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Gliomatosis Cerebri Growth Pattern: Association of Differential First-Line Treatment with Overall Survival in WHO Grade II and III Gliomas

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Keywords
Low-grade glioma · Gliomatosis cerebri · First-line treatment · Overall survival

Abstract
Introduction: Gliomatosis cerebri (GC) is defined by diffuse, widespread glial tumor growth affecting three or more cerebral lobes. Previous studies in gliomas found no distinct histological or molecular GC subtype, yet the presence of GC is associated with worse median overall survival (OS). Here, we explored whether differing therapeutic strategies in first-line treatment could account for this. ***Methods:*** From our University Cancer Center database, 47 patients with histological diagnosis of WHO grade II or III glioma and GC imaging pattern were identified. GC criteria were confirmed by independent review. Patients with WHO grade II or III glioma with non-GC pattern served as control cohort (n = 343). ***Results:*** Within the GC patient cohort, lower WHO grade, mutated isocitrate dehydrogenase 1 (IDH1) status, and absence of contrast enhancement were associated with better OS. Compared to the control cohort, patients with GC had significantly shorter OS independent of histological diagnosis or IDH1 mutation status. Patients with GC preferentially received chemotherapy alone (62 vs. 18%), and less frequently radiochemotherapy (21 vs. 27%). OS was significantly shorter in the GC cohort compared to the non-GC cohort both for chemotherapy (3.9 vs. 7.6 years, p = 0.0085) and for combined radiochemotherapy (1.1 vs. 8.4 years, p < 0.0001). However, when only patients who received biopsy plus chemotherapy were analyzed, the differences lost statistical significance (3.5 vs. 6.6 years, p = 0.196). ***Conclusion:*** We found major differences in the selection of first-line therapies of GC versus non-GC patients. Our results suggest that these differences may partly account for the worse prognosis of GC patients.

Introduction

Gliomatosis cerebri (GC) refers to glial tumors with diffuse, infiltrative tumor growth affecting three or more cerebral lobes [1, 2]. GC was formerly considered a separate glial tumor entity [3] but has been removed as such from the revised WHO classification of CNS tumors pub-

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lished in 2016 [4]. This mainly resulted from the lack of distinct pathohistological features of GC tumors, as GC growth pattern can occur in both oligodendrocytic and astrocytic tumors encompassing WHO grades II, III and IV. Moreover, GC tumors have not been found to differ in the occurrence of molecular pathologies that are commonly observed in glial tumors with non-gliomatosis growth pattern, such as mutations in tumor protein 53 (TP53) or isocitrate dehydrogenase 1 (IDH1) [5, 6]. Additionally, studies employing genome-wide DNA methylation analysis in pediatric and adult cohorts were unable to identify a subgroup exclusive to GC [7, 8].

Despite these findings, the clinical management of GC remains challenging as no standard of care exists [9]. In subgroup analyses of oligodendroglioma, astrocytoma, and glioblastoma, the presence of GC is associated with worse overall survival (OS) [10]. In the absence of a GC-specific molecular profile, the factors responsible for the worse clinical outcome of GC remain ill-defined. Possible causes include differences in clinical presentation that may be caused by the widespread CNS involvement. Among neurological manifestations of GC, neurocognitive impairment can be seen in up to 25% of the cases and may delay the diagnosis [10, 11], particularly in elderly patients. With regard to differential usage of therapy, surgical options are reduced to diagnostic biopsy in the majority of GC patients. Notably, gross total resection has been proven to be crucial for OS in low-grade glioma [12]. While in some GC patients, partial resection may be justified to reduce compression of adjacent structures or to remove tumor sections with features indicative of a more aggressive phenotype, the impact on OS is unknown. Likewise, radiotherapeutic options are limited. Involved field therapy with the current standard of 54 Gy for WHO grade II histology and 59.4 Gy for anaplastic tumors [13] is not feasible in a large proportion of GC patients due to the extent of brain involvement. However, whole-brain radiation with 45 Gy is associated with neurotoxicity and may be insufficient for anaplastic tumors. In contrast, there is no evidence of decreased efficacy of alkylating chemotherapy in GC patients.

Departing from these aspects, we asked whether differing utilization of therapeutic strategies in the first-line treatment could differentially influence the outcome of patients diagnosed with WHO grade II and III glioma and GC tumor expansion. In a retrospective study design, we analyzed clinical characteristics, histology, and treatment-matched OS of patients with histologically confirmed WHO grade II and III glioma with and without GC growth pattern.

