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Group Changes in Cognitive Performance After Surgery Mask Changes in Individual Patients with Glioblastoma

Inge S. van Loenen[1], Sophie J.M. Rijnen[1,2], Jimme Bruijn[1,2], Geert-Jan M. Rutten[2], Karin Gehring[1,2], Margriet M. Sitskoorn[1]

■ BACKGROUND: **There is a growing interest to include evaluations of cognitive performance in the clinical management of patients with glioblastoma (GBM). However, as changes in cognitive performance of a group may mask changes in individual patients, study results are often difficult to transfer into clinical practice. We focused on the comparison of group versus individual changes in neuropsychological performance of patients with GBM after initial surgical treatment.**

■ METHODS: **Patients underwent neuropsychological evaluation using CNS Vital Signs 1 day prior to and 3 months after surgery. Two-tailed paired-samples *t* tests were conducted to assess changes on the group level. Reliable change indices (RCIs) that correct for practice effects and imperfect test-retest reliabilities were used to examine changes in individual patients.**

■ RESULTS: **Cognitive dysfunction was common (>80%) both before and 3 months after surgery in this sample of 82 patients with GBM. Whereas group analyses revealed minimal changes in performance over time, RCIs demonstrated that most patients (89%) showed changes in performance in at least 1 cognitive domain. Half of these individual patients solely showed improvements, a quarter solely showed declines, and another quarter showed both improvements and declines.**

■ CONCLUSIONS: **This study clearly demonstrates that important individual changes in performance are masked when looking only at group results. Future studies should more often use an individual patient approach to enhance knowledge transfer into clinical practice.**

INTRODUCTION

Glioblastoma (GBM) is the most common and malignant type of primary brain tumor, and current standard of care is maximal safe resection followed by radio- and chemotherapy.[1-3] Candidates for resective surgery should be in a reasonable general and neurological condition. In addition, the estimated risks of surgery should be acceptable in terms of postoperative neurological deficits. The decision whether to operate or not is thus largely based on clinical grounds and predominantly focuses on the patients' general performance status (e.g., Karnofsky Performance Status Scale)[4] and their sensorimotor and language capabilities. Although current guidelines stress the importance of cognitive functioning, and prior studies demonstrate cognitive deficits in patients with GBM already prior to surgery, information on the patient's cognitive status is currently seldom embedded in the clinical management of GBM patients.[3,5-12]

It is well known that cognitive deficits can contribute to a lower quality of life of the patient.[13,14] Also, cognitive dysfunction has been found to be a valuable indicator of disease severity, and potentially even for tumor progression.[15,16] Therefore, there is growing interest to include the results of neuropsychological examinations into neuro-oncological practice. Such information

Key words
- Cognition
- Glioma
- Individual differences
- Neuropsychological tests
- Neurosurgery
- Reliable change index

Abbreviations and Acronyms
CNS VS: CNS Vital Signs
ES: Effect size
GBM: Glioblastoma
RCI: Reliable change index

From the [1]Department of Cognitive Neuropsychology, Tilburg University, Tilburg; and the [2]Department of Neurosurgery, Elisabeth-TweeSteden Hospital, Tilburg, The Netherlands

To whom correspondence should be addressed: Sophie J.M. Rijnen, M.Sc. [E-mail: s.j.m.rijnen@uvt.nl]

Inge S. van Loenen and Sophie J.M. Rijnen are co—first authors.

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would for example also be very informative when evaluating new surgical techniques (e.g., using 5-aminolevulinic A) that push the boundaries of resection, but at the same time potentially endanger brain functioning.[17-19]

