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REVIEW ARTICLE

Factors affecting cognitive functions of patients with high-grade gliomas: a systematic review

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Abstract

Background Gliomas make up approximately 26.5% of all primary CNS tumors and 80.7% of malignant tumors. They are classified according to histology, location, and genetics. Grade III and IV gliomas are considered high-grade gliomas (HGGs). The cognitive signs and symptoms are attributed to mass defects depending on location, growth rapidity, and edema. Our purpose is to review the cognitive status of patients diagnosed with HGGs; the effect of treatments including surgical resection, radiotherapy, and chemotherapy; and the predictors of the cognitive status.

Methods We utilized the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines as a template for the methodology. A comprehensive literature search was performed from three databases (PubMed, ScienceDirect, and Cochrane Library) for clinical trials and longitudinal studies on patients diagnosed with HGGs assessing their cognitive status.

Results Thirteen studies were selected among which 9 assessed cognitive function before and after treatment. One assessed the consistency of cognitive complaints and objective cognitive functioning. Three reported factors affecting disease progression and cognitive status. Most HGG patients have impairment in at least one cognitive domain. Treatments including surgical resection or radio-chemotherapy did not impair cognitive status.

Discussion The cognitive status could be used to assess sub-clinical tumor progression. Factors correlated to cognitive status were tumor location, edema, and grade. Patient characteristics correlated were pre-operative epilepsy, corticosteroid use, and age at the time of diagnosis.

Conclusion Assessment of the cognitive status of HGG patients indicates sub-clinical tumor progression and may be used to assess treatment outcomes.

Keywords Gliomas · High-grade gliomas · Cognitive function · Cognitive function · Cognitive status

Introduction

There are over a hundred histologically distinct types of primary central nervous system (CNS) tumors, each with different clinical presentation, treatment, and outcome. The total incidence of primary CNS tumors is approximately 24.25 per 100,000, and 7 out of 100,000 for malignant CNS tumors globally. Malignant CNS tumors have an average annual mortality rate of 4.43. The incidence is highest among those aged above 85 years and lowest among children and adolescents 0–19 years of age [1]. Gliomas are neuroepithelial tumors that originate from the glial cells of the CNS. Gliomas make up approximately 26.5% of all primary CNS tumors and 80.7% of malignant CNS tumors [2].

The WHO classifies CNS tumors into four grades, grades I and II being low-grade, whereas grades II and III are considered high grade. Gliomas are further divided into adult-onset or pediatric-onset. For our review, we only focus on adult-type diffuse gliomas which account for the majority of primary brain tumors. In the fifth edition of the WHO Classification of Tumors of the Central Nervous System (WHO CNS-5) (2021) the adult-type,

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diffuse gliomas include astrocytoma, IDH-mutant; oligodendroglioma, IDH-mutant, and 1p/19q-co-deleted; and glioblastoma, IDH-wildtype [3]. In the previous WHO CNS-4 (2016), they were divided into 15 categories [4]. Earlier the classifications have been changed with the editions of WHO CNS Blue books in 1979, 1993, 2000, 2007, and 2016 [5, 6]; therefore, different studies on gliomas have taken various sub-types. The prognosis of patients with high-grade gliomas has been based on clinical factors [7]. The initial therapy in the standard management of high-grade gliomas is maximal surgical resection which can rapidly reduce the mass effect and improve neurologic symptoms, followed by radiotherapy dose of 54 to 60 Gy along with chemotherapy with temozolomide (TMZ) [7].

Cognitive functions (CFs) refer to "*The mental processes involved in the acquisition of knowledge, manipulation of information, and reasoning*" [8]. The components of cognitive functions may be divided into perception, memory, learning, attention, decision-making, and language abilities [8]. The cognitive effects of gliomas are dependent on location within the brain, rapidity of growth, mass effect of the tumor, and associated edema. Gliomas may damage eloquent brain areas or connectivity and cause white matter alterations secondary to glioma infiltration, which may lead to the deterioration of specific cognitive domains. Fast-growing tumors with significant cerebral edema can lead to acute onset of cognitive deficits; slower-growing tumors are more likely to produce subtle changes in behavior or cognition. This review assesses the domains of CF mostly affected by HGGs and the factors affecting the cognitive outcome in patients with HGGs.

