

Tumour and surgery effects on cognitive functioning in high-grade glioma patients

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Abstract

Background Many high-grade glioma (HGG) patients have cognitive impairments, which impact daily functioning. Cognitive impairments can be caused by tumour-, treatment-, and patient-related factors. The effect of the tumour and of surgical resection on cognition is, however, not well known. We investigated tumour and surgical effects on cognitive functioning in patients with HGG.

Methods At baseline, preceding surgery, 62 patients with HGG underwent neuropsychological testing concerning seven cognitive domains: verbal and working memory, attention, executive functioning, psychomotor function, information processing speed, and visuoconstructive abilities. Thirty-nine patients were included in follow-up testing after surgery, but before subsequent treatment. Tumour size and site, use of anti-epileptic drugs and corticosteroids, and extent of resection were recorded.

Results Compared to healthy controls, cognitive functioning of patients was significantly impaired in all domains. Prior to surgery 79 % (49 of 62) of patients had cognitive impairment in at least one domain. At median follow-up of 5 weeks after surgery, 59 % (23 of 39) of patients were cognitively impaired

in at least one domain. At follow-up, 49 % showed improvement, while 23 % declined. Left hemisphere tumour localization was associated with worse verbal memory ($P=0.004$), and larger tumours in this hemisphere with poorer executive functioning ($P<0.001$). Changes in cognitive performance at follow-up relative to baseline were not related to tumour characteristics or extent of resection.

Conclusions Tumour-related cognitive deficits are present in a majority of HGG patients preceding surgery. Surgery does not result in cognitive deterioration in the short term in most patients.

Keywords · Cognitive functioning · Glioblastoma multiforme · Anaplastic glioma · Resective surgery

Introduction

Patients with gliomas often experience subjective and objective limitations in cognitive functioning [13, 29]. Cognitive impairment can negatively influence daily functioning [34], and might compromise patients' and partners' health-related quality of life [8]. Cognitive deficits in high-grade glioma (HGG) may be initially overshadowed by pronounced neurological deficits [30], while rapid tumour growth might cause more cognitive deficits than slowly growing tumours [10]. As patients with glioma still cannot be cured, and median survival for patients with HGG (glioblastoma multiforme (GBM) and anaplastic glioma) ranges from 15–37 months [27, 31], an important outcome measure of treatment is preservation of cognitive functions.

Cognitive functioning in HGG patients is influenced by factors related to the patient, the tumour, and its treatment [12, 13, 29]. A tumour may cause cognitive deficits by invasion of healthy brain tissue, or by compression due to edema surrounding the tumour, cyst formation, or hydrocephalus. However, data on the sole impact of an HGG on cognition

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are scarce [28, 30, 35, 36], mainly because cognitive functioning in these patients has primarily been studied following surgery. But, in the postoperative stage, tumour, surgery, and medication effects on cognition cannot clearly be distinguished. Following surgery, the vast majority of HGG patients have cognitive deficits [9]. Tumour location and volume have been related to cognitive deficits [8, 10, 17, 25, 30]. Disease progression has been associated with cognitive worsening over time [1].

Resection of the tumour will most likely result in functional improvement if serious cognitive deficits exist due to a large and rapidly developing tumour mass [28]. On the other hand, cognitive functioning may deteriorate due to damage to healthy brain tissue caused by the surgery. Despite the abundance of data on language (dys)function during and following resection of low-grade glioma (LGG) in the dominant hemisphere [6, 22], and of data on resection in non-tumour related epilepsy [15], studies specifically addressing the effects of surgery on cognitive functioning in HGG patients are virtually lacking. In the few studies, with mixed outcomes, heterogeneous patient groups with only a small number of HGG were included or cognitive measures inadequate for glioma patients were used [19, 24, 28, 35, 36]. Results regarding the effects of anti-epileptic drugs (AEDs) and corticosteroids on cognition in brain tumour patients other than LGG are ambiguous [1, 2, 4, 17, 30].

Given the impact of cognitive impairments on daily functioning and the absence of proper information on how tumour and surgery will affect cognitive functioning in HGG patients, we examined tumour and resection effects on cognition in a group of only HGG patients. With the results, neurosurgeons, and neuro-oncologists can better inform patients about the consequences of tumour and surgery on cognitive functioning, while postoperative findings may guide adequate (cognitive) treatment.

