range 19.8 – 91.5] for GSC and GBM respectively, hereinafter; $p = 0.139$). There was a male predominance in the GSC group compared to GBM individuals (71.4% vs. 59.6%, $p = 0.094$). There was no significant difference between the GSC and GBM groups regarding the proportion of patients in a poor preoperative clinical status (KPS $\leq$ 70%, GSC 33.9% vs. GBM 28.7%, $p = 0.441$). Patients with GSC showed more frequently a temporal tumor location (44.6% vs. 26.4%; $p = 0.005$) and were more often treated with microsurgical resection (N = 50; 89.3%) compared to GBM patients

Table 1
Clinical and radiographic characteristics of GSC. Preoperative MR imaging was available for evaluation in 52 of 56 individuals. For the remaining cases, the exact tumor location (n = 4), the presence of multifocal tumors (n = 2), contact to the skull base (n = 1) were identified upon the original radiographic reports.

	Number (%) or median (range)
Age (years)	61.5 (19.2 – 84.67)
Sex (male)	40 (71.4%)
Biopsy	6 (10.7%)
Temporal location	25 (44.6 %)
Tumor size (mm)	44 (8 – 88)
Cystic formation	19 (36.5%)
Necrosis	47 (90.4%)
Multifocal tumors	16 (29.6 %)
Contact to skull base	15 (28.3 %)
OS (months)	6.03 (0.13 – 25.7)

Abbreviations: OS: overall survival.

Table 2
Univariate analysis for comparison of clinical characteristics of GSC and GBM.

Parameter	OR [95% CI] or median value (range) for GSC vs. GBM	P-value
Age (continuous, years)	61.6 (19.2 – 84.7) vs. 63.8 (19.8 – 91.5)	0.179
Sex (female)	0.59 [95% CI: 0.33 – 1.06]	0.094
EOR (biopsy)	0.25 [95% CI: 0.11 – 0.58]	<0.001
Tumor location:	2.27 [95% CI: 1.32 – 3.91]	0.005
- temporal - midline	0.50 [95% CI: 0.18 – 1.39]	0.225
KPS (≤70%)	1.27 [95% CI: 0.71 – 2.28]	0.441
GFAP staining (%)	60 (2 – 90) vs. 70 (3 – 100)	0.097
P53 staining (%)	15 (0 – 90) vs. 5 (0 – 100)	0.014
ki67 (%)	20 (3 – 70) vs. 15 (2 – 70)	0.096
MGMT methylation	0.60 [95% CI: 0.27 – 1.32]	0.263
Postoperative treatment:	1.37 [95% CI: 0.60 – 3.13]	0.565
- RTX - RTX + CTX	1.09 [95% CI: 0.59 – 1.99]	0.879

Abbreviations: GSC: gliosarcoma; GBM: glioblastoma; EOR: extent of resection; KPS: Karnofsky Performance Scale; GFAP: glial fibrillary acidic protein, TP53: tumor protein p53; ki67 index: antigen Ki-67 protein; MGMT: O6-methylguanine DNA methyltransferase promotor; RTX: postoperative radiotherapy; CTX: postoperative chemotherapy.

(N = 840, 67.3%; p < 0.001).

In the subsequent multivariate analysis, a temporal tumor location (adjusted odds ratio [aOR] = 2.67 [95% CI: 1.44 – 4.95]; p = 0.002), a lower expression of GFAP (aOR = 0.98 [95% CI: 0.97 – 0.99]; p = 0.005) and higher ratio of TP53 staining (aOR = 1.03 [95% CI: 1.01 – 1.04]; p = 0.002) were independently associated with GSC diagnosis.

Finally, a propensity score matched analysis was carried out for the comparison of the radiographic characteristics of GSC and GBM patients. In this analysis adjusted for the patients' age, sex and tumor location (Supplemental Table S2), only the presence of eccentric cysts was found more characteristics for GSC than for GBM (GSC 34.7% vs. 6.6%; p < 0.001) (Table 3, Fig. 1).

