



Research Article

The Impact of Glioma Growth and Resection on Neurocognitive Impairment – a Prospective Observational Study

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Abstract

Cognitive impairments are common among patients suffering from brain tumors. Up to date, however, it is rarely assessed in clinical routine. This study aimed to evaluate pre- and postoperative neurocognitive performance in a wide range of patients suffering from gliomas representing clinical routine by using a test battery of easy-to-use and established neurocognitive tests. Patients undergoing microsurgical glioma resection between 04/2019 and 03/2021 were prospectively included. A structured test set for neurocognitive function was performed preoperatively in 33 patients and during follow-up in 14 patients. Data were converted into z-scores and combined with the corresponding cognitive domains. Thirty-three patients aged 49.2 ± 14.4 (22-81) years were included. The individual tests showed impairments preoperatively most frequently in the trail-making test B (TMT-B) in 63.6% of patients, followed by the Montreal Cognitive Assessment (MoCA) with 39.4%. Preoperatively, a clinically significant impairment was found in the domain of executive function and attention, with a mean domain score of -2.49 . At follow-up, the group domain scores were impaired on the same cognitive domains as preoperatively, with executive function and attention significantly impaired ($z = -2.58$). Neurocognitive deficits are present in the majority of patients with glioma before surgery while still performing well in conventional scores regarding functional status. We did not observe any significant surgery-related deterioration in cognitive performance; however, this finding is compromised by a considerable number of patients lost to follow-up.

Keywords

Glioma, Cognitive Deficits, Cognitive Testing, Neurocognitive Impairments

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1. Introduction

Cognitive impairments are common among patients suffering from brain tumors. Unspecific symptoms such as headaches, forgetfulness, or neurological deficits often lead to further diagnostics, including magnetic resonance imaging (MRI).

However, significant discrepancies between the actual perception of cognitive impairments and the results in neurocognitive testing can be observed [1, 2]. Testing neurocognitive performance in patients is challenging, as cognition covers many brain functions, including perception, attention, memory, language, and intelligence [3]. Those functions are related to specific brain structures and networks and their interaction. While simple tasks of perception or motor function can often be narrowed down to distinct brain areas, higher cognitive functions recruit larger brain areas, which are also subject to interindividual variability [3, 4]. However, parietal brain regions and the underlying networks play a leading role in higher cognitive functions [5].

In patients with brain tumors, impaired neurocognitive performance can be observed in at least one test in more than three out of four patients [6, 7]. Neurocognitive functioning in glioma patients can be affected by multiple factors, including the tumor itself, tumor-related epilepsy, tumor-specific treatments, including surgery and adjuvant therapy, as well as patient-related factors. Until today, preoperative neurocognitive testing is not considered a standard of care in patients diagnosed with primary brain tumors.

This study aimed to evaluate neurocognitive performance in a wide range of patients suffering from gliomas representing clinical routine by using a test battery of easy-to-use and established neurocognitive tests.

2. Materials and Methods

2.1. Ethics

Our local ethics committee approved the study (registration number: 192/18) and conducted by the Declaration of Helsinki. Written informed consent was obtained from all patients before participation in the study.

2.2. Patient Enrollment

Thirty-three patients were prospectively included from 04/2019 to 03/2021. Inclusion criteria for this study were 1) age of above 18 years, 2) German-speaking patients, 3) microsurgical tumor resection, and 4) histopathologically diagnosed glioma. Exclusion criteria were contraindications to MRI scanning.

2.3. Setup

2.3.1. Functional Status

The patient's functional status was evaluated using established

measures, including the Karnofsky Performance Scale (KPS), the modified Rankin Scale (mRS), and the Barthel Index (BI). In addition, the patient's professional status was acquired.

Motor function was rated according to the British Medical Research Council (BMRC) scale. For comparative analysis, a total motor score was defined as the lowest score obtained across all motor functions tested for each patient.

The Quick Aphasia Battery (QAB) was performed to assess language function in patients with language-eloquent left-sided tumors. A cut-off score for aphasia in the QAB of <8.9 in the total score was applied [8].

2.3.2. Cognitive Testing

All patients underwent a test set of neuropsychological tests to identify potential cognitive deficits, all fulfilling the criteria to be easily applicable in clinical routine by tests with paper and pencil. The tests performed were the Montreal Cognitive Assessment (MoCA), the Trail Making Test Part A (TMT-A), the Trail Making Test Part B (TMT-B), the Bells Test, the copying task of the Rey-Osterrieth-Complex-Figure Test (ROCFTc), the Line Bisection (LB), and the Forwards Digit Span (FDS) and Backwards Digit Span (BDS) [9-15].

In most neurocognitive tests, multiple cognitive domains are addressed. Tests were assigned to the following neurocognitive domains: executive function and attention, memory, language, visuospatial function, and processing speed. The MoCA was excluded from this categorization because it assesses various cognitive domains. Consequently, a patient with an impaired MoCA score would be classified as having impairments in all tested domains without specifying the exact subtest of difficulty.

The MoCA was developed as a screening tool to detect mild cognitive impairment in patients who achieve regular scores on tests such as the Mini-Mental State Examination. It shows a high test-retest reliability and excellent internal consistency [9]. The subtests cover the domains of visuospatial/executive function, naming, memory, attention, language, abstraction, computation, and orientation [9]. Normative data by Thomann et al. was used to compute z-scores [16].

The FDS and BDS are both assigned to short-term memory. In this test, the number of digits in the most extended reproduced series is taken as the result [14]. The BDS demands more complex brain functions and is additionally associated with executive function and attention [17]. Normative data by Monaco et al. was used to calculate the corresponding z-scores [17].

The TMT-A predominantly provides information on processing speed. On the contrary, the TMT-B reflects the ability to direct attention to changing stimuli and is assigned to the domain of executive function and attention. The TMT-A and TMT-B were performed according to the modified administration by Reitan, in which the examiner intervenes as soon as the subject makes an error and points out this error to help

him correct it. The error rates are not recorded, only the additional time the subject needs to correct it [10]. Z-scores were calculated using normative data derived from a healthy cohort published by Tombaugh et al. [18].

The (ROCFTc) was included, as successful copying of the figure requires visuospatial perception, sufficient attention and concentration, visual-motor function, planning, and organizational skills [19]. The ROCFTc was, therefore, assigned to executive function, attention, and processing speed. The ROCFTc is highly predictive of severe cognitive impairment [20]. The most widely used scoring system is the Osterrieth system, which is based on the presence and accuracy of the 18 test items (Osterrieth, 1944) [21]. The task completion time of the ROCFTc (ROCFTc-t) was assigned to the processing speed domain. Z-scores for each patient were calculated using data by Tremblay et al., who analyzed copy scores and task completion times in volunteers [22].

Visuospatial function, especially visual neglect, was assessed in the LB test, in which the patient is asked to bisect horizontal lines placed on a sheet of paper. A patient suffering from unilateral spatial neglect traditionally incorrectly estimates the center of the line towards the side of the brain defect while neglecting the other end of the line [12, 13].