Methodology

We utilized the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines as a template for the methodology.

Search strategy

Systematic searches of the PubMed, Science Direct, and Cochrane Library databases were conducted for relevant evidence. The following search was done using Medical Subject Headings (MeSH) terms (Gliomas OR High-Grade Gliomas) AND (Cognitive effects OR Cognition OR Cognitive functions) in the "Title/Abstract." Only English-language articles were considered. The eligibility of relevant articles was first assessed by screening results based on title/abstract review and removing duplicates. The full texts were then screened according to predefined inclusion and exclusion criteria.

Inclusion and exclusion criteria

Studies were included if the terms gliomas or high-grade gliomas and cognitive effects or cognition or CF were mentioned or implied in the title or the abstract.

Prospective studies on patients diagnosed with higher-grade (anaplastic astrocytoma, oligodendroglioma, anaplastic mixed glioma) or highest-grade gliomas (glioblastoma multiforme, gliosarcoma, gliomatosis cerebri) assessing their cognitive function before/after treatment were chosen. Articles assessing factors influencing the cognitive status of patients with HGGs were also included.

Review articles, trials not assessing cognitive function or impairment, articles on pediatric patients, and trials on patients with lower-grade gliomas (grade 1 or 2) or any other form of tumor were excluded. The WHO CNS classifications were limited to 2000–2021; thus, articles using classifications before these were excluded.

Data collection

Data was collected and analyzed using Zotero® software. The duplicates in the results of the initial database search were removed. The articles had titles and abstracts assessed by 2 authors MWSB and RT and articles not matching the requirement were excluded. The remaining articles were assessed for full-text by RT and MWSB. Included and excluded articles were then discussed and approved by all authors.

Data extraction and analysis

Duplicates were eliminated from the articles of the initial database searches using the Zotero software package. The titles of the articles were then reviewed independently by the authors to select articles relevant to the study. Subsequently, the abstracts of the selected articles were reviewed for eligibility within this study.

Risk of bias assessment

STROBE guidelines [9] were used to assess the quality of observational studies including case-control, cohort, and cross-sectional studies. The final included studies were assessed and approved by all authors.

Table 1 Description of populations, classification, intervention, and assessment timings of individual studies

Study	Population (*n*)	WHO classification used	Interventions/treatments	Baseline	Follow-up
Bosma I, Vos MJ et al.	68 at baseline 32 at follow-up	2016	Surgical resection, radiotherapy (not defined)	After surgery and before radiotherapy	8 and 16 months
Caramanna I, Bottomley A et al.	546	2007	Radiotherapy and chemotherapy	After radiotherapy and chemotherapy	No follow-up
Dehcordi SR, Mariano M et al.	42, out of which 27 had HGGs	2007	Surgical resection (not defined)	Pre-operatively	6 months and 1 year after surgery
Bonifazi S, Passamonti C et al.	19	2016	Awake craniotomy (6 had a gross-total resection, 1 had a near-total resection, 12 had sub-total resection). ± radio ± chemotherapy	Pre-operatively	3 and 12 months post-surgery
Habets EJ, Kloet A et al.	62 at baseline, 39 at follow-up	2007	Total or subtotal tumor resection	A week preceding surgery	At least 3 weeks following surgery, before subsequent therapy
Brown PD, Jensen AW et al.	1244	2000	Surgical resection	After surgery	6, 12, 18, and 24 months
Bian Y, Meng L et al.	18	2016	Craniotomy and integrated boost IMRT before chemotherapy with TMZ	Before IMRT	At the end of IMRT, and 3, 6, 9, and 12 months after IMRT
Bodensohn R, Corradini S et al.	44 at baseline 21 on follow-up	2007	GTR with three-dimensional conformal radiotherapy	Before radiotherapy	After radiotherapy
Wang Q, Xiao F et al.	229	2007	Surgical resection followed by fractionated external beam radiation therapy with concomitant administration of TMZ followed by up to six cycles of adjuvant TMZ	After surgery and before radiotherapy, and chemotherapy	3, 6, 9, 12, 15, and 18 months after radiotherapy
Butterbrod E, Bruijn J et al.	25	2016	Surgical resection (not defined), adjuvant chemoradiation with TMZ	One day before surgery	Every third month for 24 months
Dallabona M, Sarubbo S et al.	30	2016	Surgical resection with neoadjuvant radiotherapy ± chemotherapy	Before surgery	7 days and about 40 days after surgery
Wang Q, Qi F et al.	72	2016	6-week RT and concomitant temozolomide (TMZ) and six cycles of adjuvant TMZ	After surgery, before radio-chemotherapy	3, 6, 9, and 12 months posttherapy
Zarino B, Di Cristofori A et al.	102	2016	Surgical resection with radio- and chemotherapy	Before surgery	After surgery and at 3, 6, 9, and 12 months