3.4. Comparison of clinical outcome in GSC and GBM

OS was shorter in GSC patients, but did not differ significantly in comparison to GBM patients (median 6.0 [range 0.13 – 25.7] vs. 8.6 [range 0 – 144.9] months, p = 0.159). Also, for 1-YS and 2-YS, there was no difference between GSC and GBM patients (OR = 0.93 [95% CI: 0.53 – 1.63] p = 0.89 and OR = 0.84 [95% CI: 0.35 – 2.01] p = 0.836), respectively. In the Kaplan Meier survival analysis (Fig. 2), log-rank test revealed a significant difference between GSC and GBM (p = 0.017) with a shorter survival for patients with GSC.

To adjust the association between the diagnosis of GSC and patients' survival with regard to the common outcome confounders, we performed two models of multivariate analysis. Accordingly, the histological diagnosis of GSC was associated with OS (p = 0.004), 1-YS (p = 0.008) and 2-YS (p = 0.043) independently of the patients' age, sex, preoperative KPS, EOR and postoperative treatment (Supplemental Table S3). However, in the multivariate analysis enhanced with the molecular genetic-tumor characteristics (IDH1 mutation status und MGMT promotor methylation status), histological diagnosis of GSC was not independently associated with poorer OS, 1-YS and 2-YS (see Supplemental Table S4).

Table 3
Matched-paired analysis of radiographic parameters in GSC and GBM.

Parameter	OR [95% CI] or median value (range)	P-value
Presence of eccentric cyst	7.51 [95% CI: 2.86 – 19.75]	<0.001
Presence of intra-lesional necrosis	1.04 [95% CI: 0.30 – 3.57]	1.000
Multifocal lesion	1.00 [95% CI: 0.49 – 2.04]	1.000
Maximal diameter (mm)	44 (8 – 88) vs. 43 (5 – 86.5)	0.635
Skull base contact	1.12 [95% CI: 0.53 – 2.38]	0.847

Abbreviations: GSC: gliosarcoma; GBM: glioblastoma; ; OR: odds ratio; CI: Confidence Interval.

4. Discussion

4.1. Clinical and radiographic characteristics of GSC

During the study period, 56 patients with histological diagnosis of GSC were treated in this institution. A higher patients' age, a poor preoperative clinical status, a larger tumor diameter and also a tumor location involving midline or infratentorial structures were independently associated with a shorter OS in the GSC cohort. Age and clinical performance are well-known factors for survival in GSC as also in GBM [12,13]. In this study, EOR was not found to be a prognostic factor for GSC cohort. This finding is conflicting with strong evidence from GBM studies showing the relevant impact of EOR on patients' prognosis [14,15]. This discrepancy might be due to the small sample size of GSC patients in this study. Furthermore, combined RTX/CTX was not found to be independently associated with GSC prognosis. Again, this finding might be related to the small sample size, but another explanation is the lower rate of MGMT promotor methylation in GSC (27.3% GSC vs. 38.6% GBM). Several studies also reported lower rates of MGMT promotor methylation [6,10,16] in GSC. This difference between GSC and GBM might entail a poorer response of GSC to combined CTX/RTX with the alkylating agent temozolomide and should provoke further research on targeted therapies for GSC.

4.2. GSC vs GBM: Where do the differences lie?

Regarding clinical characteristics, age, sex and the preoperative clinical status did not differ between both groups. The location of the tumor in the temporal lobe and microsurgical resection (vs. biopsy) were more common in the GSC cohort. One recent study comparing patients with GSC and GBM found also a temporal lobe predilection and a less conservative resection rate in patients with GSC [17], which is well in line with other recent studies [6,18]. Our study confirmed these results and even found both characteristics to be independently associated with GSC diagnosis in multivariate analysis. The higher rate of resection compared to biopsy in GSC patients might partly be influenced by tumor location. In contrast to tumors infiltrating for example midline structures, for temporal tumors at least a subtotal resection might be feasible. Another argument for the higher rate of microsurgical resection in the GSC cohort is the possibility of misdiagnosis between GSC and GBM during biopsy. Patients receiving a biopsy for tumor diagnosis might be more frequently considered as GBM compared to GSC due to the smaller quantity of tumor tissue in a biopsy.