Materials and Methods

Patients

The patient data bank of the University Cancer Center (UCT) Frankfurt was screened for patients treated between 2005 and 2017 with diagnosed glioma WHO grade II or III, and with a record of GC tumor extension. Of the resulting cases, tumor extension was evaluated independently by three investigators (M.W., I.D., J.P.S.) by review of magnetic resonance imaging (MRI) scans prior to biopsy/resection and treatment initiation. In case of disagreement, images were discussed in detail in order to reach consensus. GC growth pattern was defined as tumor lesion affecting 3 or more cerebral lobes as detected by MRI on T2-weighted sequences. Basal ganglia, cerebellum, and brain stem were considered a separate lobe. MRI scans of patients with GC growth pattern were additionally evaluated for the presence of tumor contrast enhancement. Patients not matching GC criteria, patients <18 years or without histologically confirmed diagnosis were excluded from the study. The control cohort was constituted from the data bank of the University Cancer Center Frankfurt. Between 2005 and 2015, patients with histologically confirmed WHO grade II and III glioma were identified. Patients with a record of GC, patients without histological diagnosis, with unknown IDH mutation status or age <18 years were excluded from this cohort. All of the resulting 343 cases were included in the non-GC control cohort. The molecularly characterized non-GC patient cohort utilized here solely for comparisons with the GC growth pattern-cohort has been analyzed in detail regarding the impact of molecular features, grading and different treatment strategies on outcomes. A manuscript of this study [Steidl et al.] is currently in the submission process elsewhere.

Histological Classification

Histopathological diagnoses were performed on treatment-naïve, formalin-fixed, paraffin-embedded tumor samples by two experienced neuropathologists (P.N.H., K.F.). IDH1 mutation status was assessed by immunohistochemical analysis with a mutation-specific antibody against IDH1R132H. IDH1/IDH2 sequencing was rarely available. To account for this, tumors not showing IDH1 mutation as assessed by either IDH1R132H staining or sequencing were designated "IDH1R132H non-mutant." To discriminate between IDH1 mutant oligodendroglial and astrocytic tumors, we performed additional staining for trimethylation at lysine 27 of histone 3 (H3K27me3) staining in all samples for which paraffin-embedded tissue was available. As recently published [14], tumors showing a lack of nuclear H3K27me3 staining in combination with retention or non-conclusive nuclear α-thalassemia/mental retardation syndrome X-linked (ATRX) staining and IDH1R132H mutation were classified as oligodendrogliomas. O6-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation was investigated by methylation-specific PCR or DNA methylation array (Illumina).

Statistical Analysis

OS was defined as time from biopsy or surgical resection to death from any cause. It was estimated using the Kaplan-Meier method, and statistical significance between two subgroups was calculated by univariate analysis using the log-rank (Mantel-Cox) test. Time to treatment failure (TTF) was defined as beginning of one therapy to the beginning of any following therapy, or death by any cause.

For multivariate analysis, the Cox proportional hazard model was employed. A p-value of <0.05 was considered statistically significant. Univariate analysis and all data illustrations were performed with Graph Pad Prism 5.0 (GraphPad Software, Inc., San Diego, CA, USA). Cox regression analysis was performed with SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Patient Characteristics

Through our data bank research, we identified 47 patients with a histological diagnosis of WHO grade II and III glioma and radiologically confirmed GC growth pattern (Table 1). Compared to the non-GC control cohort, the GC cohort contained more male patients (62 vs. 50% in the non-GC cohort), and median age at the time of diagnosis was higher (49 vs. 42 years). The interquartile range of the GC cohort was 24 versus 18 years of the non-GC cohort. Almost 80% of the GC cohort showed astrocytic histology, this percentage being lower in the non-GC cohort (65%). Oligodendrocytic tumors were found in 21% of the GC cases versus 36% of the non-GC cases. IDH1 mutation status was determined for all non-GC and 81% of GC samples. In the remaining 19% of GC cases (n = 9), IDH status could neither be determined by IDH1R132H antibody staining nor sequencing due to lack of tumor tissue. Detailed molecular and immunohistochemical characteristics of the GC tumors are provided in supplementary Table 1.

Table 1. Characteristics of the gliomatosis cerebri (GC) and non-GC cohort

Variable	GC (n = 47)		Non-GC (n = 343)	
	n	%	*n*	%
Sex				
Male	29	62	171	50
Female	18	38	172	50
Age, median (range)	49 (27–81)		42 (19–82)	
WHO grade				
II	21	45	164	48
III	26	55	179	52
Histology				
Oligodendrocytic	10	21	121	36
Grade II	5		49	
Grade III	5		72	
Astrocytoma	37	79	222	65
Grade II	16		115	
Grade III	21		107	
IDH status				
IDH1R132H non-mutant	20	43	84	24
Mutated	18	38	259	76
Unknown	9	19	0	0
MGMT status				
Methylated	12	25	109	32
Non-methylated	7	15	36	10
Inconclusive	8	17	0	0
Unknown	20	43	198	58

IDH, isocitrate dehydrogenase; MGMT, O6-methylguanine DNA, methyltransferase. Refer to supplementary Table 1 for detailed molecular and immunohistochemical characteristics of the GC tumors.

Prognostic Factors within the GC Patient Cohort

The median OS of the GC patient cohort was 3 years (Fig. 1a). However, the course of disease was highly variable, with OS ranging from 0.5 months to 10 years. TTF was approximately 0.9 years for both first- and second-line treatment (supplementary Fig. 1a).