Prior studies on group-level cognitive function have found widespread preoperative cognitive impairment, with modest yet significant improvements in memory and information processing speed,[6,9,20] and declines in language and executive function postoperatively.[20-22] However, results on performance of a group of patients may mask performance in individual patients, thereby making results difficult to transfer into clinical practice.[23] Only very few studies focused on individual cognitive performance and change over time in patients with GBM. These studies demonstrated improved performance in 24%–49% and declined performance in 23%–38% of the patients postoperatively, where most changes were found in verbal memory, attention, and executive functioning.[6,20] Overall, improvements of performance were more frequent than declines after surgery, despite a worsening of performance immediately after surgery.[6,20,24] In these studies, fairly simple measures of change in performance (e.g., raw difference scores, subtracting preoperative from postoperative scores) were adopted. Previously, Wefel et al.[25] adopted the widely used plain version of the reliable change index (RCI) of Jacobson and Truax[23] to assess changes in cognitive performance of patients with recurrent GBM treated with bevacizumab. However, to decide on reliable changes in performance, one should account for very common methodological phenomena related to repeated neuropsychological assessment, such as practice effects.[26] Interpreting performance without considering, for instance, practice effects might result in overestimations of improvement, or underestimations of decline in performance.

In this study, cognitive impairments before and 3 months after initial surgical treatment were evaluated using a brief, computerized neuropsychological assessment (i.e., CNS Vital Signs [CNS VS] [CNS Vital Signs, LLC, Morrisville, North Carolina, USA])[27] that was implemented into clinical neuro-oncological care of patients with GBM. Furthermore, since we expect that declines and improvements of individual patients may be masked when looking at performance on the group level, we focused on the comparison of group versus reliable individual changes in neuropsychological performance of patients with GBM from pre- to postsurgery.

METHODS

Patients

We included patients who underwent resective surgery between January 2011 and March 2016. Based on tissue obtained during surgery, all patients were diagnosed with a newly, histopathologically confirmed GBM.

Exclusion criteria were 1) age below 18 years, 2) previous intracranial neurosurgery, 3) recent (≤2 years) neurologic or psychiatric disorders, 4) other major medical illnesses in the past year prior to surgery (e.g., cancer, myocardial infarct), 5) lack of basic proficiency in Dutch, 6) premorbid intelligence quotient below 85, and 7) inability to undergo neuropsychological assessment because of severe visual, motor, or cognitive problems.

All patients provided written informed consent. The study was approved by the medical ethics committee (file number NL41351.008.12).

Measures and Procedure

Patients' Characteristics. Patients underwent neuropsychological evaluation per protocol 1 day before (To) and 3 months after surgery (T3) as part of clinical care. Number of years of education was self-reported by patients during a standardized interview. Clinical information (i.e., data on medication use and adjuvant radio- or chemotherapy) was retrieved from electronic medical charts. Tumor location was identified by the neurosurgeon. Maximum tumor diameter (in axial, sagittal, or coronal plane) was determined by 3 trained researchers under direct supervision of the neurosurgeon, using contrast-enhanced T1-weighted magnetic resonance images.

CNS VS. The formal Dutch translation of the computerized neuropsychological battery CNS VS was used to examine cognitive performance.[27] CNS VS is widely used to assess cognitive functioning in patient groups (e.g., in patients with meningioma,[28] mild cognitive impairment, and early dementia[29]). It consists of 7 neuropsychological tests that are based on paper-and-pencil tests, yielding measures of performance on 11 cognitive domains.[25] Because some domains are largely based on the same test scores, we only considered the following 7 domains: verbal memory, visual memory, processing speed, psychomotor speed, reaction time, complex attention, and cognitive flexibility. After completing the battery raw cognitive domain scores, among others, were provided.

It takes 30–40 minutes to complete the CNS VS. Assessments were performed using the CNS VSX local software app, on a laptop computer running a 64-bit operating system. Background programs were shut down, and there were no connections to Internet resources. Well-trained test technicians remained present during the entire assessment.

Statistical Analyses

Patients' Characteristics. Descriptive and comparative analyses of sociodemographic and clinical variables, and baseline cognitive performance of the patients who completed both assessments, versus patients who dropped out before follow-up, were performed.

CNS VS Normed Cognitive Domain Scores. Effects of sociodemographic (i.e., age, sex, education) variables on performance, and practice effects between the first and second assessment were found to be present in a Dutch normative sample.[30,31] Therefore, raw cognitive domain scores of the patients were converted into sociodemographically adjusted z scores. With respect to the postoperative scores, practice effects were corrected for, in addition to the sociodemographic corrections.