The Bells Test is a cancellation task to cross out bells scattered in various shapes [11]. The Bells Test task completion time (BT-t) replicates the patient's processing speed. The Bells Test's accuracy score (BT-AC) describes the accuracy with which a patient crosses out the bells and is calculated from the omission errors made. It is assigned to the domain of executive function and attention. In addition, the Bells Test's asymmetry score (BT-AS) is calculated from the difference between the number of crossed-out targets on the right and the number of crossed-out targets on the left portion. The BT-AC and BT-AS are both assigned to visuospatial functioning. For comparison, normative data based on the test results of 401 healthy participants was applied [23].

2.3.3. Data analysis

Nonparametric tests were applied due to the small sample size and the variables not meeting normality criteria. Sub-analyses were performed to identify differences between tumor grades and tumor locations. The Kruskal-Wallis Test was utilized for comparison of three or more unmatched groups, followed by the Dunn test for multiple comparisons, while the Mann-Whitney test was applied for comparisons between two unpaired groups.

Neurocognitive test scores were converted into z-scores (standard equivalents) based on published normative data derived from widely accepted studies of healthy control populations, enabling comparison in the absence of established clinical cut-off values. Z-scores were not calculated for the QAB and LB tasks due to the lack of appropriate normative data.

We differentiated between individual and group analysis. For individual-level analyses, z-scores were calculated for

each patient and each applicable measurement, or performance was compared to predefined cut-off values (QAB, LB, BT-AS). The percentage of impaired patients per measurement or cognitive domain was determined by counting patients whose performance met criteria for impairment. Group-level analyses considered all patients' scores to calculate mean test scores and mean cognitive domain scores, including executive function and attention, memory, visuospatial function, and processing speed. Mean domain scores were computed by averaging z-scores across all tests within a specific domain. The language domain was excluded from group-level analyses due to the unavailability of normative data for the QAB and because it was represented by a single language test only. Impairment was defined as performance below a cut-off value (QAB, LB, BT-AS) or a z-score ≤ 1.5 standard deviations relative to normative data. For timed measurements, this means a score of ≥ 1.5 SD above normative data, whereas for other tests higher scores indicated better performance.

At the group level, a cognitive domain was considered impaired if the mean z-score exceeded ± 1.5 SD. At the individual level, a domain was classified as impaired if ≥ 1 test within that domain met criteria for impairment.

Postoperative follow-up results were compared to preoperative performance using paired nonparametric testing (Wilcoxon signed rank test with Pratts method). Sub-analyses examining differences according to tumor grade and tumor location within the FU cohort were not conducted due to the small sample size. Changes of ≥ 1.5 SD between preoperative and follow-up assessments were considered clinically significant. Change scores (Δ) were calculated by subtracting the preoperative score from the FU score (FU-preOP with FU), using z-scores when available and raw test scores otherwise.

Data analyses and descriptive statistics were conducted using GraphPad Prism (version 9.5.1 for Mac, GraphPad Software, La Jolla, CA, USA). A p-value of <0.05 was considered statistically significant.

3. Results

3.1. General Data

In total, 33 patients aged 49.2 ± 14.4 (22-81) years were included in this study, with the majority being male (72.7%). The tumor site was almost evenly distributed between the left (51.5%) and right hemisphere (48.5%). 25 patients were diagnosed with high-grade gliomas according to the classification of the WHO, and eight patients with low-grade gliomas (Table 1). Eleven (33.3%) patients had tumors in the frontal lobe, nine (27.3%) in the parietal lobe, five (15.2%) in the temporal lobe, five (15.2%) in the insular lobe, and three (9.1%) in other areas (Table 1). The average time between the preoperative examination and surgery was 5.8 ± 4.1 (1-14) days, excluding one outlier at five months.

Follow-up cognitive testing was available for 14 patients (mean age 44 ± 12.5 years) and was performed 5.6 ± 4.4 (0.5

– 15) months after surgery; tumor grades were 29% grade 2, 36% grade 3 and 36% grade 4 tumors. 19 patients were lost to FU (mean age 53 ± 14.7 (22-81) years), including 21% grade 2, 26% grade 3, and 53% grade 4 tumors. Patients lost to follow-up were statistically significantly older ($p=0.021$) than those who completed FU, while no difference was observed in tu-

mor grade ($p=0.42$) (Table 1). Seven patients (50%) underwent radiotherapy before FU-testing (adjuvant therapy (AT) group).

Patient and tumor characteristics for all patients (preOP), for those lost to follow-up (lost to FU), and the follow-up cohort (FU).

Table 1. Patient and tumor characteristics.

	preOP (n=33)	lost to FU (n=19)	FU (n=14)	p-value (lost to FU/ FU)
Gender (n (%))				
1) Male	24 (72.7)	13 (68.4)	11 (78.6)	-
2) Female	9 (27.3)	6 (31.6)	3 (21.4)	
Age				
Mean $\pm$ SD (Min - Max)	49.2 $\pm$ 14.4 (22-81)	53 $\pm$ 14.7 (22-81)	43.6 $\pm$ 12.5 (25-72)	0.021
Hemisphere (n (%))				
1) Left	17 (51.5)	10 (52.6)	7 (50)	-
2) Right	16 (48.5)	9 (47.4)	7 (50)	
Localization (n (%))				
1) Frontal	11 (33.3)	6 (31.6)	5 (35.7)	-
2) Parietal	9 (27.3)	6 (31.6)	3 (21.4)	
3) Temporal	5 (15.15)	2 (10.5)	3 (21.4)	
4) Insular	5 (15.15)	2 (10.5)	3 (21.4)	
5) Other	3 (9.1)	3 (15.8)	0 (0.0)	
WHO-Grade (n (%))				
1) 2	8 (24.2)	4 (21.1)	4 (28.6)	0.416
2) 3	10 (30.3)	5 (26.3)	5 (35.7)	
3) 4	15 (45.5)	10 (52.6)	5 (35.7)	
Previous surgeries (n (%))				
1) Primary resection	20 (60.6)	10 (52.6)	10 (71.4)	0.310
2) Recurrence	13 (39.4)	9 (47.4)	4 (28.6)	

3.2. Functional Status

Preoperatively, most of the included patients were independent in daily life. Preoperatively, the median KPS was 90 (80-100) in 31 patients, the median BI was 100 (90-100) in 32 patients, and the median mRS was 0 (0-3) in all 33 patients. Among the 14 patients who underwent FU assessment, comparison between preoperative testing (preOP with FU) and FU demonstrated a statistically significant worsening in KPS ($p=0.012$), but not in mRS ($p=0.055$) or BI ($p=0.125$). Overall,

ten patients (71.4%) showed deterioration and three patients (21.4%) showed improvement in at least one of the three measures (Figure 1, Table 2). When comparing patients lost to FU with those who completed FU, a statistically significant difference was observed in mRS scores, with patients lost to FU demonstrating poorer performance ($p=0.048$). No significant differences were found for BI ($p=0.742$) or KPS ($p=0.202$). Additionally, no significant differences were identified between the AT and nonAT groups for mRS ($p=0.499$), KPS ($p=0.722$) or BI ($p=0.437$).