The WHO grade was prognostic with median OS of 5.3 years in the WHO grade II subgroup versus 1.1 years in the grade III subgroup (p = 0.0002) (Fig. 1b). There was a trend towards better OS for the oligodendrocytic subgroup compared to astrocytic tumors, but values did not yield statistical significance (p = 0.0627) (Fig. 1c). The presence of IDH1R132H mutation was highly prognostic and was 5.3 versus 1.1 years in the IDH1R132H non-mutant group (p < 0.0001) (Fig. 1d). MGMT methylation status was not a significant prognosticator, but the sample size was too small for a definitive conclusion (shown in supplementary Fig. 2a). However, the presence of pathological contrast enhancement of the tumor in the initial MRI was associated with significantly shorter OS (supplementary Fig. 2b).

OS of GC and Non-GC Patient Cohorts

Next, we analyzed OS of the GC patient cohort in comparison to the non-GC group. As expected, patients with GC had significantly shorter OS. Median OS of the whole GC cohort was 3 years as opposed to 11.7 years in the non-GC group (p < 0.0001) (Fig. 2a). This difference persisted when GC patients were compared to non-GC patients regarding WHO grade (Fig. 2b). OS for WHO grade II tumors was 5.3 years in the GC and 12.8 years in the non-GC group (p < 0.0001), and for WHO grade III tumors 1.1 and 7.7 years, respectively (p < 0.0001). Differences between the groups were equally significant in relation to histomorphological diagnosis (fig. 2c, supplementary Fig. 3). For IDH1R132H mutated as well as non-mutant tumors, OS of the GC cohort was significantly shorter (Fig. 2d). Median OS for IDH mutated GC-tumors was 5.3 years as opposed to 12.8 years in the non-GC