Additionally, a lower ratio of GFAP and a higher ratio of TP53 staining was predictive of GSC diagnosis. Cachia et al. found in their series of 11 GCS TP53 mutations in 8 cases (73%) [19]. Other studies report on lower rates of TP53 mutations in GSC [3,20]. Often, overexpression of TP53 in immunohistochemistry is presumed to be predictive for TP53 gene mutation. But in previous studies, the presence of TP53 mutation was not always associated with TP53 staining results [20–22]. As to the GFAP staining, it is commonly being assessed for the determination of glial differentiation of tumor cells. Therefore, the finding on GFAP staining reflects the higher proportion of glial cells in GBM compared to GSC with its mesenchymal tumor parts.

Regarding the radiographic signs of tumors in the preoperative imaging, the presence of eccentric cysts was independently associated with GCS diagnosis. This finding is supported by several case reports and literature reviews, which also describe cystic formations in GCS patients [23,24]. Yi and colleagues also found a high proportion of eccentric tumor cysts in GSC (19/48, 39.6%) [25].

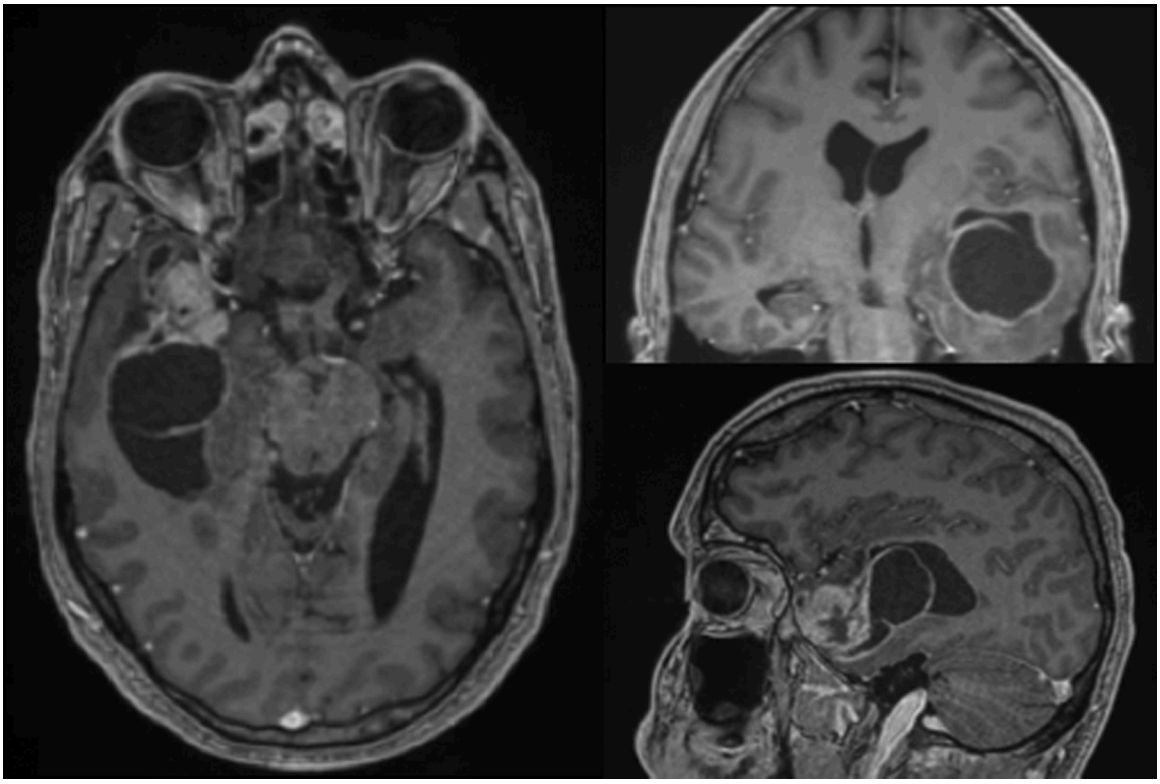

Fig. 1. Preoperative MRI showing a large temporal located gliosarcoma with eccentric tumor cysts.