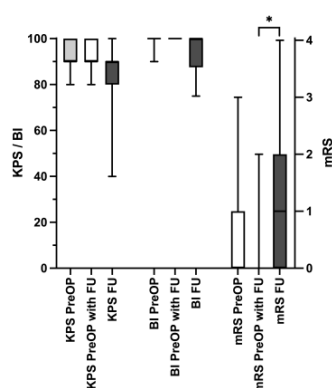


Figure 1. Functional status.

Figure 1 shows the results of the Karnofsky Performance Scale (KPS), Barthel Index (BI), and mRS (modified Rankin Scale) preoperatively (preOP), as well as cohort of 14 patients with follow-up data preoperatively (preOP with FU) and at follow-up (FU)

* = $p < 0.05$

Functional status of all patients preoperatively (preOP), those lost to follow-up (preOP lost to FU), and the follow-up cohort both preoperatively (preOP with FU) and at follow-up (FU). The table also compares preoperative and FU scores within the FU cohort as well as preoperative scores between patients lost to FU (preOP lost to FU) and the FU cohort (preOP with FU).

Table 2. Functional status.

	preOP	preOP lost to FU	preOP with FU	FU	p-value (preOP with FU/ FU)	p-value (preOP lost to FU/ preOP with FU)
Number of patients (n)	KPI: 31; BI: 32; mRS: 33	KPI: 17; BI: 16; mRS: 19	14	14	-	-
Karnofsky Performance Index (KPI) (Median (Min-Max))	90 (80-100)	90 (80-100)	90 (80-100)	90 (40-100)	0.055	0.202
Barthel-Index (BI) (Median (Min-Max))	100 (90-100)	90 (80-100)	100 (90-100)	100 (75-100)	0.125	0.743
Modified Rankin Scale (mRS) (Median (Min-Max))	0 (0-3)	1 (0-4)	0 (0-2)	1 (0-4)	0.012	0.048

3.3. Occupational Status

Preoperatively, 32 patients provided detailed information on their occupational status. 19 patients (59.4 %) were employed, with nine patients (28.1%) fully engaged with 100 % of regular working hours.

At FU, 13 patients provided information on their professional life status. Four patients (30.8%) were employed at the time immediately preceding assessment, with two patients (6.3%) reporting occupation of 100%. Comparison between the two test time points revealed no statistically significant change in the amount of occupation at the group level ($p=0.21$). No significant differences were observed between the AT and nonAT groups at FU ($p>0.999$) or in the change score (FU-preOP with FU) ($p=0.511$). Additionally, no differences were found between patients who were lost to FU and those who completed FU ($p=0.667$).

3.4. Motor Function and Language Performance

Preoperatively, five patients (15.2%) showed motor deficits.

At FU, four out of 14 patients (28.6%) demonstrated deterioration in motor function, whereas ten patients (71.4%) remained stable. This change was not statistically significant ($p=0.125$) (Table 3). No significant differences in motor function were observed between the adjuvant-therapy and non-adjuvant therapy groups ($p=0.706$). Additionally, no statistically significant differences were found between patients lost to FU and those who completed FU ($p=0.321$). Preoperatively, language function in the QAB was in median 11.2 (8.4-12.0) in twelve patients, with only one patient showing aphasia (8.3%). At FU, QAB test results were available in only three patients, with two showing aphasia. Both patients had tumors in the insular lobe of the left hemisphere and didn't show aphasia preoperatively.

Motor function according to the British Medical Research Council (BMRC) scale for all patients at the preoperative assessment (preOP), patients lost to follow-up (preOP lost to FU), and the follow-up cohort both preoperatively (preOP with FU) and at follow-up (FU). The table also compares pre-operative and FU scores within the FU cohort, as well as pre-operative motor scores between patients lost to FU and those included in FU.

Table 3. Status of motor function.

	preOP n (%)	preOP lost to FU	preOP with FU n (%)	FU n (%)	p-value (preOP with FU/FU)	p-value (preOP lost to FU/ preOP with FU)
Motor Function (BMRC)	33	19	14	14		
BMRC 5/5	28 (84.8)	15 (78.9)	13 (92.9)	9 (64.3)	0.125	0.321
BMRC 4/5	4 (12.1)	3 (15.8)	1 (7.1)	4 (28.6)		
BMRC <4/5	1 (3.1)	1 (5.3)	0	1 (7.1)		

3.5. Neurocognitive Testing

33 patients completed testing preoperatively, including two patients canceling the ROCFTc due to fatigue, while 14 patients were tested at FU. Preoperatively, 84.8% of the patients in this inhomogeneous cohort showed deficits in at least one of the measurements. In the TMT-B, impairments were found most frequently (63.6% of patients), followed by the MoCA, with 57.6% of patients showing a lower score compared to the average population and the TMT-A and BT-AC, with 36.4% of patients each (Table 4). Impairments were observed at the individual patient level for all measurements except for the ROCFTc-t (Table 4). On the group level, preoperatively, all measures except the ROCFTc and ROCFTc-t showed worse results compared to normative data from healthy subjects. Clinically significant impairments (≥ 1.5 SD) were only found for the TMT-B, TMT-A, BT-AS, and BT-AC (Figure 2, Table 5).

At follow-up, 85.7% of the patients showed deficits in at least one of the tests. At FU, the BT-AC showed impairments most frequently (57.1% of patients), followed by the TMTB with 50% of patients, the MoCA (42.9%), as well as TMTA and LB (28.6%) (Table 5). Impairments occurred individually in all measurements except for the ROCFTc and ROCFTc-t. On the group level at FU, all measures except ROCFTc, ROCFTc-t, and BT-t showed worse results than healthy subjects' normative data. In contrast, clinically significant impairments (≥ 1.5 SD) were found in the TMTB, TMTA, BT-AS, and BT-AC (Table 5).

The only domain showing clinically significant impairments preoperatively was executive function and attention,

with a mean domain score of -2.49. The group-level preoperative performance was within 1.5 SD for all other domains compared to an average healthy population. However, a negative group domain score was observed compared to the average population.

At FU, the group domain scores were impaired on the exact cognitive domains preoperatively. The only domains showing clinically significant impairment were executive function and attention, with a mean domain score of -2.58. The most dynamic domain was the domain of the visuospatial function ($FU_{PRE} z = -0.56$, $FU z = -0.94$), while the most stable domain was the memory domain ($FU_{PRE} z = -0.36$, $FU z = -0.35$) (Table 5). No statistically significant differences between the preoperatively and at FU test results were observed regarding all individual neurocognitive tests, as well as between patients with and without radiotherapy prior to FU-testing.