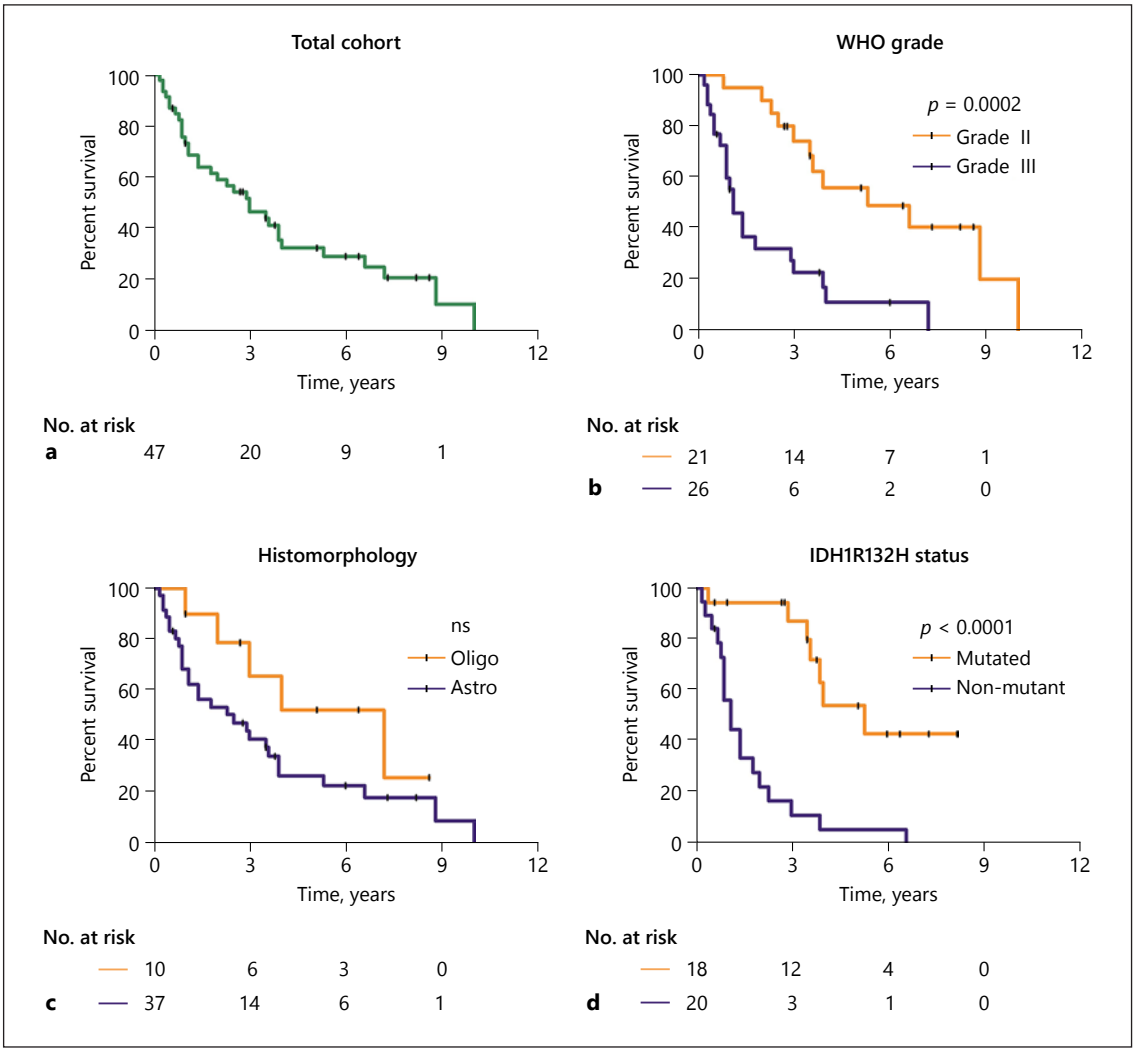

Fig. 1. Overall survival (OS) of WHO grade II and III glioma patients with gliomatosis cerebri (GC) growth pattern. **a** OS of the whole GC patient cohort (n = 47). Median OS percentages according to (**b**) WHO grade, (**c**) histomorphological diagnosis, and (**d**) IDH1R132H mutation status (log-rank test). Tick marks indicate censored patients. oligo, oligodendroglioma and oligodendrocytic tumors; astro, astrocytoma; IDH, isocitrate dehydrogenase; ns, not significant.

cohort (p = 0.0011). This difference persisted with regard to TTF for first-line treatment, being 2.2 years in the GC cohort (supplementary Fig. 1b) versus 5.1 years in the non-GC cohort (data not shown).

For IDH1R132H non-mutant GC-tumors, median OS was 1.1 versus 3.1 years in the non-GC cohort (p = 0.0001). In a multivariate cox regression analysis, increased age, WHO grade III, lack of IDH1R132H mutation, presence of GC growth pattern and lack of surgical intervention were identified as unfavorable prognostic factors (supplementary Table 2).

First-Line Treatment Regimen

The clinical data was then analyzed with regard to the first-line treatment (Fig. 3). Of the whole GC cohort, 9% of the patients did not receive any treatment after the diagnosis was established by stereotactic biopsy; in the non-GC cohort, this percentage was lower (3%) (Fig. 3a). The majority of all GC patients received chemotherapy (62%) as first-line treatment, as opposed to 18% of the non-GC cohort. This imbalance persisted when we only included those patients who received biopsy and chemotherapy (51 vs. 10%, respectively) (Fig. 3b), and was less