Data synthesis

The demographic details including sample size, WHO classification used in the study, treatment interventions, baseline assessment, and follow-up time were tabulated in Table 1. Table 2 reports the neuro-cognitive domains assessed, the assessment tool, baseline, and follow-up outcomes. The effects of tumor

Table 2 Neurocognitive assessments of individual studies

Authors	NCFs assessed	Measurements used	Baseline (compared to healthy population)	Follow-up(s)	
Bosma I, Vos MJ et al.	Information-processing speed	A standardized battery of tests	–	(8 months) ↓	(16 months) ↓↓
	Psychomotor function		–	↓	↓
	Attentional function		–	–	–
	Verbal memory		–	–	–
	Working memory		–	–	–
	Executive function		–	↓	↓
Caramanna I, Bottomley A et al.	Verbal learning and memory	Hopkins Verbal Learning Test-Revised	↓	No follow-up	
	Attention, speed, mental flexibility	Trail Making Test (A and B)	↓		
	Spontaneous production of words	Controlled Oral Word Association Test	↓		
	Patient's subjective NCF	Questionnaire from Medical Outcomes Study	Patients aware of their cognitive deficits		
Dehcordi SR, Mariano M et al.	Visual-spatial-intelligence and logical capacity	Raven's colored progressive matrices	–	–	
	Verbal memory	Rey's Word Test	–	Slight improvement	
	Working memory, short-term memory	Digit Span Test	↓	↑	
	Attention, speed, mental flexibility	Trail Making Test (A and B)	↓	↓	
	Lexical score	Fluency verbal test	–	Slight improvement	
	Problem solving	Tower of London Test	–	–	
Bonifazi S, Passamonti C et al.	Language functions	Laiacona-Capitani Naming Test	↓	Transient language impairments in the immediate post-operative phase	The majority of patients showed recovery within 3/6 months.
		Battery for Analysis of Aphasic Deficits			
	Verbal memory	Rey Word List	–	No significant difference from BL	
	Lexical score	Verbal fluency test	↓		
	Executive functions	Frontal Assessment Battery	↓		

Table 2 (continued)