33 patients completed testing preoperatively, including two patients canceling the ROCFTc due to fatigue, while 14 patients were tested at FU. Preoperatively, 84.8% of the patients in this inhomogeneous cohort showed deficits in at least one of the neurocognitive measurements. Impairments were most frequently observed on the TMT-B, affecting 63.6% of patients, followed by the MoCA, with 39.4% of patients scoring below the healthy population mean, and the TMT-A and BT-AC, with 36.4% of patients each (Table 4). At the individual patient level, impairments were identified across all measurements except the ROCFTc-t (Table 4).

Rates of impaired test results across all neurocognitive tests performed in this study. Results are reported for all patients at the preoperative assessment (preOP), stratified by primary versus recurrent tumors, for patients lost to FU (preOP lost to FU) and for the FU cohort, both preoperatively (preOP with FU) and at follow-up (FU).

Table 4. Impairments in neurocognitive tests.

Test	preOP		Primary tumor (preOP)		Recurrent tumor (preOP)		preOP lost to FU		preOP with FU		FU		Cut-off
	n	Impaired (n (%))	n	Impaired (n (%))	n	Impaired (n (%))	n	Impaired (n (%))	n	Impaired (n (%))	n	Impaired (n (%))	
MoCA	33	13 (39.4)	20	9 (45.0)	13	4 (30.8)	19	9 (47.4)	14	4 (28.6)	14	6 (42.9)	*
TMT-A	33	12 (36.4)	20	7 (35.0)	13	5 (38.5)	19	9 (47.4)	14	3 (21.4)	14	4 (28.6)	*
TMT-B	33	21 (63.6)	20	13 (65.0)	13	8 (61.5)	19	13 (68.4)	14	8 (57.1)	14	7 (50.0)	*
BT	33		20		13		19		14		14		
BT-AC		12 (36.4)		4 (20.0)		8 (61.5)		9 (47.4)		3 (21.0)		8 (57.1)	*
BT-AS		6 (18.2)		4 (20.0)		2 (15.4)		5 (26.3)		1 (7.1)		3 (21.4)	≥3
BT-t		2 (6.1)		1 (5.0)		1 (7.7)		1 (5.3)		1 (7.1)		2 (14.3)	*
LB													
Score	33	5 (15.2)	20	4 (20.0)	13	1 (7.7)	19	3 (15.8)	14	2 (14.3)	14	4 (28.6)	≤14 **
FBDS	33		20		13		19		14		14		
FDS		9 (27.3)		5 (25.0)		4 (30.8)		4 (21.1)		5 (35.7)		3 (21.4)	*
BDS		5 (15.2)		4 (20.0)		1 (7.7)		2 (10.5)		3 (21.4)		2 (14.3)	*
ROCFTc	31		20		13		17		14		14		
Score		4 (12.1)		4 (20.0)		0		3 (17.6)		1 (7.1)		0	*
Time		0 (0.0)		0		0		0		0		0	*
QAB	12	1 (8.33)	5	1 (20.0)	7	0	10	1 (10.0)	2	0	3	2 (66.7)	<8.9

TMT-A: Trail Making Test Part A; TMT-B Trail Making Test Part B; ROCFT Rey-Osterrieth-Complex-Figure Test; ROCFT-t Rey-Osterrieth-Complex-Figure Test time; LB Line-Bisection; FDS Forward Digit Span; BDS Backwards Digit Span; BT-AC Bells Test accuracy score; BT-AS Bells Test asymmetry score; BT-t Bells Test task completion time; QAB Quick Aphasia Battery * z-scores derived from normative data, impairment is defined as ≥ 1.5 SD below norm, ** minimum difference of three errors between sides

At the group level, preoperative performance was significantly worse than normative data from healthy control populations for all measures except the ROCFTc and ROCFTc-t. Clinically significant impairments (≥ 1.5 SD) were only found for the TMT-B, TMT-A, BT-AS, and BT-AC (Figure 2, Table 5).

At FU, 85.7% of the patients showed impairment in at least one test. The most frequently affected was BT-AC, with deficits observed in 57.1% of patients, followed by TMTB (50%), MoCA (42.9%), and TMTA and LB (28.6%) (Table 5). Impairments occurred individually in all measurements except for the ROCFTc and ROCFTc-t. At the group level at FU, all measures except ROCFTc, ROCFTc-t, and BT-t showed worse results than healthy subjects' normative data. In contrast, clinically significant impairments (≥ 1.5 SD) were found in the TMTB, TMTA, BT-AS, and BT-AC (Table 5).

The only domain showing clinically significant impairments preoperatively was executive function and attention,

with a mean domain score of -2.49. Group-level preoperative performance in all other domains remained within 1.5 SD of the healthy reference population. However, a negative group domain score was observed compared to the population mean.

At FU, the group domain scores were impaired on the exact cognitive domains preoperatively. The only domains showing clinically significant impairment were executive function and attention, with a mean domain score of -2.58. The most dynamic domain was the domain of the visuospatial function (preOP with FU $z=-0.56$, FU $z=-0.94$), while the most stable domain was the memory domain (preOP with FU $z=-0.36$, FU $z=-0.35$) (Table 5). No statistically significant differences between the preoperatively and at FU test results were observed regarding all individual neurocognitive tests.

Comparisons of preoperative performance between patients lost to FU and those who completed FU revealed a statistically significant difference in the ROCFTc score, with poorer per-

formance observed in the lost to FU cohort ($p=0.009$). No statistically significant differences were identified between the two groups for any of the other neurocognitive measurements. Nevertheless, at the group level, patients lost to FU demonstrated lower mean performance on most tests (MoCA, TMTB, TMTA, BT-AC, BT-AS, LB, BDS, ROCFTc), whereas patients who completed FU showed lower performance only on BT-t and FDS (Table 5).

Z-scores are reported for all individual tests where available, as well as aggregated scores for neurocognitive domains. Results are presented for the full patient cohort preoperatively (preOP), for the FU cohort preoperatively (preOP with FU) and at follow-up (FU), as well as for the lost to FU cohort (preOP with FU). Z-scores worse than the comparative cohort are underlined, and z-scores with a standard deviation >1.5 are written in bold.

Table 5. Impairments in neurocognitive domains (z-scores).