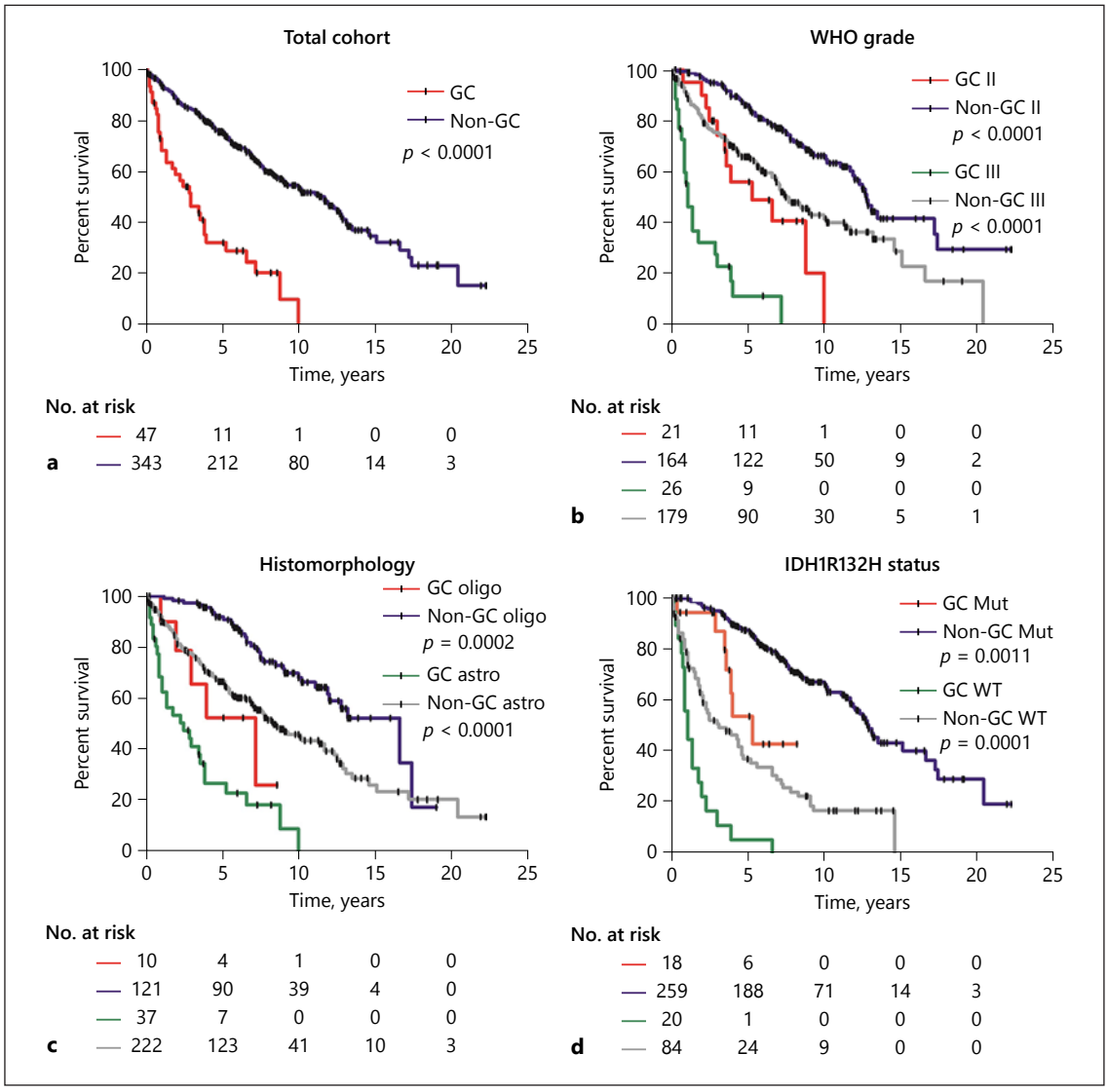

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Fig. 2. Comparison of overall survival of the gliomatosis cerebri (GC) cohort to the non-gliomatosis cohort. **a** OS of the GC patient cohort (n = 47) and the non-GC cohort (n = 343). OS percentages according to WHO grade (**b**), histomorphological diagnosis (**c**), or IDH mutation status (log-rank test) (**d**). Tick marks indicate censored patients. oligo, oligodendrocytic tumors; IDH, isocitrate dehydrogenase as assessed by immunohistochemistry of IDH1R132H; Mut, IDH1R132H mutated tumors; WT, IDH1R132H non-mutant tumors.

pronounced for the combination of surgical resection and chemotherapy (11 vs. 8%) (Fig. 3c). Radiochemotherapy was less represented in the GC cohort. In the GC cohort, radiotherapy alone was much less frequently administered (2% of the cases only vs. 20% in the non-GC group). The non-GC cohort more frequently underwent surgical resection without adjuvant treatment. Corresponding absolute numbers are depicted in supplementary Table 3.

OS of Treatment-Matched Subgroups

Owing to the unbalanced distribution of first-line treatment choices among the 2 patient cohorts, we hypothesized that the OS difference between the GC and non-GC cohort would be less pronounced when comparing treatment-matched subgroups. Therefore, we analyzed OS for GC and non-GC patients that had received the same first-line therapy (Fig. 4). A comparison of OS of the patients who received no additional treatment after