Authors	NCFs assessed	Measurements used	Baseline (compared to healthy population)	Follow-up(s)
Habets EJ, Kloet A et al.	Verbal memory	Verbal learning test	↓	No significant difference from BL
	Working memory	Digit span forward and backward	↓	
	Executive function	Concept Shifting Test	↓	
	Psychomotor function		↓	
	Information processing speed	Letter digit modalities test	↓	↑
	Attention	Stroop color-word test	↓	No significant difference from BL
	Visuoconstruction	Rey complex figure test	↓	↑
Brown PD, Jensen AW et al.	Overall cognitive status	MMSE	Declined in 33.94% of the population	Cognitive deterioration of 18% at 6 months, 16% at 12, 14% at 18, and 13% at 24 months
	Functional status	ECOG	Worse in patients with declined MMSE	
Bian Y, Meng L et al.	Overall cognitive status	MMSE	–	No significant differences between BL
		MoCA	↓	
Bodensohn R, Corradini S et al.	Overall cognitive status	NeuroCogFx	Depended on tumor and patient characteristics	No significant change after radiotherapy
Wang Q, Xiao F et al.	Overall cognitive status	MoCA	–	67% of patients developed cognitive impairment.
Butterbrod E, Bruijn J et al.	Neurocognitive and behavioral assessment	CNS Vital Signs	–	Patients with cognitive decline showed a five times higher chance of progressive disease.
	Working memory	Digit Span Test		
	Verbal function	Letter fluency task		
Dallabona M, Sarubbo S et al.	Language	A battery of 31 neuropsychological tests	Depended on tumor volume, mass effect, and age of the patients at diagnosis	A short-term decline in a few neuro-cognitive domains, but no significant worsening in late follow-up with improvement in some domains
	Memory			
	Attention and executive functions			
	Praxis			
Wang Q, Qi F et al.	Overall cognitive status	MMSE	–	No significant change after radio- or chemotherapy
Zarino B, Di Cristofori A et al.	Neurophysiological functioning	Milano-Bicocca Battery	Impaired in 29% pre-operatively and 34% post-operatively	Tumor progression leads to a decline in 14 out of 27 cognition tests.

↓: impaired/reduced; ↑: significant improvement; –: not reported/not significant

Table 3 Effects of tumor characteristics and treatment modalities on neuro-cognitive functions

Authors	Location	Edema	Size/volume	Recurrence	Medication	Surgical resection	Radiotherapy	Chemotherapy	Other
Bosma I, Vos MJ et al.	–	–	–	Lower information-processing capacity, psychomotor, and executive function	The neuro-cognitive decline could be attributed to the use of antiepileptic drugs.	–	–	–	
Caramanna I, Bottomley A et al.	–	–	–	–	–	–	–	–	
Dehcordi SR, Mariano M et al.	Left-sided lesions were associated with lower scores on verbal tests. Right-sided tumors were related to lower scores on a test of facial recognition.	Tumor size <4 cm showed improvement in the processing speed after surgery.	Verbal Short-time memory and correct responses in executive functions	–	–	–	–	–	
Bonifazi S, Passamonti C et al.	–	–	–	–	–	Awake craniotomy does not affect NCGs in the majority of patients.	–	–	
Habets EJ, Kloet A et al.	Tumors in the left hemisphere had poorer baseline verbal memory, working memory, and attention.	–	Larger tumors in the left hemisphere had a poorer baseline executive and slower psychomotor functioning.	–	Patients on corticosteroids had worse baseline attention and executive functioning, and lower information processing speed.	No significant effect of surgery in NCFs	–	–	
Brown PD, Jensen AW et al.	Worse cognition at baseline in frontal tumors	–	–	–	–	–	–	–	Advanced age and GBM diagnoses correlated to decreased cognitive outcomes. Tumor progression was correlated to cognitive decline.

Table 3 (continued)

Authors	Location	Edema	Size/volume	Recurrence	Medication	Surgical resection	Radiotherapy	Chemotherapy	Other
Bian Y, Meng L et al.	–	–	–	–	–	–	No apparent significant effect on cognitive function	No apparent significant effect on cognitive function	–
Bodensohn R, Corradini S et al.	Lower verbal memory in left-sided tumors Better figural memory in tumors directly invading the hippocampus	–	–	–	Worse cognitive outcomes in patients on higher doses of corticosteroids	GTR may improve some subsets of cognition.	–	No significant effect on cognitive function	Age was significantly correlated with the decreased verbal memory and word fluency.
Wang Q, Xiao F et al.	–	–	Residual tumor volume > 5.58 cm^3 was an independent risk factor for cognitive impairment.	–	–	–	Grade IV glioma has a higher risk of cognitive impairment after CCRT.	–	Negative MGMT promoter methylation and GBM diagnoses were risk factors for cognitive impairment.
Butterbrod E, Bruijn J et al.	–	–	–	–	–	–	–	–	Progressive disease was correlated to cognitive decline. Age was not a significant predictor of cognitive decline.