Group-Level Performance. To explore differences in mean CNS VS performance on the 7 cognitive domains between patients with GBM and the normative sample before and 3 months after surgery, one-tailed one-sample z tests were performed (test values: mean z = 0, SD = 1). To examine the magnitude of differences, we considered the mean z score for each cognitive domain (representing the

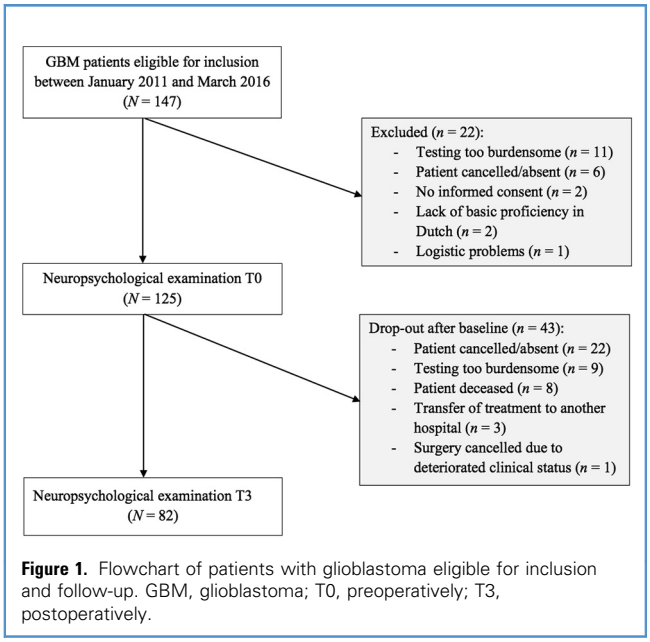

Figure 1. Flowchart of patients with glioblastoma eligible for inclusion and follow-up. GBM, glioblastoma; T0, preoperatively; T3, postoperatively.

difference between the patient sample and the normative sample in terms of SDs) as the effect size (ES). This equals Cohen's *d* ES when calculated according to the formula $Mean_{patients} - Mean_{controls}/SD$, as here again $Mean_{controls} = 0$ and $SD = 1$. Small, medium, and large effects are considered to be represented by $d \leq 0.50$, *d* between 0.51 and 0.80, and $d \geq 0.80$, respectively.[32]

Change. Two-tailed samples *t* tests were conducted to assess changes over time in cognitive domain scores on the group level. ES were calculated and expressed as Cohen's *d* following the formula: $Mean_{difference\,T3\,-\,T0}/SD_{difference}$. Again, $d \leq 0.50$ = small effect, *d* between 0.51 and 0.80 = medium effect, and $d \geq 0.80$ = large effect.[32]

Individual Performance. To categorize cognitive performance of individual patients, *z* scores of ≤ -2.00 were classified as very low, scores between -1.99 and -1.50 as low, scores between -1.49 and 1.49 as average, and scores of ≥ 1.50 as high.[33] Performance was defined as impaired if the *z* score fell in the very low or low category (≤ -1.50). The numbers and percentages of patients scoring within each category for cognitive domains, and the number of impaired domains, were counted for both time points.

Changes. In order to determine whether observed changes in scores reliably reflect true changes in performance while taking into account methodological confounds (e.g., practice effects, imperfect test-retest reliabilities), RCI values were calculated for each domain for each patient. A standardized regression-based RCI described by Maassen et al.[26] was adopted. Rijnen et al.[31] described details regarding the RCI formulae for changes in CNS VS performance, which are established based on results on repeated testing in a Dutch normative sample (N = 158) at baseline and 3-month follow up. RCI formulae were established for each cognitive domain. No effects of age, sex, and education on changes over time in the normative sample were found; consequently, these variables were not included in the formulae. Change was defined by RCI values exceeding ± 1.645 (corresponding with a 2-tailed α of 0.10, 90% confidence interval), where positive values represented improvement, and negative values represented declined performance. The numbers of patients with improved, stable, or declined cognitive performance were counted for each cognitive domain. In addition, a Chi-square test of independence was conducted to compare the proportion of patients with GBM in whose