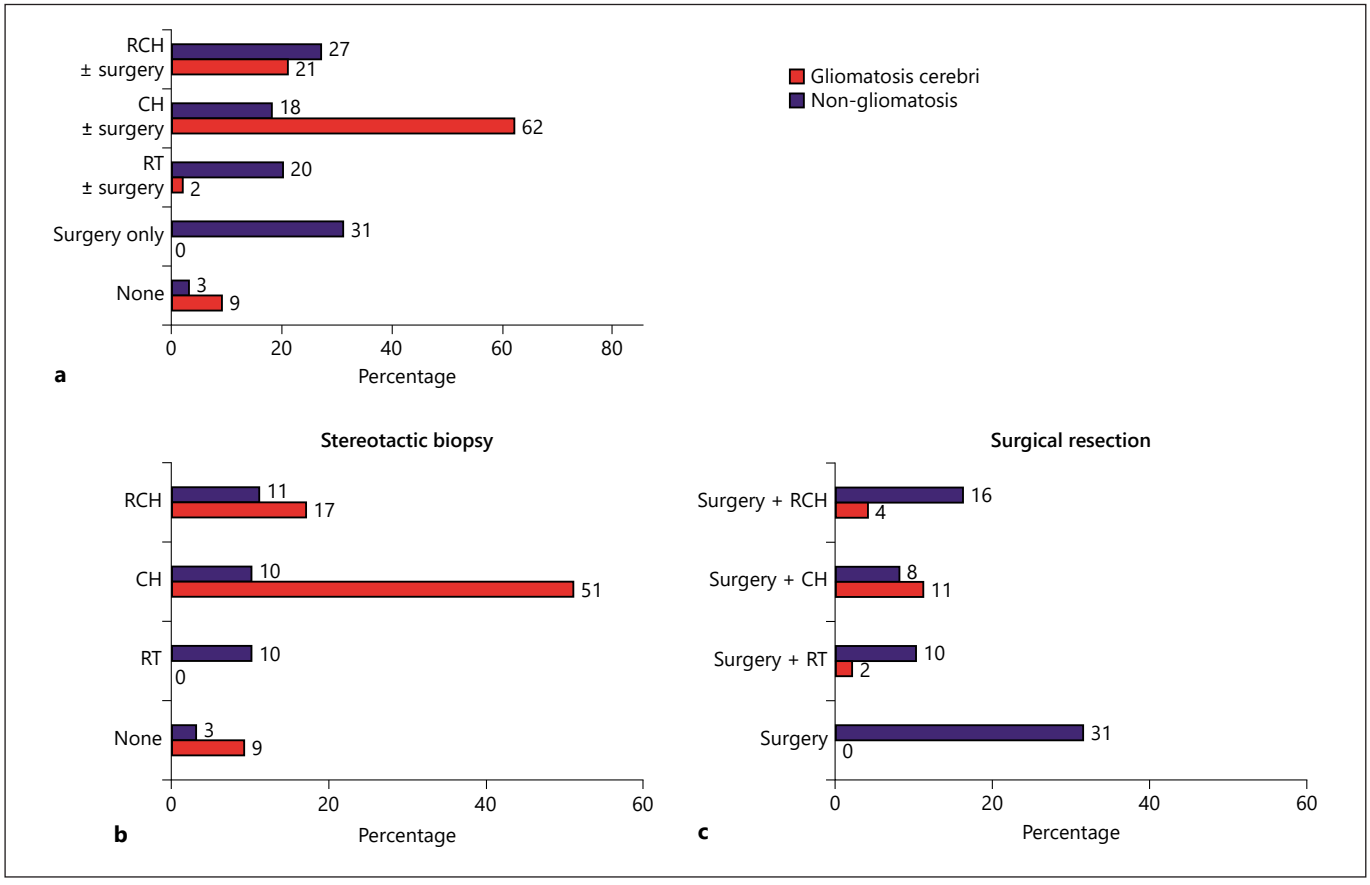

Fig. 3. Comparison of first-line treatment strategies. **a** Summary of adjuvant treatment with or without prior surgical resection. **b** Summary of first-line treatment following biopsy. **c** Summary of first-line treatment following surgical partial or complete resection. Numbers depicted correspond to the percentage of the whole gliomatosis cerebri or non-GC cohort that received the indicated treatment. RT, radiotherapy; CH, chemotherapy; RCH, radiochemotherapy.

biopsy revealed no statistical significance, possibly due to the small number of patients in each group encompassing 3 patients in the GC, and 12 in the non-GC group (data not shown). In the chemotherapy subgroup, OS was significantly shorter for GC patients with a median survival of 3.9 versus 7.6 years for non-GC cohort (p = 0.0085) (Fig. 4a). This effect persisted with regard to radiochemotherapy, OS of GC patients being 1.25 years as opposed to 8.4 years for non-GC patients ($p < 0.0001$) (Fig. 4b). Due to the small numbers in the GC cohort, the comparison for radiotherapy or surgery alone was not feasible.

To avoid potential bias caused by the unequal distribution of surgical resections performed, we separately analyzed GC and non-GC patients who received biopsy (Fig. 4c) or surgical resection (Fig. 4d) prior to chemotherapy. In these treatment-matched comparisons, OS of GC and non-GC patients lost statistical significance. For biopsy and chemotherapy, median OS was 3.6 years in the GC versus 6.6 years in the non-GC cohort (p = 0.196). For resection and chemotherapy, median OS was 7.2 and 9 years (p = 0.103), respectively. In order to further purify the cohort comparison, we then compared OS following biopsy and chemotherapy for IDH mutant tumors only (Fig. 4e) which again was not significantly different (median OS 5.3 vs. 12.5 years, p = 0.556). Due to small patient numbers, the analysis for the combination of resection and chemotherapy as well as resection and radiochemotherapy was not feasible.

Discussion

In this retrospective, single-center study, we analyzed patient characteristics, first-line treatment and treatment-matched OS of 47 patients with GC growth pattern