Table 3 (continued)

Authors	Location	Edema	Size/volume	Recurrence	Medication	Surgical resection	Radiotherapy	Chemotherapy	Other
Dallabona M, Sarubbo S et al.	Patients with left-lateralized tumors had worse verbal memory than patients with right-sided tumors in both the short and long term. Tumors in the right dorsal stream had worse selective attention.	Edema leads to mass effect which significantly correlated to overall cognitive decline.	Increased volume significantly correlated to overall cognitive decline.	–	–	Short-term worsening in the repetition of sentences and numbers, short-term and long-term verbal memory, and visual attention. No significant worsening in late follow-up. Improvement in visual comprehension of sentences, naming verbs and nouns, short-term spatial memory, recognition memory, long-term spatial memory, and orofacial praxis.	–	–	Patients younger than 65 years old had better long-term verbal memory, attention, and executive functions. They also had better constructive skills.
Wang Q, Qi F et al.	–	–	–	–	–	–	No significant effect on cognitive function	No significant effect on cognitive function	–
Zarino B, Di Cristofori A et al.	–	–	–	–	–	–	–	–	Cognitive decline predicted tumor progression.

characteristics and treatment modalities on CF were tabulated in Table 3.

Results

A total of 1703 articles were identified through database search and 3 through additional resources (institute libraries). After removing duplicates 991 articles were left. Nine hundred twenty out of the 991 articles were removed in the initial screening of title and abstracts for relevance. Out of the 71 remaining articles, 58 could be accessed for full text. Forty-five were excluded according to exclusion criteria and 13 were included in the systematic review. The PRISMA flowchart is illustrated in Fig. 1.

Results of individual studies

Nine articles [10–18] assessed CFs before and after treatment. Caramanna et al. assessed the consistency of cognitive