Table 1. Baseline Characteristics of Patients with Glioblastoma (N = 125)

Characteristic	Value
Sociodemographic characteristics	
Age (years), mean ± SD (range)	58.6 ± 11.9 (18–81)
Education (years), mean ± SD*	13.7 ± 3.3
Sex, female/male	41 (33)/84 (67)
Clinical characteristics	
Hemisphere, left/right	45 (36)/80 (64)
Supratentorial lobe	
Frontal	38 (31)
Fronto-insular	4 (3)
Fronto-temporal-insular	4 (3)
Fronto-parietal	2 (2)
Temporal	26 (21)
Temporo-occipital	10 (8)
Temporo-parietal	8 (6)
Temporo-insular	11 (9)
Parietal	14 (11)
Parieto-occipital	5 (4)
Occipital	3 (2)
Tumor diameter (mm), mean ± SD (range)†	54 ± 15 (18–101)
Use of AEDs and corticosteroids	
None	13 (10)
Corticosteroids	64 (51)
AEDs	21 (17)
AEDs and corticosteroids	18 (14)
Unknown	9 (7)
Additional treatment between T0 and T3	
None	3 (4)
Radiotherapy	8 (9)
Radiotherapy and chemotherapy	71 (87)

Values are number of patients (%) or as otherwise indicated.
AED, antiepileptic drug; T0, preoperatively; T3, postoperatively.
*Number of years of completed education.
†In the axial, sagittal, or coronal plane, as determined by using contrast-enhanced T1-weighted magnetic resonance imaging.

Table 2. Comparison of Mean Performance of Patients with Glioblastoma Pre- and Postoperatively

Cognitive Domain*	Mean *z* Score ± SD	Number of Patients†	*z* Test	*p* Value	Cohen's *d*‡
Preoperative assessment§					
Verbal memory	−0.91 ± 1.28	117	−9.82	<0.001‖	−0.91
Visual memory	−0.96 ± 1.28	120	−10.57	<0.001‖	−0.96
Processing speed	−1.45 ± 1.37	122	−16.09	<0.001‖	−1.45
Psychomotor speed	−1.59 ± 1.84	121	−17.72	<0.001‖	−1.59
Reaction time	−2.16 ± 2.85	117	−23.58	<0.001‖	−2.16
Complex attention	−2.98 ± 3.23	117	−32.29	<0.001‖	−2.98
Cognitive flexibility	−2.36 ± 2.53	116	−25.37	<0.001‖	−2.36
Postoperative assessment					
Verbal memory	−0.89 ± 1.39	77	−7.79	<0.001‖	−0.89
Visual memory	−0.69 ± 1.20	78	−6.05	<0.001‖	−0.69
Processing speed	−1.27 ± 1.24	81	−10.84	<0.001‖	−1.27
Psychomotor speed	−1.20 ± 1.54	81	−11.42	<0.001‖	−1.20
Reaction time	−2.22 ± 2.60	82	−20.11	<0.001‖	−2.22
Complex attention	−2.00 ± 2.93	79	−17.77	<0.001‖	−2.00
Cognitive flexibility	−1.85 ± 2.14	81	−16.62	<0.001‖	−1.85
T0-T3 Pairs¶	**Mean Difference ± SD**	**Number of Patients†**	***t* Test**	***p* Value**	**Cohen's *d*‡**
Verbal memory	−0.01 ± 1.14	71	−0.09	0.93	−0.01
Visual memory	0.09 ± 1.31	75	0.60	0.55	0.07
Processing speed	0.15 ± 1.12	79	1.19	0.24	0.13
Psychomotor speed	0.33 ± 1.57	79	1.88	0.06	0.21
Reaction time	−0.18 ± 2.32	76	−0.67	0.51	−0.08
Complex attention	0.76 ± 3.01	73	2.17	0.03‖	0.25
Cognitive flexibility	0.36 ± 2.15	74	1.44	0.15	0.17