Domains and tests	n (pre OP)	Z-scores mean (SD) preOP	Group domain scores preOP	n (pre OP lost to FU)	Z-scores mean (SD) preOP lost to FU	Group domain scores preOP lost to FU	n (pre OP with FU)	Z-scores mean (SD) preOP with FU	Group domain scores preOP with FU	n (FU)	Z-scores mean (SD) FU	Group domain scores FU
Executive and attention												
TMT-B	33	7.30 (7.77)		19	8.53 (7.82)		14	5.63 (7.65)		14	5.24 (6.57)	
BDS	33	-0.73 (1.61)	-3.45	19	-0.80 (1.19)	-4.16	14	-0.64 (2.11)	-2.49	14	-0.49 (1.38)	-2.58
BT-AC	33	2.32 (3.61)		19	3.15 (4.27)		14	1.21 (2.10)		14	2.0 (1.99)	
Memory												
BDS	33	-0.73 (1.61)	-0.40	19	-0.80 (1.19)	-0.43	14	-0.64 (2.11)	-0.36	14	-0.49 (1.38)	-0.35
FDS	33	-0.06 (1.76)		19	-0.06 (1.51)		14	-0.07 (2.11)		14	-0.20 (2.16)	
Visuospatial functioning												
BT-AC	33	2.32 (3.61)		19	3.15 (4.27)		14	1.21 (2.10)		14	2.0 (1.99)	
BT-AS	33	1.54 (1.88)	-1.24	19	1.94 (2.22)	-1.75	14	1.0 (1.16)	-0.56	14	1.55 (1.18)	-0.94
ROCFTc	31	0.15 (2.1)		17	-0.16 (2.18)		14	0.52 (2.01)		14	0.74 (0.6)	
Processing speed												
TMT-A	33	2.46 (5.66)		19	2.65 (4.57)		14	2.22 (7.05)		14	2.41 (6.43)	
ROCFTc-t	31	-0.87 (0.91)	-0.57	17	-0.70 (1.08)	-0.68	14	-1.06 (0.64)	-0.44	14	-0.83 (0.65)	-0.51
BT-t	33	0.12 (1.24)		19	0.10 (1.18)		14	0.16 (1.36)		14	-0.06 (0.97)	
General												

Domains and tests	n (pre OP)	Z-scores mean (SD) preOP	Group domain scores preOP	n (pre OP lost to FU)	Z-scores mean (SD) preOP lost to FU	Group domain scores preOP lost to FU	n (pre OP with FU)	Z-scores mean (SD) preOP with FU	Group domain scores preOP with FU	n (FU)	Z-scores mean (SD) FU	Group domain scores FU
cognition												
MoCA	33	-1.04 (1.43)	-	19	-1.20 (1.36)	-	14	-0.83 (1.54)	-	14	-0.92 (1.71)	-

TMT-A Trail Making Test Part A; TMT-B Trail Making Test Part B; ROCFT Rey-Osterrieth-Complex-Figure Test; ROCFT-t Rey-Osterrieth-Complex-Figure Test time; LB Line-Bisection; LB-t Line-Bisection task completion time; FDS Forward Digit Span; BDS Backwards Digit Span; BT-AC Bells Test accuracy score; BT-AS Bells Test asymmetry score; BT-t Bells Test task completion time; MoCA Montreal Cognitive Assessment

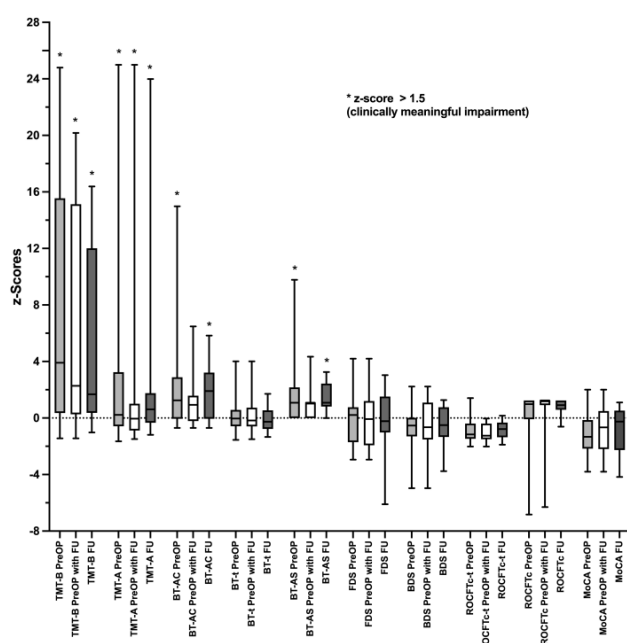


Figure 2. Z-scores of the individual neurocognitive tests.

Figure 2 illustrates the z-scores of the individual tests for all 33 patients preoperatively (preOP), as well as for the cohort of 14 patients with follow-up data preoperatively (preOP with FU) and at follow-up (FU). Values exceeding the mean by two standard deviations were excluded to enhance visualization. TMT-B Trail Making Test Part B; TMT-A Trail Making Test Part A; BT-AC Bells Test accuracy score; BT-t Bells Test task completion time; BT-AS Bells Test asymmetry score; FDS Forward Digit Span; BDS Backwards Digit Span; ROCFT Rey-Osterrieth-Complex-Figure Test; ROCFT-t Rey-Osterrieth-Complex-Figure Test time; MoCA Montreal Cognitive Assessment

3.6. Tumor Location

Between the four main tumor locations - frontal, parietal, insular, and temporal - we found a statistically significant difference regarding mRS ($p=0.03$) and the BT-AC ($p=0.045$), with parietal tumors performing worse. In the multiple comparisons testing, a statistically significant difference was observed in the BT-AC between frontal and parietal lesions ($p=0.034$), with the patients with parietal tumors performing worst.

3.7. Histopathological Results

Comparing tumor grades according to the World Health Organization Classification of Tumors of the Central Nervous System (WHO CNS) [24], we found a statistically significant difference in the distribution of KPS ($p=0.01$), mRS ($p=0.049$), BI ($p=0.03$), MoCA ($p=0.036$), with patients suffering from higher WHO CNS performing worse. In the multiple comparisons, differences were observed between WHO CNS 2 and 3 for KPS ($p=0.01$), between WHO CNS 2 and 4 for mRS ($p=0.046$), as well as for BI ($p=0.04$) between WHO CNS 3 and 4. Comparisons between high-grade glioma (HGG) and low-grade glioma (LGG) groups demonstrated statistically significant differences in KPS ($p=0.01$), mRS ($p=0.025$), MoCA ($p=0.036$) and TMTA ($p=0.044$), with the HGG group performing worse.

3.8. Adjuvant Therapy

Seven patients received adjuvant radiotherapy between surgery and the FU. At FU, patients who received adjuvant therapy (AT) performed significantly worse on the LB compared with patients who did not receive adjuvant therapy (nonAT) ($p=0.006$). In the adjuvant therapy cohort, two patients exhibited neglect both preoperatively and at FU, and two additional patients developed neglect at FU despite

no preoperative neglect. In contrast, no patients in the nonAT group showed neglect at either testing point. No statistically significant differences in performance status (mRS, KPS, BI) were observed. Descriptively, two patients in the nonAT group developed aphasia postoperatively despite normal preoperative language function, whereas no aphasia was observed in the AT group at either testing point. Analysis of within-subject change scores (calculated as the difference between FU and preoperative z-scores) revealed significantly greater declines in the non-adjuvant therapy group on the TMTA (mean change z-score: AT = -4.6 ± 9.6 , nonAT = 5.0 ± 8.9 ; $p=0.026$) and TMTB (mean change z-score: AT = -5.0 ± 7.5 , nonAT = 4.2 ± 6.9 ; $p=0.017$), and BDS (mean change z-score: AT = 1.2 ± 1.9 , nonAT = -0.87 ± 1.6 ; $p=0.044$). No significant change in scores was observed for the remaining cognitive measures.