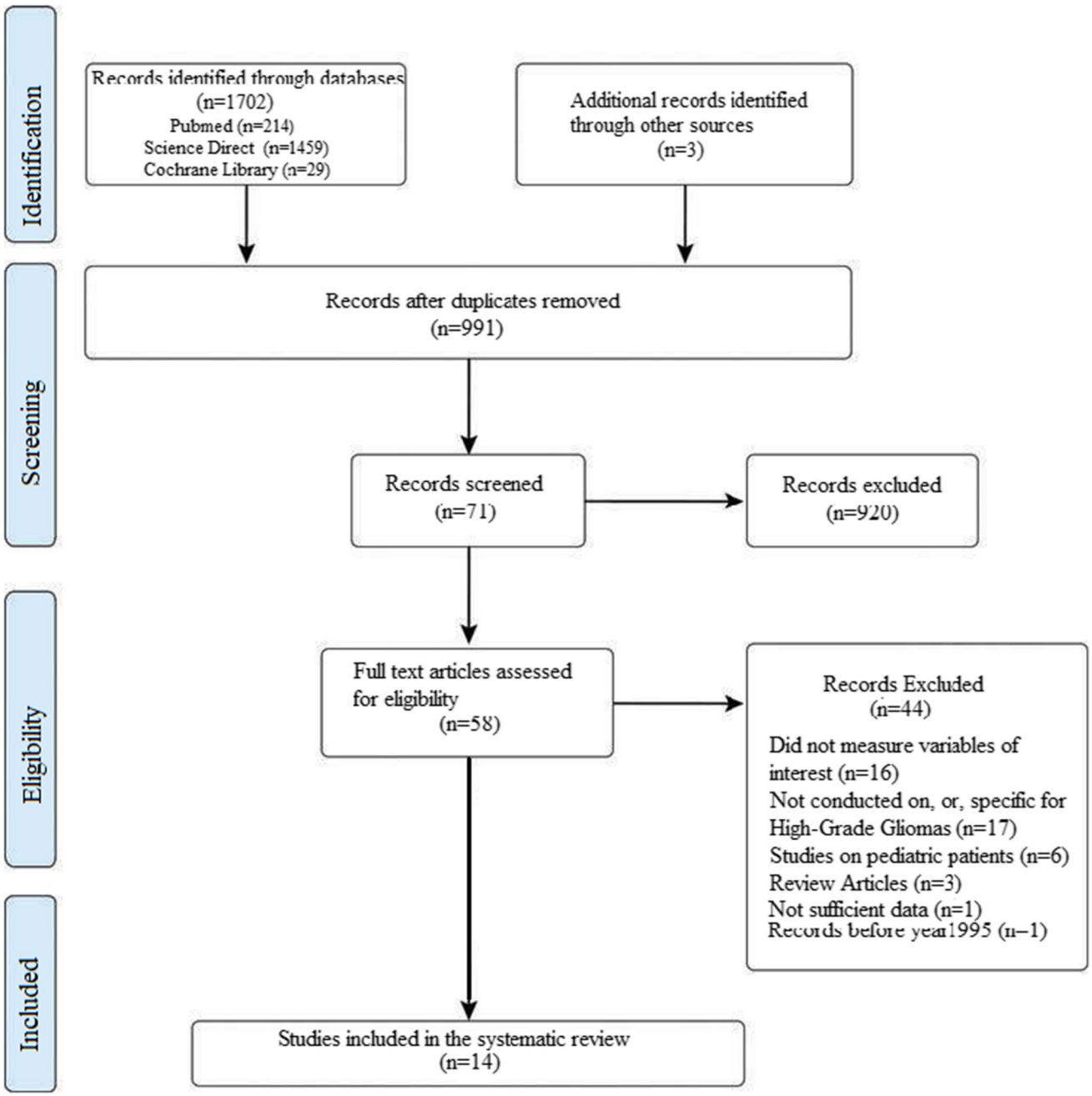

Fig. 1 PRISMA flowchart

complaints and objective cognitive functioning [19]. Butterbrod et al. and Dallabona et al. reported factors affecting disease progression and neuro-cognitive status, respectively [18, 20]. Zarino et al. studied neuropsychological function status predicting patient's outcome after treatment [21].

Table 1 summarizes the populations of individual studies, the WHO-CNS classification used to select the tumors, treatment modalities, and CF assessment timings including baseline and follow-ups.

Table 2 summarizes the CF assessments of individual studies including the CF assessed, the tool used to assess the CF, and baseline and follow-up scores as compared to the healthy population.

Table 3 summarizes the effects of tumor characteristics and treatment modalities on CFs. The tumor characteristics included the location of the tumor, edema, size/volume, and recurrence. The treatment modalities included medication, surgical resection, radiotherapy, chemotherapy, age, and others.

Cognitive function before treatment

Before treatment, 79% of HGG patients showed impairment in at least one cognitive domain, while 21% were not impaired. Thirty-five percent of patients had mild, 34% moderate, and 10% severe impairment [13]. Cognitively impaired patients reported more complaints than patients without cognitive impairment [19].

Cognitive function following treatment and on follow-up

Following surgical resection, patients deteriorated in CF; however, this functional decline was not statistically significant [10]. Verbal memory, attention, and psychomotor function were the domains most frequently impaired [13].

An improvement in memory functions and in processing speed was seen after surgery, especially in patients with widespread edema [11, 12]. Awake craniotomy was reported to contribute to preserving language and decrease the risk of postoperative permanent aphasic deficits when operating in eloquent areas [12]; thus, despite the deterioration of neuropsychological performances at early follow-up, surgery is also effective for improving the cognitive performances of patients and thus their quality of life [18].

Predictors of CFs

The possible predictors and their effects on CFs have been summarized in Table 3.