T0, preoperatively; T3, postoperatively.
*Reaction time is based on time components of neuropsychological tests; all other domains reflect response (i.e., correct/incorrect) components of neuropsychological tests.
†The number of patients differs over cognitive domains as a consequence of missing or invalid scores on the pre- or postoperative assessment.
‡Cohen's *d* effect size: ≤0.50 = small, 0.51 - 0.80 = medium, ≥0.80 = large.
§Negative *z* scores imply lower performance of patients compared with the normative group, and vice versa for positive *z* scores.[23]
‖$p < 0.05$.
¶Positive change scores imply higher performance of patients on T3 compared with T0, and vice versa for a negative change score.

performance changed to the proportion of participants in the normative sample whose performance changed over a 3-month interval (i.e., to test whether changes were significantly more frequent in patients with GBM than in controls).

All statistical analyses were performed using SPSS version 24.0 (IBM, Armonk, New York, USA). Alpha was set at 0.05.

RESULTS

Patients' Characteristics

Figure 1 shows the flowchart of patients with GBM in this study. At baseline, 125 patients were included. Forty-three patients (34%) did not complete follow-up, resulting in 82 patients with pre- and postoperative measurements. Table 1 presents sociodemographic and clinical characteristics of the GBM sample. There were no significant differences regarding sociodemographic and clinical variables, and baseline cognitive performance between patients who completed pre- and postoperative assessment and patients who dropped out of the study (*p* values > 0.05; data not shown).

Group-Level Performance

We found significantly lower performance of patients with GBM compared with the normative sample on all cognitive domains both before (ES ranging from −0.91 to −2.98) and 3 months after

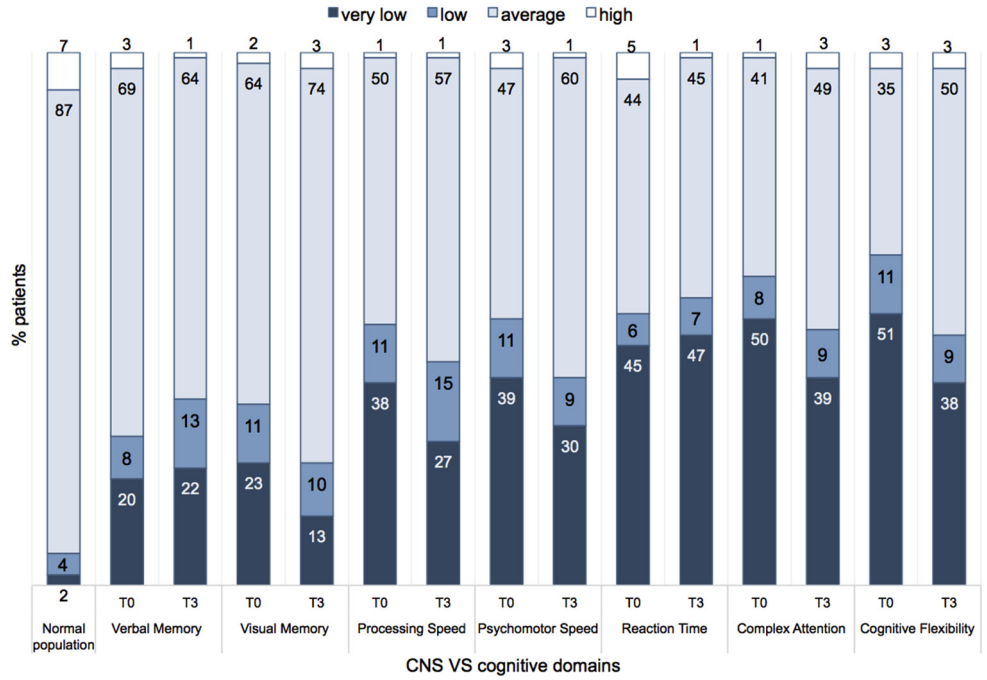

Figure 2. Percentages of patients with glioblastoma with a *z* score in the very low, low, average, or high category for each cognitive domain, pre- and postoperatively. Preoperative data are available for a range of 116–125 patients; postoperative data are available for a range of 78–82 patients. CNS VS, CNS Vital Signs; T0, preoperatively; T3, postoperatively.

surgery (ES ranging from −0.69 to −2.22) (*p* values <0.001) (Table 2).