Methods

Patients and procedure

Consecutive de novo adult patients planned to undergo total or subtotal tumour resection for a radiologically suspected HGG (i.e. GBM or anaplastic glioma) were recruited from the Medical Centre Haaglanden between July 2007 and December 2010. Patients were informed about the study by the neurosurgeon and the neuropsychologist, and gave informed consent to undergo repeated cognitive testing if there was a histology confirmed HGG. Exclusion criteria were (1) history of neurological or severe psychiatric disorder potentially interfering with cognitive functioning, (2) insufficient command of the Dutch language. Baseline neurocognitive assessment was carried out in the week preceding surgery and follow-up assessment at least 3 weeks following surgery, but before subsequent therapy was initiated. All participants gave informed consent.

Outcome measures

Cognitive functioning was assessed by a battery of various standardized neuropsychological tests covering the wide range of cognitive functions which can be affected in glioma patients and are sensitive for detecting changes in cognitive functioning over time [17, 19, 30]. Based on previous studies and consensus in neuropsychological practice, we combined test scores into seven cognitive domain scores (Table 1) [5, 18, 19].

Performance of the patients on the tests was compared to performance data of healthy controls [11]. These controls were individually matched with respect to age, sex, and educational level [3]. For working memory and visuoconstruction, published normative data were used, corrected for age and educational level [7, 33]. Individual patients test scores were converted into standardized z scores with use of mean and standard deviation (SD) of the matched healthy controls on that test. Domain summary measures were calculated for the patients at baseline and at follow-up.

We categorized the extent of resection into either total resection (more than 95 % of tumour tissue removed) or subtotal resection (less than 95 % removed), based on post-surgical MRI scan compared to pre-surgical MRI scan, or otherwise on the neurosurgeon's opinion.

Statistical analysis

According to neuropsychological practice, an individual z-score of ≥ 1.5 SD below the mean of controls was defined as a clinically significant cognitive impairment [18]. We defined impairment as mild if one domain was affected, moderate if two to three domains were affected, and severe if four or more domains were affected. If a z-score progressed ≥ 1.5 SD between baseline and follow-up, and the post-operative score fell into the normal performance range of controls, it was called clinically significant improvement. A z-score worsening of ≥ 1.5 SD, or if the post-operative score dropped to ≥ 1.5 SD below the mean of controls, was called clinically significant deterioration. In all other situations a score was defined as stable. If one domain score improved or declined between baseline and follow-up, it was called mild improvement or mild deterioration, respectively. If a score on more than one domain significantly improved or declined, it was called evident improvement or decline, respectively.

Statistical analyses were performed with SPSS. Pearson χ^2 test or Students' *t*-test for independent samples were used to compare differences in sociodemographic and clinical characteristics between patients who completed follow-up and patients who dropped out of the study. Students' *t*-test was used

Table 1 Cognitive domains and tests

Domain	Test(s)
Verbal memory	Verbal learning test (first trial, total of five trials, delta score trial 5–trial 1, active delayed recall and delayed recognition) [26]
Working memory	Digit span forward and backward [33]
Executive functioning	Concept Shifting Test (condition A [numbers], B [letters], C [number–letter]); categoric word fluency test [18]
Psychomotor function	Concept Shifting Test (condition 0) [32]
Information processing speed	Letter digit modalities test (written) [18]
Attention	Stroop color word test (word condition, color condition, color–word condition and interference score) [18]
Visuoconstruction	Rey Complex figure test–copy [20]

to analyse differences between patients and healthy controls. Wilcoxon signed-rank test for paired samples were used to analyse changes in performance between baseline and follow-up within the patient group. Possible predictors of cognitive functioning (pre-operative symptoms as epilepsy, neurological deficits and headache, tumour size, tumour location, use of corticosteroids, use of AEDs, age, and amount of resection) were analysed with Pearson χ^2 tests or logistic regression analysis. The level of significance was set at $P < 0.05$, but for the seven cognitive domain scores, a Bonferroni correction was applied to adjust for multiple comparisons, requiring $P < 0.007$ for statistical significance.