Tumors in the left hemisphere had worse verbal function [11, 13, 16, 18], working memory, and attention [13]. Right-sided tumors were related to worse facial recognition [11]. Tumors in the frontal lobe had an overall worse cognition [14]. Increased tumor volume was associated with overall cognitive decline [18], and so was a greater residual tumor volume after surgery [17]. Along with tumor volume, the surrounding edema also constituted a mass effect and lead to cognitive decline [18]. Epilepsy before surgery also contributed to the decline in cognition preoperatively and was also found to cause deteriorated cognition postoperatively [13]. Corticosteroids [13, 16] and anti-epileptics [10] could also contribute to cognitive impairment. Advanced age at diagnosis may be a risk factor for a worse cognitive outcome [14, 16, 18].

Following surgical resection, there was no specific effect reported on the CF. Bodensohn et al. reported that gross-total resection (GTR) may improve some subsets of cognition [16]. Dallabona et al. reported a short-term decline in some CFs but no significant worsening in late follow-up [18].

No study reported any evidence of cognitive impairment in glioma patients who had undergone radio-chemotherapy at least within the first year [15, 16, 22]. Wang et al. reported that grade IV glioma has a higher risk of cognitive impairment after concurrent chemoradiation [17].

Tumor progression was correlated to cognitive decline [14, 20]; thus, a decline in CFs may predict sub-clinical tumor progression [21].

Discussion

We conducted a systematic review and evaluated the neuro-CF of patients with high-grade gliomas before and after treatment along with the predictors of cognitive status in HGGs. Before surgical resection HGG, patients have impairment in at least one cognitive domain. Following surgical resection and/or chemo/radiotherapy, some aspects of CF deteriorated with time; however, this functional decline was not statistically significant. The predictors of greater cognitive decline were tumor localization, the mass effect of tumor and edema, pre-operative epilepsy, medication including anti-epileptics and corticosteroids, and greater age of the patient at diagnosis. Chemo- or radiotherapy has no significant effect on CFs.

Archibald et al. studied the long-term CFs of HGG survivors and reported impaired baseline CFs of several survivors and deterioration on specific tasks of the rest within 2 years of baseline testing [23]. Archibald et al. also reported that the most impaired CFs at baseline were verbal memory and sustained attention, whereas verbal learning and flexibility in thinking were the most frequent to decline over time [23]. Weitzner and Meyers reviewed similar studies before 1996 and reported that a decline in CFs is inevitable following successful treatment of HGGs; however, contrary to our

analysis, this decline is irrespective of tumor localization or grade; instead was related to the type of therapy and tumor lateralization [24]. These differences may be explained by the disparities in WHO-CNS classifications and different treatment approaches of chemo- and radiotherapy. Similar to our results, Taylor et al. reported no significant effect of radiotherapy on CFs; older age, lower baseline CFs, and subclinical tumor progression were reported to be the predictors of cognitive decline [25]. There is no significant effect of radiotherapy on CFs in low-grade gliomas either [26].

Tucha et al. studied the cognitive impairments among patients with brain tumors of the frontal or temporal lobes and reported that lesions of the left temporal lobe are often associated with disturbances of language functions similar to our findings [27]. The difference based on location is also due to the dominancy of the left cerebral hemisphere over the right cerebral hemisphere. The reason behind these deficits is the presence of Broca's area and Wernicke's area in the left hemisphere. Tumors that were found to be diagnosed and reported to be in the temporal lobe also significantly decreased the cognition in patients with HGGs. This also can be explained by the presence of Wernicke's area in the posterior one-third of the temporal convolution in the left hemisphere of the brain. De Baene et al. reported that the local efficiency of the contralesional hemisphere was associated with reaction time and contralesional activity was associated with attention and cognitive flexibility [28]. Further, HGGs were associated with decreased verbal memory, worse attention, and cognitive flexibility; tumor volume was associated with visual memory; however, age at diagnosis, epilepsy, and the use of anti-epileptic medication were not associated with decline in any of the assessed CF [28]. Acevedo-Vergara et al. reviewed the effects of specific tumor localizations and also reported that language function was associated with lesion in the dominant cerebral hemisphere, memory function in the left-hemisphere, and executive functioning in prefrontal cortex of the frontal lobes [29].