4. Discussion

4.1. Testing of Cognition in Clinical Routine

In this study, cognitive testing was performed in 33 German-speaking patients, with 84.8% of patients showing deficits in at least one of the measurements for cognitive function. Tumor location as well as tumor entity were found to have an impact on cognitive performance. In clinical routine, preoperative testing before glioma surgery is rarely performed. However, recording a detailed neurological status, including cognitive performance, is of great value. Regarding selecting specific tests for glioma patients, Liouta et al. showed that MMSE, TMT-B, and semantic COWAT are independently and significantly associated with overall survival in patients with newly diagnosed glioblastoma [25].

The general functional status depicted by KPS, mRS, and BI appears insufficient to screen for cognitive impairments. Preoperatively, the vast majority of patients in this study showed a good functional status with a KPS of 90 (80-100), mRS of 0 (0-3), and BI of 100 (90-100). In contrast, cognitive impairments were already present preoperatively in a vast majority of patients, even in an inhomogeneous cohort. At FU, the functional status of the patients included in this study significantly decreased regarding mRS, and also decreased regarding KPS and BI. In contrast, surgery showed no clinically meaningful decrease in cognitive performance when compared to the preexisting preoperative impairment, underlining the discrepancy between cognitive performance and functional status in glioma patients. A study performed by Forster et al. analyzed patients with glioma in the corpus callosum and observed that all cognitive domains were affected in up to two-thirds of the patients while presenting a median KPS of 100% (range 60–100%) [26].

4.2. Impact of Glioma on Cognitive Performance

When analyzing our data regarding histopathological findings, we can see that the overall cognitive impairment in HGG exceeds that of LGG, which can be observed in the test results of the MoCA and TMT-A. Previous studies showed comparable results, with higher-grade gliomas showing significantly worse cognitive performance [27, 28]. Furthermore, a deterioration in neurocognitive function might indicate tumor recurrence in patients with glioma [29, 30].

4.3. Impact of Surgical Treatment

The effect of surgical resection of eloquent glioma on neurocognitive performance is still widely discussed. However, most studies showed no significant surgery-related cognitive decline at follow-up, whereas an initial negative effect was partially seen for specific cognitive domains [31-34]. Several studies have reported detrimental effects of radiotherapy on cognitive function, attributed to radiation-induced neuroinflammation and microvascular injury, synaptic and large-scale network dysfunction, as well as oligodendroglial damage and disruption of white matter integrity. [35-37]. The role of chemotherapy on cognitive performance remains unclear [38, 39]. On the contrary, the tumor itself significantly and clinically meaningful impacts the cognitive status, which can be observed in the preoperative cognitive status amongst different entities and tumor locations and appears to be a consistent factor throughout the course of the disease [34, 38]. To accurately delineate the effects of surgical treatment, adjuvant radiotherapy, and chemotherapy, structured longitudinal assessments are required to account for delayed and long-term treatment-related effects. As the present study design does not incorporate such sequential testing, comparisons between patients with and without adjuvant therapy reflect a composite treatment effect driven by surgery and radiotherapy. Consequently, these findings do not allow attribution of observed effects to individual treatment modalities.

To ensure an optimal extent of resection while preserving cognitive function during glioma surgery, the implementation of awake brain mapping has to be considered, depending on the location of the lesion and the patient's functional status. In most cases, awake surgery was usually performed in patients with tumors located in language-eloquent locations of the dominant hemisphere. More recently, awake surgery has also been applied in resections of the non-dominant hemisphere, testing for higher cognitive functions, such as visuospatial cognition and working memory [40-42]. Mapping of these functions demands a tailored protocol of selected function-specific tasks and testing [43]. Yet, complex cognitive processes spanning various cognitive subdomains rely on extensive, synchronized networks, making their intraoperative identification by DES and task-specific testing even more challenging [44].

4.4. Implications on Clinical Routine

Cognitive testing is a valuable tool to identify cognitive impairments, amongst various tumor entities and locations, especially for the individual patient. These findings play an important role in determining patients at risk and planning individualized neurological rehabilitation strategies, which reach beyond addressing obvious neurological impairments, such as aphasia or motor deficits. Preoperative testing is also crucial for consulting patients and their relatives regarding tumor-related symptoms, treatment strategies, and clinical outcomes, especially due to an apparent mismatch between the patient's perceived cognitive impairments and the results of objective cognitive testing [1, 2]. In addition, formal neurocognitive testing should be used to monitor individual treatment- and tumor-related impairments, because global functional status scores such as KPS, mRS, and BI insufficiently capture cognitive deficits. These performance measures are largely defined by categories reflecting basic activities of daily living and are therefore primarily linked to physical health and motor function, with only limited representation of language function and higher cognitive abilities. Consequently, the threshold for detecting cognitive impairment based solely on these scales is relatively high, which is consistent with the frequently observed discrepancy between objective or patient-reported cognitive function and traditional functional scores in glioma patients.

4.5. Limitations

When assessing the outcomes of this study, certain limitations have to be considered. Firstly, the total cohort size of 33 patients is considerably small, given that it covers a wide range of tumor locations. It is subsequently insufficient for conducting further subgroup analyses, such as those based on tumor location or age. Furthermore, the limited availability of follow-up testing in only 14 patients restricts the generalizability of the findings on surgery-related cognitive decline. Older age and greater functional impairment may limit patients' ability to attend follow-up visits or complete assessments, thereby contributing to the higher loss-to-follow-up rate. A potential confounder to be reckoned with is the fact that the time span until FU testing varied among patients, with only parts of the cohort undergoing testing before adjuvant radiotherapy. Statistically significant differences in change scores were observed for some tests between patients who received adjuvant therapy and those who did not, with greater declines in the nonAT group. However, the present study design does not incorporate sequential testing, therefore comparisons between patients with and without adjuvant therapy reflect a composite and even opposite treatment effect driven by surgery and radiotherapy, dependent on multiple confounders, including the preoperative status. In addition, the small sample size precluded further subgroup

analyses by tumor location or grade. Consequently, these findings should be interpreted with caution, as clear and clinically meaningful differences between groups could not be established.

5. Conclusions

Neurocognitive deficits are present in the vast majority of patients suffering from glioma before surgery, while they still perform well in conventional scores representing the functional status. The cognitive domain, which mainly was impaired, was executive function and attention. In particular, the TMT-B and the BT-AC showed impairments most frequently. The neurocognitive status correlated with pathological findings, being worse in patients with high-grade gliomas compared to patients with low-grade gliomas. Consistent with previous reports tumor resection only had a minor impact on the patient's neurocognitive performance.