Results

Patients' characteristics

Sixty-two of the 93 patients who underwent resection for a suspected HGG during the study period, participated at baseline preceding surgery. Of the 31 patients not included, informed consent could not be obtained in time in 22 patients (in six cases due to emergency operation, in 16 cases due to time constraints caused by other reasons). The remaining nine patients declined participation because they considered testing to be too burdensome. Non-participating patients did not differ from participating patients according to age or tumour histology. Table 2 shows the sociodemographic and clinical characteristics of the patient group.

Analyses of cognitive performance were done with all patients who participated at baseline ($N=62$). Eighteen patients (29 %) could not complete more than half of the test battery. This was due to fatigue, visual or dysphasic disorder, emotional disturbances, and/or time constraints. The few patients with anaplastic glioma were significantly younger than patients with GBM ($z=-2.72$, $P=0.004$).

At follow-up after surgery, 36 patients (58 %) could be tested again with a median interval of 5 weeks. Reasons for

drop-out were refusal because testing was considered too burdensome (13 patients); no further tumour treatment started due to progressive disease immediately following surgery (six patients); tumour treatment elsewhere (four patients); post-surgical complications including brain infarction or hemorrhage (three patients). Because we considered post-surgical complications as an effect of the surgery, these last three patients were included in the follow-up analyses and were considered severely cognitively impaired. Extent of resection was based on post-operative MRI scan in 44 cases (71 %). Twenty-four patients (39 %) underwent a total resection (table 2).

Patients who could not be tested post-operatively were significantly older than patients who stayed in the study ($t=2.8$, $P=0.007$), were more often women (χ^2 ; $P=0.009$), and had completed fewer tests at baseline compared to patients who were also tested at follow-up ($t=-3.09$, $P=0.003$).

Cognitive functioning in mean domain scores at baseline and follow-up

At baseline preceding surgery, mean domain z-scores of all seven domains were significantly lower compared to healthy controls (verbal memory: $t=-4.74$, $P < 0.001$; working memory: $t=-3.11$, $P=0.003$; attention: $t=-4.38$, $P < 0.001$; executive functioning: $t=-6.33$, $P < 0.001$; psychomotor function: $t=-3.57$, $P=0.001$; information processing speed: $t=-5.46$, $P < 0.001$; visuoconstruction: $t=-4.66$, $P < 0.001$; Fig. 1). Cognitive domain scores did not differ between patients lost to follow-up and patients who had follow-up.

To evaluate changes in cognitive functioning after surgery, only patients with cognitive domain scores both at baseline and follow-up were included in this analysis ($N=39$). Individual trajectories and mean group scores on each of the seven domains at baseline and follow-up are depicted in Fig. 2. At the group level, significant improvement was observed in information processing speed ($z=2.98$, $P=0.003$) and visuoconstruction ($z=3.19$, $P=0.001$).

Table 2 Sociodemographic and clinical characteristics of the study patients

	No. of patients at baseline, pre-surgery (N=62)	No. of patients with follow-up post-surgery (N=39)	No. of patients without follow-up post-surgery (N=23)
Age ¹ ; mean±SD	60.6±12.5	57.8±12.7*	66.6±10.5*
Sex			
Male/Female	38 (61 %)/24 (39 %)	29 (74 %)/10 (26 %)*	9 (39 %)/14 (61 %)*
Educational level ² ; mean±SD	3.7±2.2	4.2±2.3*	2.7±1.6*
Tumour histology			
GBM	57 (92 %)	34	23
Astrocytoma oligoastrocytoma (AO, O)	5 (8 %)	5	0
Tumour localization			
Left/Right	28 (45%)/34 (55%)	19 (49%)/20 (51%)	9 (39%)/14 (61%)
Left frontal	12	10	2
Left frontoparietal	2	1	1
Left temporo (occipital)	5	3	2
Left parietal	1	0	1
Left parietooccipital	5	3	2
Left parietotemporal	3	2	1
Right frontal	6	4	2
Right frontoparietal	1	1	0
Right temporal	12	7	5
Right temporoinsular	1	1	0
Right parietal	5	2	3
Right parietooccipital	7	3	4
Right parietotemporal	2	2	0
Tumour size ³			
Overall mean±SD/median	51.5 ± 18.1/52	52.0 ± 20.2/52	50.6 ± 14/53
Left mean±SD/median	45.6 ± 18.2*/44	46.2 ± 20.5/42	44.4 ± 13.2/45
Right mean±SD/median	56.3 ± 16.7*/56	57.6 ± 18.8/56	54.6 ± 13.5/56
Symptoms prior to surgery			
Epilepsy	31 (50%)		
Neurological deficits	30 (48%)		
Headache	19 (31%)		
Use of AEDs			
At Baseline	34 (55%)	18	16
At follow-up		30 (77%)	
Use of corticosteroids			
At Baseline	40 (65%)	20	20
At follow-up		12 (31%)	
Interval baseline and surgery ⁴ ;			
Mean ± SD/median	4 ± 7.9/1		
Range	1–49		
Test interval (baseline vs. follow-up) ⁴ ;			
Mean ± SD/median		38.4 ± 13.4 / 36	
Range		20–91	
Extent of resection			
Subtotal (<95%)		22 (56%)	14 (61%)
Total (>95%)		15 (39%)	9 (39%)
Unknown		2 (5%)	
Number of test completed; mean ± SD			
At baseline/at follow-up	4.6 ± 2/–	5.18 ± 2*/5.6 ± 1.8	3.7 ± 1.5*/–