Preoperatively, mean z scores as low as −2.98 and −2.36 were found for complex attention and cognitive flexibility, respectively. Postoperatively, the lowest mean z scores were observed for reaction time (−2.22) and complex attention (−2.00).

Group-Level Changes

On the group level, paired-samples *t* tests revealed no significant changes in neuropsychological performance over time for CNS VS cognitive domains, except for complex attention, where postoperative performance was significantly higher ($t(73) = 2.17$, $p = 0.03$) (Table 2). ESs were small for each cognitive domain, with Cohen's *d* ranging from −0.08 to 0.25.

Individual Performance

Figure 2 shows the percentage of patients scoring within each category (i.e., very low, low, average, high) for each cognitive domain. Prior to surgery, 101 patients (82%) showed an impaired score ($z \leq -1.5$) on at least 1 cognitive domain, whereas 67 patients (60%) showed an impaired score on at least 3 cognitive domains. On average, performance of patients was impaired in 3.2 domains. Cognitive flexibility (n = 72, 62%) and complex attention (n = 68, 58%) were most frequently affected.

Postoperatively, 68 patients (84%) showed an impaired score on at least 1 cognitive domain, and 31 patients (41%) showed an impaired score on at least 3 cognitive domains. Performance was impaired on an average of 2.8 cognitive domains. Most frequently impaired were the domains of reaction time (n = 44, 54%) and complex attention (n = 38, 48%).

Individual Changes

Up to 89% (n = 67) of the patients demonstrated reliable changes in performance in at least 1 cognitive domain from pre- to postsurgery, whereas 41% (n = 31) of the patients showed reliable changes in 3 or more domains. The Chi-square test of independence demonstrated that changes in at least 1 cognitive domain were significantly more frequent in patients with GBM (89%) than in normative controls (49%; $\chi^2(1) = 33.75$, $p \leq 0.001$). The same held for changes in at least 3 cognitive domains: this was found significantly more often in patients with GBM (41%) than in normative control subjects (5%; $\chi^2(1) = 41.06$, $p \leq 0.001$).

Half of the 67 patients demonstrating changes solely showed improvements (51%, n = 34) and 27% of the patients solely declined, whereas 22% showed both improvements and declines on separate cognitive domains. Change was most common for reaction time (55%) and cognitive flexibility (50%); the fewest changes occurred in verbal (13%) and visual memory (16%).

Forty-eight of the 67 patients (72%) who demonstrated preoperative cognitive impairments showed postoperative improvement, and up to 60% of these improvers now demonstrated unimpaired levels of performance on at least 1 of the preoperative