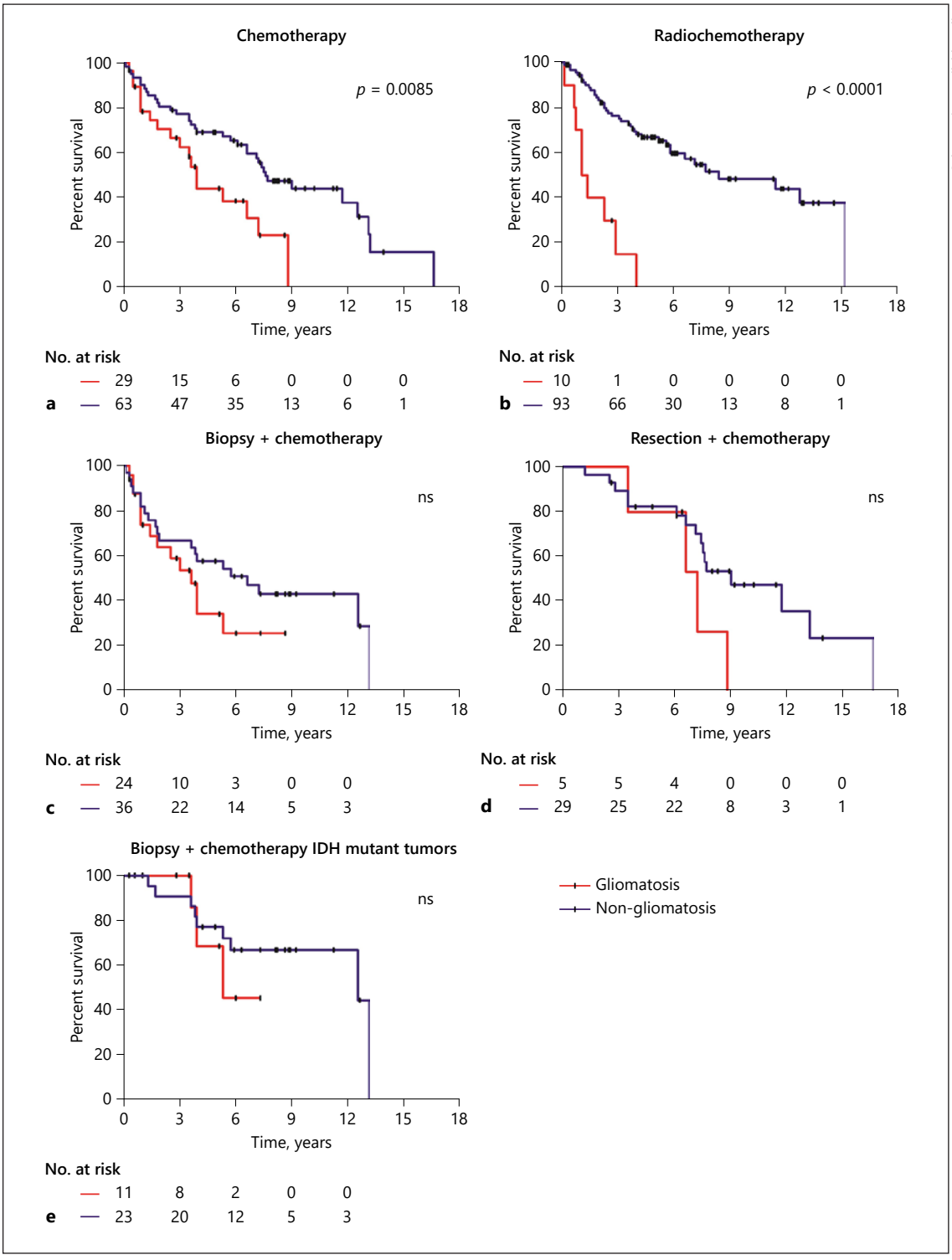

Fig. 4. Overall survival for gliomatosis and non-gliomatosis patients in treatment-matched subgroups. Treatment-matched OS analysis with regard to both the chemotherapy (**a**) and the radiochemotherapy subgroup (**b**). The analysis depicted includes all patients who received chemotherapy or radiochemotherapy, regardless of previous surgery. OS of patients who received chemotherapy following biopsy (**c**) or surgical resection (**d**) as first-line treatment. **e** The OS analysis of biopsy and chemotherapy for IDH1 mutant tumors only. Tick marks indicate censored patients. ns, not significant; IDH, isocitrate dehydrogenase.

as compared to 343 patients without GC. Our findings confirm the presence of GC as prognosticator for worse OS in WHO grade II/III glioma. Of note, this was independent of histological diagnosis and IDH1 mutation status, and the hazard ratio for GC of 3.772 was second only to that of IDH1 mutation (HR = 13.815) in the multivariate Cox regression analysis (supplementary Table 2). With regard to treatment strategies, we found that patients with GC predominantly received chemotherapy alone. Surgical resection and radiotherapy were rarely performed, while the percentages of patients who received combined radiochemotherapy were similar in both cohorts (Fig. 3). Thus, our study of this monocentric cohort of a large German brain tumor center confirms that the therapeutic strategies pursued in GC patients differed from those in non-GC patients. In OS analysis matched for either chemotherapy alone or radiochemotherapy, the GC group continued to show statistically significant shorter OS as compared to non-GC patients (Fig. 4). However, after excluding patients receiving resection, OS of GC and non-GC patients receiving chemotherapy did not differ significantly, while there was still considerable difference in median OS (3.6 years in the GC vs. 6.6 years in the non-GC cohort) (Fig. 4c–d). Similarly, when only IDH1 mutated cases without resection were compared, OS did not differ with statistical significance. Overall, our findings suggest that differences in first-line treatment might, at least in part, account for the worse prognosis of patients with GC pattern.

Our study has several limitations. First, due to the limited number of cases in subgroup analyses, the results must be interpreted with caution. Second, the potential impact of second-line and salvage therapies not analyzed here has to be taken into account. However, although salvage therapies were frequently employed in the pivotal studies demonstrating efficacy for radiochemotherapy in unselected lower grade glioma cohorts [15], they were not able to nullify the large survival benefit brought about by first-line combination therapy. Moreover, regarding our pivotal finding of chemotherapy alone (Fig. 4c–d), non-GC patients would be expected to derive more benefit from salvage radiotherapy. Third, the interpretation of our findings is arguably limited by the composition of the GC cohort. As compared to the non-GC group, the GC group contained a higher percentage of WHO grade III, astrocytic, and IDH wild-type tumors. In line with previous studies [16–20], these attributes were associated with shorter OS (Fig. 1, 2). As IDH1 mutation was predominantly assessed by IDH1R132H staining, rare IDH mutations might not have been detected. The discrimination between IDH1R132H mutated oligodendroglial and astrocytic tumors was facilitated by additional evaluation of H3K27me3 by immunohistochemistry [14]. However, of the IDH1R132H-mutated GC cases, tumor tissue was only available in about 40%, leaving the possibility of an even higher percentage of astrocytic tumors in this cohort. Hence, a selection bias in favor of the non-GC cohort cannot be excluded.