Tucha et al. also reported that patients with larger lesions and those with accompanying edema displayed significantly more cognitive impairments [27]. Edema is a leading factor that causes compression of the brain matter; its removal during surgical resection helped improve the results [11, 12]. Upon eradicating associated edema, with drugs like bevacizumab and temozolomide, an improvement in processing speed and memory functions can be observed [27, 30]

Cognitive and social functioning, physical, emotional, and spiritual well-being collectively comes under the health-related quality of life (HRQOL). Since HGGs have a poor prognosis and low life expectancy, HRQOL is an important concern for doctors and caregivers. There are several determining factors including sex, tumor location, and histological classification. Rogers et al. reported lower QOL in females than in males [31]. Although tumor location and its relation to QOL is controversial, however, several studies reported that HGG patients with left-sided brain lesions were found with increased memory problems [32], poor fluency while speaking [32, 33], and more depressed state and symptoms [32] and difficulty in communication [34]. GBM patients are reported to have low HRQOL as compared to others because of its aggressively growing nature, shorter time of progression, and faster deterioration in cognition [35, 36].

Additionally, the drugs used in the treatment after resection such as dexamethasone and previously used anti-epileptic drugs [27] to treat seizures (carbamazepine, valproic acid, and phenytoin) taken alongside the radiotherapy had a correlation with the declined cognitive functions. Apart from the medicine intake, patients who presented with epileptic seizures preoperatively could have higher rates of deteriorated cognitive function. A possible explanation can be the deteriorating effects of epilepsy preoperatively which worsened postoperatively along with anti-epileptic drugs. Patients were also taking corticosteroids which was found to be associated with a decline in executive functioning, information processing, and attentive behavior preoperatively.

Moreover, the age of the patient at the time of diagnosis was also found to have an impact on the progression of the disease and the related impairment. Older patients were found to have greater cognitive impairment than the younger ones who were found to be less impaired and showed a good prognosis.

Only one study reported a molecular subgroup in relation to cognitive impairment with negative MGMT promoter methylation being a risk factors for cognitive impairment [17]. Derks et al. studied cognitive performances of HGG patients in relation to IDH-mutation status and reported that patients with IDH-with gliomas had poorer cognitive performances as compared to patients with IDH-mut gliomas [37].

Tumor progression was correlated to cognitive decline [14, 20, 21]. Klein et al. assessed the prognostic value of cognitive functioning in HGGs and reported that the measurement of CF in HGG patients may be of high clinical relevance throughout the disease [38]. Meyers et al. also reported that the assessment of CFs, HRQOL, and patient function in terms of ability to perform activities of daily living can be important in predicting the survival of patients with recurrent malignant brain tumors [39]. Taphoorn and Klein reported that cognitive deterioration may be the first indicator of progressive disease after treatment [40]. van Kessel et al. conducted a retrospective analysis of CF of HGG patients and concluded that impaired executive functions and memory were significantly correlated with survival, whereas language, psychomotor speed, and visuospatial functioning were not [41].

Specific limitations of individual studies included a risk of bias associated with the sample sizes and the number of people who showed up on all the follow-ups and participated in tests. The first limitation of our study is the heterogeneity of WHO-CNS classifications used; thus, different tumors being considered in the category of HGGs. Further limitations include non-specification in different brain tumors, variability of sample sizes, and heterogeneity of the CF tests used by individual studies.

Conclusion

HGG patients have CF impairments in at least one cognitive domain. These impairments tend to increase with time and disease progression. Factors that impact CF include tumor localization, grade, recurrence, mass impact of both tumor volume and surrounding edema, corticosteroids and antiepileptic drugs intake during radiotherapy, and patients age at diagnosis. Treatment modalities including surgical resection and radio- or chemotherapy have no significant effect on CFs. An important clinically relevant finding was that the deterioration of cognitive status may indicate subclinical tumor progression thus emphasizing the importance of CF assessment throughout the course of the disease.

Declarations

Ethical approval Not applicable.

Conflict of interest The authors declare no competing interests.

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