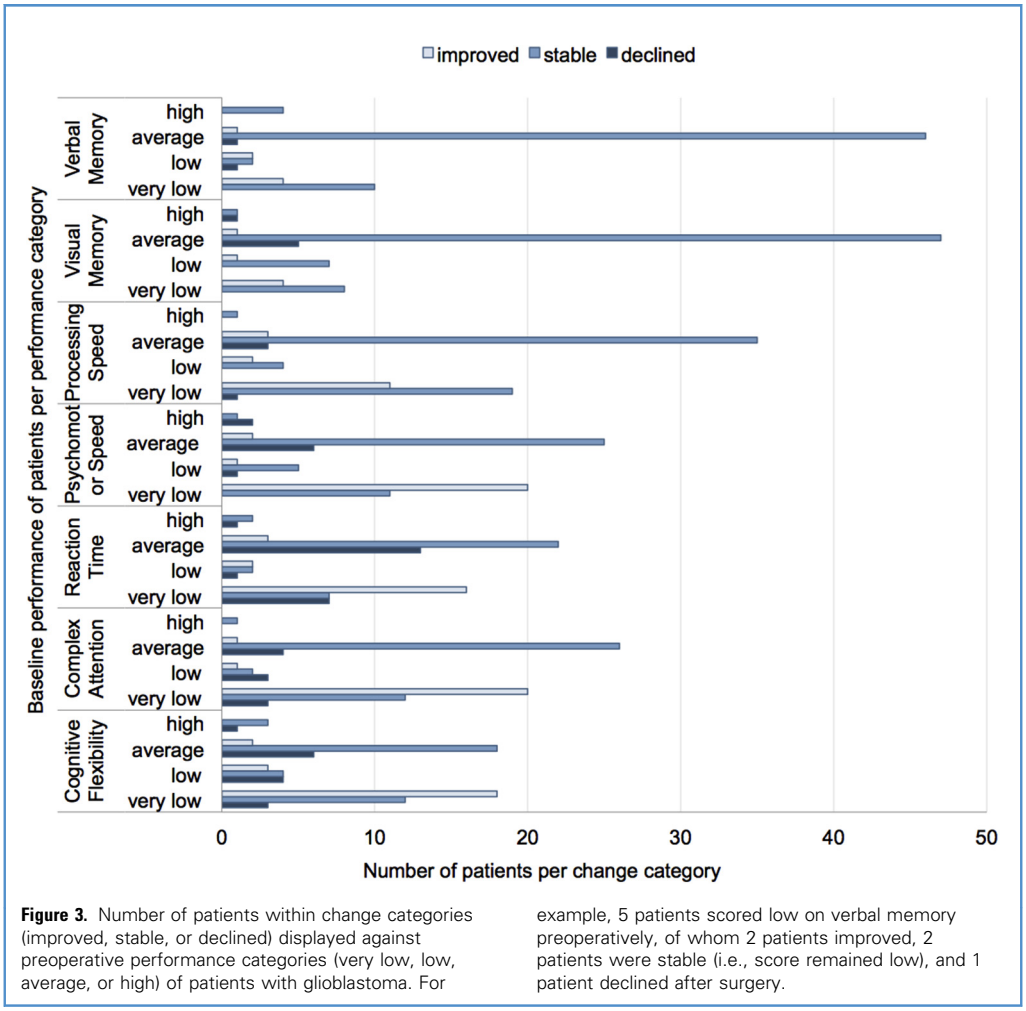

Figure 3. Number of patients within change categories (improved, stable, or declined) displayed against preoperative performance categories (very low, low, average, or high) of patients with glioblastoma. For example, 5 patients scored low on verbal memory preoperatively, of whom 2 patients improved, 2 patients were stable (i.e., score remained low), and 1 patient declined after surgery.

impaired domains. Improvement of prior impaired performance was most common for reaction time (n = 25, 31%) and psychomotor speed (n = 23, 28%). Performance of 14 patients (21%) declined even further after surgery on domains that were already impaired preoperatively. Further decline was most common for reaction time (n = 8, 10%) and cognitive flexibility (n = 7, 9%). Of the 75 patients who showed unimpaired performance on domains preoperatively, 33% (n = 27) showed postoperative decline in these domain(s); in 70% of those with declines, performance dropped to an impaired level. Declined performance in previously unimpaired domains was most common for reaction time (n = 15, 18%) and psychomotor speed (n = 9, 11%). Fifteen percent (n = 12) of the patients showed further postoperative improvements on preoperatively already unimpaired domains, which was most common for reaction time (n = 4, 5%) (Figure 3).

DISCUSSION

This study evaluated cognitive functioning before and 3 months after surgical treatment in patients with GBM using a computerized clinical neuropsychological battery to compare group and individual changes.