¹ Years; ² Code 1–8 [3] ³ Largest diameter in mm on MRI T1 with contrast; ⁴ Days; * significant difference ($p < 0.05$)

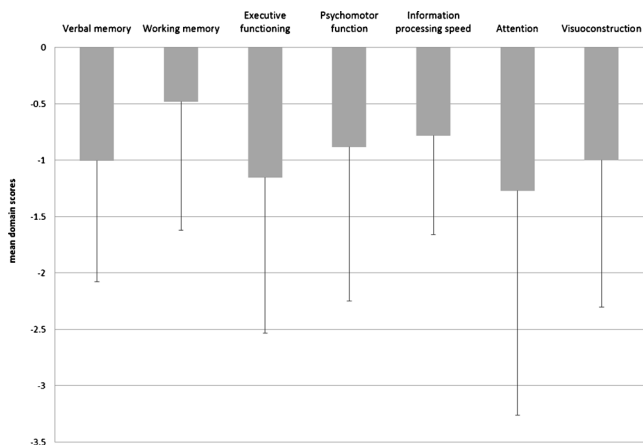


Fig. 1 bar graph with mean z-scores (SD) of the patients for each cognitive domain at baseline. The patients' performance is compared to age-, sex-, and education-matched healthy controls (represented by the 0 line). A score closer to 0 means a better performance. All mean domain scores of patients are significantly lower compared to healthy controls ($p < 0.005$)

Cognitive functioning in percentages at baseline and follow-up

At baseline, 79 % (49 of 62 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 (22, 21, and six patients, respectively). Of the 39 patients who were included in follow-up after surgery, preceding surgery 20 % (eight patients) were not cognitively impaired, 36 % (14 patients) were mildly, 31 % (12 patients) were moderately, and 13 % (five patients) were severely impaired. Verbal memory and attention were the domains most frequently impaired (Fig. 3). At follow-up, 59 % (23 of 39 patients) had impairment in at least one cognitive domain, while no impairment was observed in 41 %. Impairment was mild in 33 %, and moderate or severe in 13 % of patients (13, five, and five patients, respectively). Psychomotor function was the most frequently impaired domain (Fig. 3).

Cognitive functioning at the individual level: changes between baseline and follow-up

Individual patient scores on the cognitive domains at baseline and follow-up are depicted in Fig. 2. In the 39 patients included, we observed clinically significant improvement between baseline and follow-up primarily in the domains of visuoconstruction (24 %; seven of 29 patients), verbal memory (21 %; six of 29 patients) and attention (18 %; six of 33 patients). In the other domains, only few patients improved significantly. Clinically significant decline was observed mainly in verbal memory in 17 % (five of 29 patients), in

attention in 15 % (five of 33 patients), and in psychomotor function in 15 % (four of 27 patients). In the other domains, few patients deteriorated significantly. Taking all seven domains together, 49 % of patients showed improvement, with 36 % (14 of 39 patients) showing mild improvement and 13 % (five of 39 patients) showing evident improvement. Ten percent had mild and 13 % had evident deterioration (four and five patients, respectively).