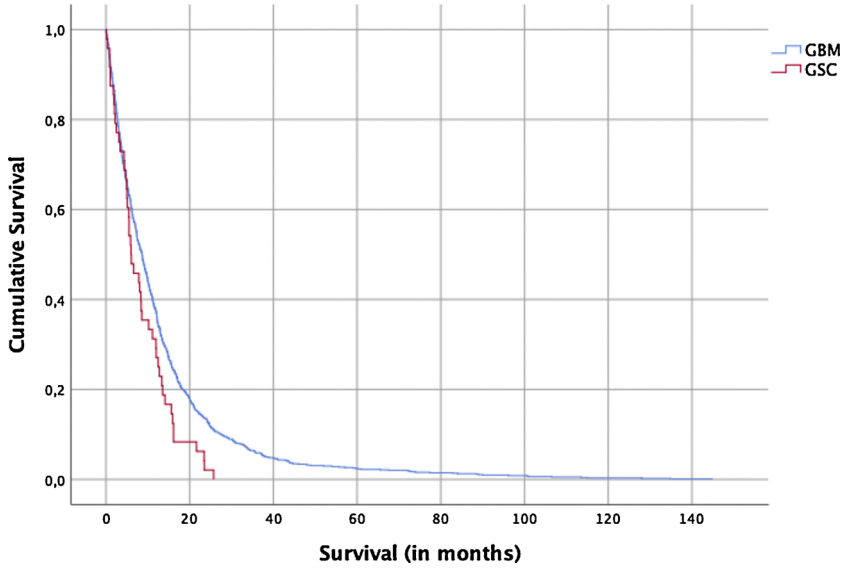

Fig. 2. Survival analysis with Kaplan-Meier Curve between gliosarcoma (GSC) and glioblastoma (GBM).

4.3. Outcome predictors in GSC and GBM

One strongly discussed aspect is the outcome of GSC in comparison to GBM.

In the multivariate analysis, the histological diagnosis of GSC was associated – independently of age, preoperative KPS, EOR and post-operative treatment – with a poorer outcome. This association is most likely due to a lower rate of MGMT promotor methylation and a lower frequency of IDH1 mutations in the GSC cohort. After including only the IDH1-wildtype patients in the analysis and considering MGMT promotor methylation as an additional confounder, the histological diagnosis of GSC was not found to be associated with a poorer outcome anymore. Previous studies reported ambiguously about survival rates in GBM and GSC patients; while several studies did not detect a significant difference in survival between both groups [6], other trials found a worse prognosis for patients with GSC [10]. To some extent, the very heterogeneous landscape with different distribution of genetic changes in GBM as also GSC might explain these differing results of previous studies. Other known outcome confounders, like age, preoperative clinical status and the administration of combined RTX/CTX [12,13,26] could be confirmed in our study as independent survival predictors.

4.4. Limitations

The main limitations of this study are in consequence of the study design. There are typical drawbacks of a retrospective study as limited completeness of data and a restricted accuracy of data compared to prospectively collected data.

5. Conclusion

In summary, GSC is as a rare variant of GBM and shows a predilection for temporal lobe and development of eccentric cysts. This study confirms well-known prognostic factors, like patients' age, preoperative clinical condition or postoperative treatment for GBM and GSC. GSC were associated with a poorer prognosis compared to GBM. These survival differences between GSC and GBM patients might be related to molecular-genetic features of the tumors. Prospective studies with a more detailed genetic and radiographic analysis are needed to further elucidate the nature and prognosis of GSC and to allow for targeted therapies for patients with GSC.

Credit Author Statement

Daniela Pierscianek: Conceptualization and design of the study, analysis and interpretation of data, drafting the article, final approval of the version to be submitted

Yahya Ahmadipour: acquisition of data, drafting the article, final approval of the version to be submitted

Anna Michel: acquisition of data, drafting the article, final approval of the version to be submitted

Laurèl Rauschenbach: acquisition of data, drafting the article, final approval of the version to be submitted

Marvin Darkwah Oppong: acquisition of data, drafting the article, final approval of the version to be submitted

Cornelius Deuschl: analysis and interpretation of data, revising the article critically for important intellectual content, final approval of the version to be submitted

Sied Kebir: analysis and interpretation of data, revising the article critically for important intellectual content, final approval of the version to be submitted

Karsten H. Wrede: design of the study, revising the article critically for important intellectual content, final approval of the version to be submitted

Martin Glas: design of the study, revising it critically for important intellectual content, final approval of the version to be submitted

Martin Stuschke: design of the study, revising the article critically for important intellectual content, final approval of the version to be submitted

Ulrich Sure: design of the study, revising the article critically for important intellectual content, final approval of the version to be submitted

Ramazan Jabbarli: Conceptualization and design of the study, analysis and interpretation of data, final approval of the version to be submitted

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clineuro.2020.106348.