Abbreviations

AT	Adjuvant Therapy
BDS	Backwards Digit Span
BI	Barthel Index
BMRC	British Medical Research Council
BT-AC	Bells Test's Accuracy Score
BT-AS	Bells Test's Asymmetry Score
BT-t	Bells Test Task Completion Time
FDS	Forwards Digit Span
FU	Follow-up
HGG	High-grade Glioma
KPS	Karnofsky Performance Scale
LB	Line Bisection
LGG	Low-grade Glioma
Lost to FU	Lost to Follow-up Cohort
MoCa	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
nonAT	Non-adjuvant Therapy
preOP with FU	Preoperative Test Result of the Follow-up Cohort
QAB	Quick Aphasia Battery
ROCFTc	Copying task of the Rey-Osterrieth-Complex-Figure Test
ROCFTc-t	Task Completion Time of the ROCFTc-t
TMT-A	Trail Making Test Part A
TMT-B	Trail Making Test Part B
WHO CNS °	Tumor Grades According to the World Health Organisation Classification of Tumors of the Central Nervous System

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Data Availability Statement

In the interest of patient privacy, all the collected raw data of individual cases is imparticipable. The anonymous datasets used and analyzed during the current study, the study protocol, and the statistical analysis plan are available up on reasonable request from the corresponding author to researchers who provide a methodologically sound proposal beginning 3 months and ending 5 years following article publication. Proposals should be directed to Maximilian.Schwendner@med.uni-heidelberg.de; to gain access, data requestors will need to sign a data access agreement.

Conflicts of Interest

The authors declare no conflicts of interest.

References

- [1] Gehring K, Taphoorn MJ, Sitskoorn MM, Aaronson NK (2015) Predictors of subjective versus objective cognitive functioning in patients with stable grades II and III glioma. *Neurooncol Pract* 2: 20-31. <https://doi.org/10.1093/nop/npu035>
- [2] Pertz M, Kowalski T, Jetschke K, Schmieder K, Schlegel U, Miller D (2022) Pre- and postoperative self-reported and objectively assessed neurocognitive functioning in lower grade glioma patients. *J Clin Neurosci* 106: 185-193. <https://doi.org/10.1016/j.jocn.2022.10.026>
- [3] Fuster JM (2006) The cognit: a network model of cortical representation. *Int J Psychophysiol* 60: 125-132. <https://doi.org/10.1016/j.jpsycho.2005.12.015>
- [4] Kanai R, Rees G (2011) The structural basis of inter-individual differences in human behaviour and cognition. *Nat Rev Neurosci* 12: 231-242. <https://doi.org/10.1038/nrn3000>
- [5] Humphreys GF, Lambon Ralph MA (2015) Fusion and Fission of Cognitive Functions in the Human Parietal Cortex. *Cereb Cortex* 25: 3547-3560. <https://doi.org/10.1093/cercor/bhu198>
- [6] Habets EJ, Kloet A, Walchenbach R, Vecht CJ, Klein M, Taphoorn MJ (2014) Tumour and surgery effects on cognitive functioning in high-grade glioma patients. *Acta Neurochir (Wien)* 156: 1451-1459. <https://doi.org/10.1007/s00701-014-2115-8>
- [7] Tucha O, Smely C, Preier M, Lange KW (2000) Cognitive deficits before treatment among patients with brain tumors. *Neurosurgery* 47: 324-333; discussion 333-324. <https://doi.org/10.1097/00006123-200008000-00011>
- [8] Wilson SM, Eriksson DK, Schneck SM, Lucanie JM (2018) A quick aphasia battery for efficient, reliable, and multidimensional assessment of language function. *PLoS One* 13: e0192773. <https://doi.org/10.1371/journal.pone.0192773>
- [9] Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 53: 695-699. <https://doi.org/10.1111/j.1532-5415.2005.53221.x>
- [10] Reitan RM (1955) The relation of the trail making test to organic brain damage. *J Consult Psychol* 19: 393-394. <https://doi.org/10.1037/h0044509>
- [11] Gauthier L, Dehaut F, Joanne Y (1989) The Bells Test: A quantitative and qualitative test for visual neglect. *International Journal of Clinical Neuropsychology* 11: 49-54.
- [12] Milner AD, Harvey M, Roberts RC, Forster SV (1993) Line bisection errors in visual neglect: misguided action or size distortion? *Neuropsychologia* 31: 39-49. [https://doi.org/10.1016/0028-3932\(93\)90079-f](https://doi.org/10.1016/0028-3932(93)90079-f)
- [13] Schenkenberg T, Bradford DC, Ajax ET (1980) Line bisection and unilateral visual neglect in patients with neurologic impairment. *Neurology* 30: 509-517. <https://doi.org/10.1212/wnl.30.5.509>
- [14] Humpstone HJ (1919) Memory Span Tests. *Psychol Clin* 12: 196-200.
- [15] Osterrieth PA (1944) Le test de copie d'une figure complexe; contribution à l'étude de la perception et de la mémoire. [Test of copying a complex figure; contribution to the study of perception and memory.]. *Archives de Psychologie* 30: 206-356.
- [16] Thomann AE, Goettel N, Monsch RJ, Berres M, Jahn T, Steiner LA, Monsch AU (2018) The Montreal Cognitive Assessment: Normative Data from a German-Speaking Cohort and Comparison with International Normative Samples. *J Alzheimers Dis* 64: 643-655. <https://doi.org/10.3233/JAD-180080>
- [17] Monaco M, Costa A, Caltagirone C, Carlesimo GA (2013) Forward and backward span for verbal and visuo-spatial data: standardization and normative data from an Italian adult population. *Neurol Sci* 34: 749-754. <https://doi.org/10.1007/s10072-012-1130-x>