Regarding clinical management of GC, no guidelines exist. Consequently, the key question remains whether GC gliomas should be treated in reference to their histological and/or molecular non-GC counterparts. For anaplastic oligodendroglioma and oligoastrocytoma, the EORTC26951 [21] and RTOG 9402 [22] trials have established the beneficial role of combined radiochemotherapy. Subgroup analyses of both trials have shown that this effect is driven by IDH mutant tumors. Likewise, the RTOG 9802 and CATNON trials showed longer OS with combined radiochemotherapy for high-risk low-grade tumors and 1p/19q non-codeleted anaplastic gliomas as compared to radiotherapy alone, respectively [15, 23]. Again, benefit was only shown for tumors displaying IDH mutations. In contrast, we found that GC patients who received radiotherapy, either alone or in combination with chemotherapy, showed worse OS ($p = 0.0047$) (supplementary Fig. 4a) and shorter TTF (supplementary Fig. 4b). Of note, most of the 11 GC patients who underwent RT had astrocytic tumors without IDH mutation (supplementary Table 3), thus not matching the histological criteria of the aforementioned studies. In one of the cases, radiotherapy was employed as salvage therapy due to rapid tumor progression. No obvious radiation-related complications, such as radionecrosis, were observed. However, negative impact on cognition cannot be excluded. Overall, our findings highlight the challenges of the use of radiotherapy for GC patients. Radiotherapy has been attributed efficacy for GC treatment in case studies as well as retrospective studies containing a variety of radiation protocols [10, 24–26]. In contrast, studies with larger patient numbers failed to evidence the beneficial impact of radiotherapy on OS in GC patients [11, 27, 28]. Furthermore, no association between radiotherapy dose/volume and OS has been established until now [10, 29]. Notably, to the best of our knowledge, no prospective studies investigating the impact of radiotherapy on OS in molecularly well-defined GC patient groups exist. Hence, the ambivalent role of radiotherapy for GC reported in the literature might be explained by the lack of adequately designed trials.

To date, the only GC-specific prospective therapy trial was the NOA-05 trial which was designed to investigate

the efficacy of primary chemotherapy with procarbazine and lomustine in patients with GC [20]. While the study underlined the feasibility of chemotherapy in this patient cohort, the informative value of the study is limited by the heterogeneity of the study population, including WHO grades II-IV as well as IDH mutated and wildtype tumors. In retrospective studies as well as our cohort analysis (Fig. 3), most patients with GC tumor expansion received chemotherapy. A correlation of response to chemotherapy and MGMT promotor methylation status was not feasible, due to the small percentage of MGMT availability and the resulting small numbers in subgroups. Still, it remains unclear (i) which alkylating substance or protocol (i.e., temozolomide, lomustine, PCV or lomustine plus temozolomide) should be chosen for first-line treatment [30], (ii) if chemotherapy should be combined with radiotherapy, possibly guided to aggressive tumor regions by amino acid PET or advanced MRI techniques, (iii) if the widespread tumor expansion may be a target for other strategies, such as IDH inhibitors for IDH mutant tumors, immune therapies (IDH vaccines, checkpoint inhibitors), or even antiangiogenesis treatment [31, 32].

In conclusion, our study identifies significant imbalances in first-line treatment approaches between GC and non-GC cohorts of WHO grade II/III gliomas. Our subgroup analyses suggest that these imbalances could potentially impact OS of GC patients. Even considering the limited number of patients in our study, the lack of systematic treatment guidelines for GC tumors strongly encourages validation of our findings in a prospective, multicenter study design.

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Statement of Ethics

The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The study, clinical data collection, histological, immunohistochemical and molecular pathological analyses were approved by the institutional Review Boards of the University Cancer Center Frankfurt (UCT) and the Ethical Committee at the University Hospital Frankfurt (project No.: SNO-02-2017). Patient data used in this study was provided by the University Cancer Center Frankfurt (UCT). Informed consent for data collection and publication in anonymized form was obtained from all patients registered in the UCT database.

Conflict of Interest Statement

J.P. Steinbach has received grants from Merck and UCB as well as honoraria for lectures, travel or advisory board participation from Abbvie, Bristol-Myers Squibb, Medac, Roche, Novocure and UCB. U. Herrlinger has received lecture and/or advisory board honoraria from Medac, Bristol-Myers Squibb, Novocure, Novartis, Daiichi-Sankyo, Noxxon, AbbVie, Bayer, Janssen, Riemser and Karyopharm. O. Bähr has received honoraria for lectures, travel or advisory board participation from Medac, Bristol-Myers Squibb, Novocure and Daiichi-Sankyo. M.C. Burger has received honoraria for lectures or advisory board participation from Bristol-Myers Squibb and Gilead Sciences. All other authors declare that they have no conflict of interest.

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Author Contributions

Conceptualization: I. Divé, J.P. Steinbach. Data curation: I. Divé, E. Steidl, M. Wagner, K. Filipski, P.N. Harter, J.P. Steinbach. Analysis and interpretation of data: all authors. Visualization and writing of the original draft: I. Divé. Review and final editing of the manuscript: all authors.

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