Predictors of cognitive functioning at baseline and follow-up

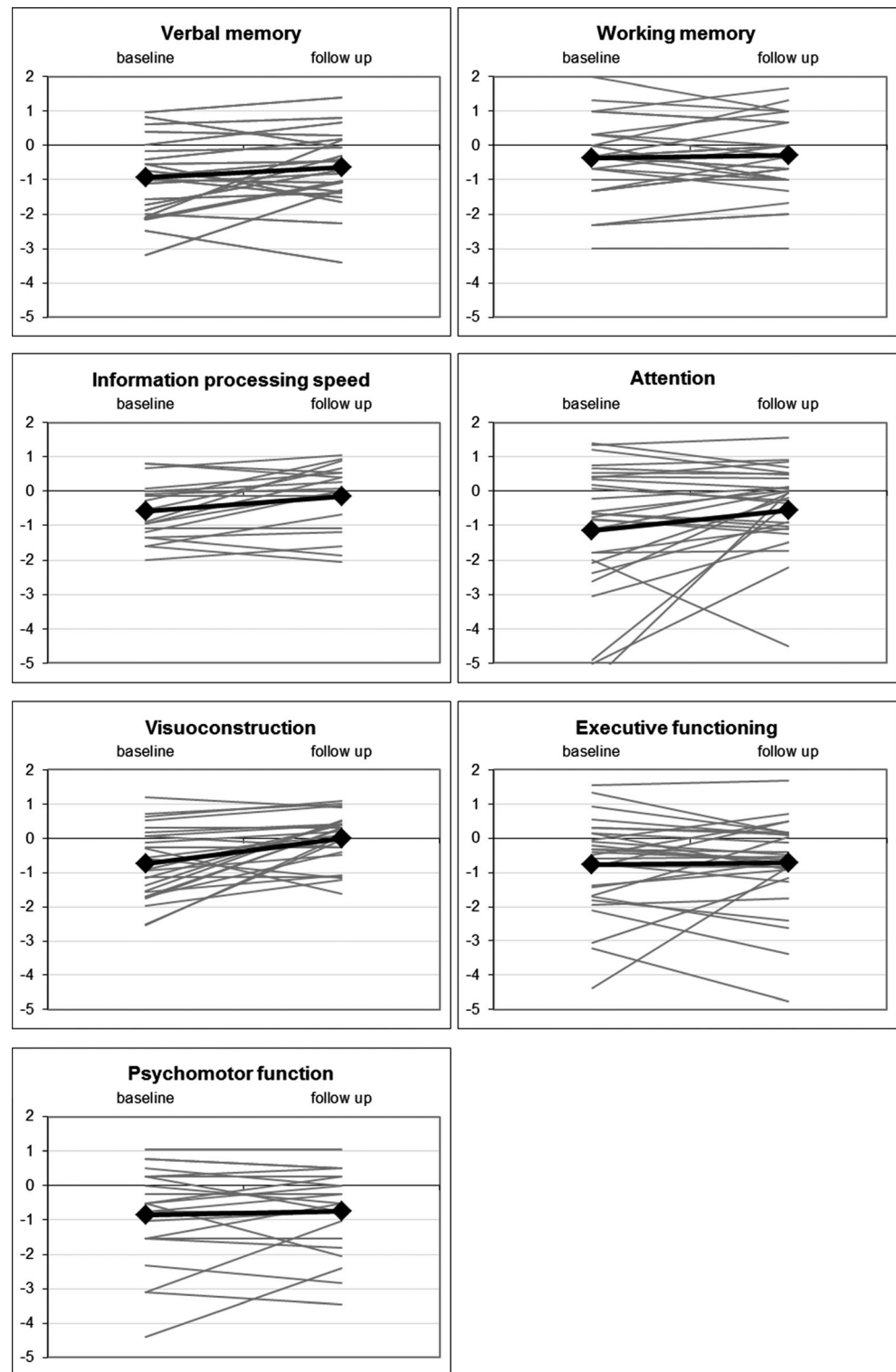
Tumours in the dominant hemisphere were smaller than those in the non-dominant hemisphere ($t = -2.41$, $P = 0.019$). Also after taking tumour size as a covariate in the comparison for hemispheric tumour location, patients with tumours in the left hemisphere had significantly poorer baseline verbal memory ($F = 10.08$, $P = 0.004$) and tended to have worse working memory ($F = 7.28$, $P = 0.009$) and attention ($F = 5.15$, $P = 0.028$) than patients with tumours in the right hemisphere. For patients with left hemispheric tumours, a larger tumour was a predictor of significantly poorer baseline executive ($t = -4.09$, $P < 0.001$) and a trend towards slower psychomotor functioning ($t = -3.1$, $P = 0.008$). For patients with right hemispheric tumours, tumour size was not related to cognitive functioning.