- [18] Tombaugh TN (2004) Trail Making Test A and B: normative data stratified by age and education. *Arch Clin Neuropsychol* 19: 203-214.
[https://doi.org/10.1016/S0887-6177\(03\)00039-8](https://doi.org/10.1016/S0887-6177(03)00039-8)
- [19] Shin MS, Park SY, Park SR, Seol SH, Kwon JS (2006) Clinical and empirical applications of the Rey-Osterrieth Complex Figure Test. *Nat Protoc* 1: 892-899.
<https://doi.org/10.1038/nprot.2006.115>
- [20] Youn YC, Pyun JM, Ryu N, Baek MJ, Jang JW, Park YH, Ahn SW, Shin HW, Park KY, Kim SY (2021) Use of the Clock Drawing Test and the Rey-Osterrieth Complex Figure Test-copy with convolutional neural networks to predict cognitive impairment. *Alzheimers Res Ther* 13: 85.
<https://doi.org/10.1186/s13195-021-00821-8>
- [21] Canham RS, Stephen & Tyrrell, Andy (2000) Automated Scoring of a Neuropsychological Test: The Rey Osterrieth Complex Figure.
- [22] Tremblay MP, Potvin O, Callahan BL, Belleville S, Gagnon JF, Caza N, Ferland G, Hudon C, Macoir J (2015) Normative data for the Rey-Osterrieth and the Taylor complex figure tests in Quebec-French people. *Arch Clin Neuropsychol* 30: 78-87.
<https://doi.org/10.1093/arclin/acu069>
- [23] Mancuso M, Damora A, Abbruzzese L, Navarrete E, Basagni B, Galardi G, Caputo M, Bartolini B, Bartolo M, Zucchella C, Carboncini MC, Dei S, Zoccolotti P, Antonucci G, De Tanti A (2018) A New Standardization of the Bells Test: An Italian Multi-Center Normative Study. *Front Psychol* 9: 2745.
<https://doi.org/10.3389/fpsyg.2018.02745>
- [24] Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, Soffietti R, von Deimling A, Ellison DW (2021) The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol* 23: 1231-1251.
<https://doi.org/10.1093/neuonc/noab106>
- [25] Liouta E, Koutsarnakis C, Komaitis S, Kalyvas AV, Drosos E, Garcia-Gomez JM, Juan-Albarracin J, Katsaros V, Stavrinou L, Stranjalis G (2023) Preoperative neurocognitive function as an independent survival prognostic marker in primary glioblastoma. *Neurooncol Pract* 10: 527-535.
<https://doi.org/10.1093/nop/npad027>
- [26] Forster MT, Behrens M, Lortz I, Conradi N, Senft C, Voss M, Rauch M, Seifert V (2020) Benefits of glioma resection in the corpus callosum. *Sci Rep* 10: 16630.
<https://doi.org/10.1038/s41598-020-73928-x>
- [27] Talacchi A, Santini B, Savazzi S, Gerosa M (2011) Cognitive effects of tumour and surgical treatment in glioma patients. *J Neurooncol* 103: 541-549.
<https://doi.org/10.1007/s11060-010-0417-0>
- [28] Noll KR, Sullaway C, Ziu M, Weinberg JS, Wefel JS (2015) Relationships between tumor grade and neurocognitive functioning in patients with glioma of the left temporal lobe prior to surgical resection. *Neuro Oncol* 17: 580-587.
<https://doi.org/10.1093/neuonc/nou233>
- [29] Bosma I, Vos MJ, Heimans JJ, Taphoorn MJ, Aaronson NK, Postma TJ, van der Ploeg HM, Muller M, Vandertop WP, Slotman BJ, Klein M (2007) The course of neurocognitive functioning in high-grade glioma patients. *Neuro Oncol* 9: 53-62.
<https://doi.org/10.1215/15228517-2006-012>
- [30] Meyers CA, Hess KR (2003) Multifaceted end points in brain tumor clinical trials: cognitive deterioration precedes MRI progression. *Neuro Oncol* 5: 89-95.
<https://doi.org/10.1093/neuonc/5.2.89>
- [31] Klein M, Duffau H, De Witt Hamer PC (2012) Cognition and resective surgery for diffuse infiltrative glioma: an overview. *J Neurooncol* 108: 309-318.
<https://doi.org/10.1007/s11060-012-0811-x>
- [32] Kaleita TA, Wellisch DK, Cloughesy TF, Ford JM, Freeman D, Belin TR, Goldman J (2004) Prediction of neurocognitive outcome in adult brain tumor patients. *J Neurooncol* 67: 245-253.
<https://doi.org/10.1023/b:neon.0000021900.29176.58>
- [33] Satoer D, Visch-Brink E, Dirven C, Vincent A (2016) Glioma surgery in eloquent areas: can we preserve cognition? *Acta Neurochir (Wien)* 158: 35-50.
<https://doi.org/10.1007/s00701-015-2601-7>
- [34] Satoer D, Visch-Brink E, Smits M, Kloet A, Looman C, Dirven C, Vincent A (2014) Long-term evaluation of cognition after glioma surgery in eloquent areas. *J Neurooncol* 116: 153-160.
<https://doi.org/10.1007/s11060-013-1275-3>
- [35] Greene-Schloesser D, Robbins ME (2012) Radiation-induced cognitive impairment--from bench to bedside. *Neuro Oncol* 14 Suppl 4: iv37-44. <https://doi.org/10.1093/neuonc/nos196>
- [36] Greene-Schloesser D, Moore E, Robbins ME (2013) Molecular pathways: radiation-induced cognitive impairment. *Clin Cancer Res* 19: 2294-2300.
<https://doi.org/10.1158/1078-0432.CCR-11-2903>
- [37] Connor M, Karunamuni R, McDonald C, Seibert T, White N, Moiseenko V, Bartsch H, Farid N, Kuperman J, Krishnan A, Dale A, Hattangadi-Gluth JA (2017) Regional susceptibility to dose-dependent white matter damage after brain radiotherapy. *Radiother Oncol* 123: 209-217.
<https://doi.org/10.1016/j.radonc.2017.04.006>
- [38] Kirkman MA, Hunn BHM, Thomas MSC, Tolmie AK (2022) Influences on cognitive outcomes in adult patients with gliomas: A systematic review. *Front Oncol* 12: 943600.
<https://doi.org/10.3389/fonc.2022.943600>
- [39] Laack NN, Brown PD, Ivnik RJ, Furth AF, Ballman KV, Hammack JE, Arusell RM, Shaw EG, Buckner JC, North Central Cancer Treatment G (2005) Cognitive function after radiotherapy for supratentorial low-grade glioma: a North Central Cancer Treatment Group prospective study. *Int J Radiat Oncol Biol Phys* 63: 1175-1183.
<https://doi.org/10.1016/j.ijrobp.2005.04.016>
- [40] Nakada M, Nakajima R, Okita H, Nakade Y, Yuno T, Tanaka S, Kinoshita M (2021) Awake surgery for right frontal lobe glioma can preserve visuospatial cognition and spatial working memory. *J Neurooncol* 151: 221-230.
<https://doi.org/10.1007/s11060-020-03656-9>

- [41] Motomura K, Chalise L, Ohka F, Aoki K, Tanahashi K, Hirano M, Nishikawa T, Wakabayashi T, Natsume A (2018) Supratotal Resection of Diffuse Frontal Lower Grade Gliomas with Awake Brain Mapping, Preserving Motor, Language, and Neurocognitive Functions. *World Neurosurg* 119: 30-39. <https://doi.org/10.1016/j.wneu.2018.07.193>
- [42] Duffau H (2010) Awake surgery for nonlanguage mapping. *Neurosurgery* 66: 523-528; discussion 528-529. <https://doi.org/10.1227/01.NEU.0000364996.97762.73>
- [43] Sarubbo S, Tate M, De Benedictis A, Merler S, Moritz-Gasser S, Herbert G, Duffau H (2020) Mapping critical cortical hubs and white matter pathways by direct electrical stimulation: an original functional atlas of the human brain. *Neuroimage* 205: 116237. <https://doi.org/10.1016/j.neuroimage.2019.116237>
- [44] Herbert G (2021) Should Complex Cognitive Functions Be Mapped With Direct Electrostimulation in Wide-Awake Surgery? A Network Perspective. *Front Neurol* 12: 635439. <https://doi.org/10.3389/fneur.2021.635439>