References

[1] G.V. Walker, M.R. Gilbert, S.S. Prabhu, P.D. Brown, M.F. McAleer, Temozolomide use in adult patients with gliosarcoma: an evolving clinical practice, J Neurooncol. 112 (1) (2013) 83–89, https://doi.org/10.1007/s11060-012-1029-7.

[2] K.R. Kozak, A. Mahadevan, J.S. Moody, Adult gliosarcoma: epidemiology, natural history, and factors associated with outcome, Neuro Oncol. 11 (2) (2009) 183–191, https://doi.org/10.1215/15228517-2008-076.

[3] R.M. Reis, D. Konu-Leblebicioglu, J.M. Lopes, P. Kleihues, H. Ohgaki, Genetic profile of gliosarcomas, Am J Pathol. 156 (2) (2000) 425–432, https://doi.org/10.1016/S0002-9440(10)64746-3.

[4] S. Adeberg, D. Bernhardt, S.B. Harrabi, et al., Radiotherapy plus concomitant temozolomide in primary gliosarcoma, J Neurooncol. 128 (2) (2016) 341–348, https://doi.org/10.1007/s11060-016-2117-x.

[5] J.E. Oh, T. Ohta, N. Nonoguchi, et al., Genetic Alterations in Gliosarcoma and Giant Cell Glioblastoma, Brain Pathol. 26 (4) (2016) 517–522, https://doi.org/10.1111/bpa.12328.

[6] S. Frandsen, H. Broholm, V.A. Larsen, et al., Clinical Characteristics of Gliosarcoma and Outcomes From Standardized Treatment Relative to Conventional Glioblastoma, Front Oncol. 9 (2019) 1425, https://doi.org/10.3389/fonc.2019.01425.

[7] E. Galanis, J.C. Buckner, R.P. Dinapoli, et al., Clinical outcome of gliosarcoma compared with glioblastoma multiforme: North Central Cancer Treatment Group results, Journal of neurosurgery 89 (3) (1998) 425–430, https://doi.org/10.3171/jns.1998.89.3.0425.

[8] G. Zhang, S. Huang, J. Zhang, Z. Wu, S. Lin, Y. Wang, Clinical outcome of gliosarcoma compared with glioblastoma multiforme: a clinical study in Chinese patients, J Neurooncol. 127 (2) (2016) 355–362, https://doi.org/10.1007/s11060-015-2046-0.

[9] A. Ortega, M. Nuno, S. Walia, D. Mukherjee, K.L. Black, C.G. Patil, Treatment and survival of patients harboring histological variants of glioblastoma, Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia 21 (10) (2014) 1709–1713, https://doi.org/10.1016/j.jocn.2014.05.003.

[10] D.R. Smith, C.C. Wu, H.J. Saadatmand, et al., Clinical and molecular characteristics of gliosarcoma and modern prognostic significance relative to conventional glioblastoma, J Neurooncol. 137 (2) (2018) 303–311, https://doi.org/10.1007/s11060-017-2718-z.

[11] Y. Ahmadipour, O. Gembruch, D. Pierscianek, U. Sure, R. Jabbarli, Does the expression of glial fibrillary acid protein (GFAP) stain in glioblastoma tissue have a prognostic impact on survival? Neurochirurgie (2020) https://doi.org/10.1016/j.neuchi.2019.12.012.

[12] C. Hartmann, B. Hentschel, M. Simon, et al., Long-term survival in primary glioblastoma with versus without isocitrate dehydrogenase mutations, Clin Cancer Res. 19 (18) (2013) 5146–5157, https://doi.org/10.1158/1078-0432.CCR-13-0017.