Because of small subgroups, no statistical analyses on the association between precise tumour location and cognitive domain scores could be performed. Exploratory analyses only showed that for both hemispheres, non-frontal tumours tended to be associated with worse visuoconstructive abilities compared to frontally located tumours.

Patients on corticosteroids had worse baseline attention ($t = 3.23$, $P = 0.002$) and executive functioning ($t = 2.83$, $P = 0.006$), and lower information processing speed ($t = 3.02$, $P = 0.003$) than patients not using corticosteroids. Use of AEDs and pre-operative symptoms were not predictors of cognitive functioning.

At follow-up after surgery, patients who showed improvement were compared to patients who did not improve (stable or decline). No factors (including age, pre-operative epilepsy, headache and neurological deficits, tumour site, tumour size, and amount of tumour resected) could be identified as predictors of improvement of cognitive performance. Because of the small number of patients deteriorating ($N = 9$), no statistical analysis could be performed to detect possible predictors of deterioration (versus stable or improved cognition). Descriptive analyses showed that pre-operative epilepsy was correlated with deterioration (χ^2 ; $P = 0.032$), while older age showed a non-significant correlation with deterioration. With exploratory analysis, we did not find an association between precise tumour location and improvement or decline.

Fig. 2 line graphs with mean group z-scores (represented by the black line) and individual patient z-scores (represented by the grey lines) at baseline and follow-up for each of the seven cognitive domains. Patients scores are compared to age-, sex-, and education-matched healthy controls, represented by the 0 line. A higher score means better performance



Despite improvement following surgery, patients with left hemispheric tumours tended to remain performing worse than patients with right hemispheric tumours in executive functioning ($F=5.98$, $P=0.021$) and attention ($F=5.51$, $P=0.026$) after surgery, but differences were not significant.

Discussion

We prospectively investigated the influence of tumour and tumour resection on cognitive functioning in HGG patients. Not unexpectedly, the majority of the HGG patients had

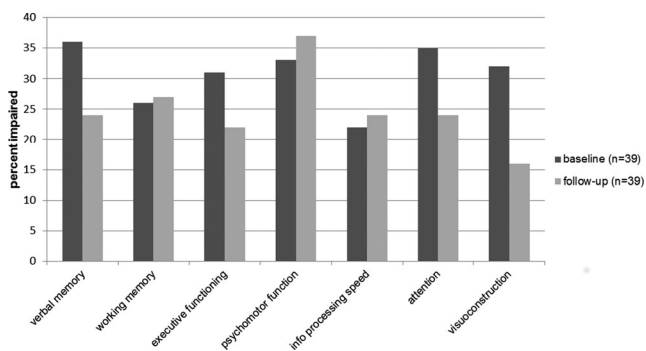


Fig. 3 Bar graph with percentage of patients with impairment at baseline and follow-up for each cognitive domain

cognitive impairments preceding surgical treatment, particularly caused by the tumour itself.

To our knowledge, this is the first study to evaluate pre- and post-operative cognitive functioning in a patient sample of only HGG. In previous research including various types of brain tumour patients, the percentage of patients with cognitive impairments preceding surgery varied from 30 % to 91 %, with memory and executive functioning as the most frequently affected domains [24, 28, 30, 35]. This large variation can partly be explained by differences in patient sample and methodology.

Even after correcting for the smaller tumour size in the dominant hemisphere, we found a correlation between cognitive functioning and tumour site, in line with earlier research [8, 17, 25, 36]. Tumour size was related to baseline cognition only for left hemisphere location, probably reflecting that cognitive testing is mainly influenced by dominant hemisphere functioning. As to medication, the use of corticosteroids was related to worse baseline cognitive functioning, which may be due to more mass effect in these patients, also beyond tumour size. In earlier studies, use of AEDs has been related to a negative effect on working memory, psychomotor speed and executive functioning in HGG patients [1, 17], although a positive effect was found for verbal memory [4]. We, and others [30], did not find an effect of AEDs on baseline cognition, perhaps because our patients had only recently started AEDs.

Following surgery, nearly half of our patients showed cognitive improvement, while 23 % of patients declined, partly due to post-surgical complications. Most changes were seen in verbal memory and attention, while domains related to speed tended to be vulnerable for decline. Fifty-nine percent of our studied patients had some cognitive impairment post-operatively. In previous research, 38 % of LGG and HGG patients were found to be impaired shortly after surgery [28], while in a small sample of post-operative GBM patients as much as 89 % had cognitive deficits, also including patients with biopsies [9]. The effect of tumour resection on cognition in HGG patients has only sporadically been studied before, with results varying from generally no change [36], to a subtle decline [24, 35], to improvement of some cognitive functions [23, 28]. In some of these studies, a subgroup

of patients received chemotherapy or radiotherapy before follow-up assessment [24, 35], which may have affected cognition as well [29].

Unfortunately, we could not identify possible predictors of cognitive improvement after surgery. Perhaps this is due to the relatively small patient sample included in the post-surgery analysis. Earlier results regarding the influences of extent of resection, tumour location, and tumour size on changes in cognitive functioning after surgery compared to pre-operative performance were mixed [24, 28]. We found pre-operative epilepsy to be correlated with post-operative cognitive deterioration. Although negative effects of epilepsy and use of AEDs have been observed in glioma patients [1, 16], it remains speculative if the cognitive decline post-operatively is due to anti-epileptic medication. The finding that patients with left hemispheric tumours in our sample, despite improvement after resection, did not reach the level of right hemispheric tumour patients for attention and executive functioning, might be an advocate for developing intraoperative monitoring of these cognitive functions during awake surgery [14].

Regarding our study, we tested many patients the day before surgery. This design could have resulted in an overestimation of cognitive deficits, because some patients might have been so preoccupied with the upcoming surgery that concentrating on the tests was difficult. On the other hand, patients in whom complete assessment was too burdensome would likely have shown deficits in the non-evaluated cognitive domains. The exclusion of patients who only had biopsies may have added to an underestimation of cognitive deficits on presentation, since biopsy is the preferred method for large, deeply, and/or eloquently located tumours.

Clearly, there may be a bias towards improved cognition in our postoperative results. Only 58 % of patients could be tested following surgery. In other surgery studies on gliomas, drop-out was reported less frequently, perhaps related to the malignancy of the tumour [28, 35]. A selection bias might exist towards a larger percentage of follow-up data in better functioning patients. Also, in patients who refused to be tested again and in patients who deteriorated rapidly following surgery due to progressive tumour growth, cognitive functioning must have declined compared to baseline level. Nonetheless, patients without baseline data due to severe cognitive dysfunction and improving postoperatively, were also not included in our study. It is difficult, however, to overcome these limitations in patients diagnosed with malignant brain tumours. Although parallel versions of the cognitive tests were applied, practice effects due to the relatively short test interval cannot be ruled out completely. On the other hand, transient post-surgical neurological deficits and fatigue may have negatively affected cognition apart from surgery. Furthermore, anxiety and depression, which were observed in some glioma patients [21, 28], were not systematically investigated.

In conclusion, the results of our study emphasize the need to be aware of frequently occurring cognitive deficits already present early in the disease course of HGG. Although resective surgery appears to be a safe treatment in terms of cognitive functioning, still many patients have cognitive impairments following surgery. Adequate information, counseling and (cognitive) rehabilitation programs should, therefore, be integrated early in the disease course. More research with larger sample size is needed to detect which patients benefit the most from resection. With baseline measurements, changes in cognitive functioning in the course of disease or further treatment can be more easily related to the cause, thereby optimizing future treatment decisions.

Conflict of interest None

Ethical standards This study was considered part of standard patient care, therefore no approval of a medical ethics committee was required. All patients gave informed consent prior to their inclusion in this study.

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