[13] H. Gittleman, D. Lim, M.W. Kattan, et al., An independently validated nomogram for individualized estimation of survival among patients with newly diagnosed glioblastoma: NRG Oncology RTOG 0525 and 0825, Neuro Oncol. 19 (5) (2017) 669–677, https://doi.org/10.1093/neuonc/now208.

[14] Y.M. Li, D. Suki, K. Hess, R. Sawaya, The influence of maximum safe resection of glioblastoma on survival in 1229 patients: Can we do better than gross-total resection? Journal of neurosurgery 124 (4) (2016) 977–988, https://doi.org/10.3171/2015.5.JNS142087.

[15] W. Stummer, U. Pichlmeier, T. Meinel, et al., Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial, Lancet Oncol. 7 (5) (2006) 392–401, https://doi.org/10.1016/S1470-2045(06)70665-9.

[16] Y. Zhang, J.P. Ma, J.C. Weng, et al., The clinical, radiological, and immunohistochemical characteristics and outcomes of primary intracranial gliosarcoma: a retrospective single-centre study, Neurosurg Rev. (2020), https://doi.org/10.1007/s10143-020-01285-4.

[17] Q. Huang, F. Li, Y. Chen, F. Hong, H. Wang, J. Chen, Prognostic factors and clinical outcomes in adult primary gliosarcoma patients: a Surveillance, Epidemiology, and End Results (SEER) analysis from 2004 to 2015, Br J Neurosurg. (2019) 1–7, https://doi.org/10.1080/02688697.2019.1699903.

[18] A.E. Romero-Rojas, J.A. Diaz-Perez, L.M. Ariza-Serrano, D. Amaro, A. Lozano-Castillo, Primary gliosarcoma of the brain: radiologic and histopathologic features, Neuroradiol J. 26 (6) (2013) 639–648, https://doi.org/10.1177/197140091302600606.

[19] D. Cachia, C. Kamiya-Matsuoka, J.J. Mandel, et al., Primary and secondary gliosarcomas: clinical, molecular and survival characteristics, J Neurooncol. 125 (2) (2015) 401–410, https://doi.org/10.1007/s11060-015-1930-y.

[20] B. Actor, J.M. Cobbers, R. Buschges, et al., Comprehensive analysis of genomic alterations in gliosarcoma and its two tissue components, Genes Chromosomes Cancer. 34 (4) (2002) 416–427, https://doi.org/10.1002/gcc.10087.

[21] W. Biernat, A. Aguzzi, U. Sure, J.W. Grant, P. Kleihues, M.E. Hegi, Identical mutations of the p53 tumor suppressor gene in the gliomatous and the sarcomatous components of gliosarcomas suggest a common origin from glial cells, J Neuropathol Exp Neurol. 54 (5) (1995) 651–656, https://doi.org/10.1097/00005072-199509000-00006.

[22] E.W. Newcomb, W.J. Madonia, S. Pisharody, F.F. Lang, M. Koslow, D.C. Miller, A correlative study of p53 protein alteration and p53 gene mutation in glioblastoma multiforme, Brain Pathol. 3 (3) (1993) 229–235, https://doi.org/10.1111/j.1750-3639.1993.tb00749.x.

[23] A.M. Langlois, A.K. Alarfaj, A. Sagga, J.M. Findlay, S. Das, Gliosarcoma in a Young Filipino Woman: A Case Report and Review of the Literature, Am J Case Rep. 20 (2019) 914–919, https://doi.org/10.12659/AJCR.916020.

[24] A. Tabibkhooei, A. Fattahi, F. Ebrahimnia, Gliosarcoma with long progression free survival: A case report and literature review, Surg Neurol Int. 9 (2018) 227, https://doi.org/10.4103/sni.sni_225_18.

[25] X. Yi, H. Cao, H. Tang, et al., Gliosarcoma: a clinical and radiological analysis of 48 cases, Eur Radiol. 29 (1) (2019) 429–438, https://doi.org/10.1007/s00330-018-5398-y.

[26] R. Stupp, W.P. Mason, M.J. van den Bent, et al., Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma, N Engl J Med. 352 (10) (2005) 987–996, https://doi.org/10.1056/NEJMoa043330.