We found extensive (i.e., mean z scores ranging from −0.69 to −2.98) pre- and postoperative cognitive deficits in cognitive domains for patients with GBM on the group level. Correspondingly, the vast majority of patients (>80%) showed impaired performance on at least 1 cognitive domain pre- and postoperatively when looking at individual patients with GBM. This corresponds to prior studies using conventional paper-and-pencil neuropsychological tests.[6,9,20,24] Complex attention, cognitive flexibility, and reaction time were most severely impaired (z scores ranging from −1.85 to −2.98), but also most frequently impaired following from the individual patient analyses. As many social, family, and professional activities rely on abilities covered by these cognitive functions (e.g., switching between tasks or conversations, decision-making, controlling behavior), patients are likely to experience far-reaching consequences of these impairments in their daily lives.[34] Compared with other studies, we found relatively few impairments in verbal and visual memory.[6,9,20,21] CNS VS memory tests do not include a free recall condition, but solely rely on recognizing items, whereas studies reporting higher rates of memory impairments assessed memory performance using free recall conditions.[6,9,20,21,24] This might explain the lower rate of memory impairments in the current study.

Only minimal changes in neuropsychological performance on the group level were found from pre- to postsurgery. However, when using RCI values representing reliable changes in performance in individual patients, up to 89% of the patients showed substantial changes on at least 1 out of 7 cognitive domains over time. Half of these patients solely showed improvements, a quarter solely showed declines, and another quarter of the patients showed both improvements and declines. These findings clearly demonstrate that group results mask changes on the individual level.

Although postoperative improvement in performance was common, this does not imply return to unimpaired levels of cognitive functioning: more than one third of the patients who showed postoperative improvement on preoperatively impaired domains remained impaired (since performance can improve from very low to low). Individual change (both improvements and declines in performance) was most common for reaction time. Overall, it seems that the lower the performance the more improvement, and the higher the performance the more decline for the different cognitive domains (**Figure 3**). From a methodological point of view, very low performance leaves the most room for improvements, whereas higher performance leaves the most room for decline. At the group level, only performance on complex attention improved significantly after surgery.

The rates of individual changes in cognitive performance in patients with GBM described in this study were higher than change rates that were found in prior studies (e.g., ranging from 24% to 49%[6,20]). This may be because of different definitions of change that were used over studies. For example, according to Habets et al.,[6] clinically significant improvement was defined as an increase in z score of at least 1.5 SD from baseline to follow-up, and also, if the follow-up score fell into the normal performance range of controls. Talacchi et al.[20] used yet another definition of change, as impairments had to be less frequent (i.e., fewer domains impaired) or more frequent (additional domains impaired) to speak of changed performance. Furthermore, follow-up assessments in these studies were conducted at an earlier stage (i.e., acute postoperative phase,[20] 3 weeks after surgery[6]), whereas patients in the current study were assessed substantially later after surgery, when chemo- and/or radiotherapy had already started in most patients.

Of the preoperatively assessed patients, 66% also completed postoperative neuropsychological evaluation. Considering the severity of the illness and its profound treatment, this number is rather high, also when compared with other follow-up studies in patients with GBM.[6,35,36] The good retention of patients may be explained by the fact that the neuropsychological assessment was an essential part of clinical aftercare that was combined with other clinical appointments, and by the use of a rather short cognitive instrument. Implementing a brief neuropsychological assessment in the clinical care of patients with brain tumors is an important step towards actually using neuropsychological information in the clinical management of these patients. Since patient burden (in terms of energy and time) should be limited, the CNS VS may be a suitable and valuable method. However, one might consider supplementing the CNS VS limited memory tests (i.e., solely relying on recognition) with memory tests that also appeal to retrieval and learning efficiency.

We solely included patients who were considered appropriate candidates for surgery and capable of pre- and postoperative neuropsychological assessment. Consequently, results are likely biased toward an overestimation of cognitive performance in patients with GBM in general.

As a consequence of multimodal treatment of GBM, survival in patients with GBM has improved with overall survival reaching 27% at 2 years.[31,37] Future studies should examine predictors of (changes in) individual cognitive performance, its effects on daily functioning and quality of life, and examine the longer-term course of cognitive functioning in patients with GBM.

CONCLUSIONS

We found extensive and serious cognitive impairments both before and 3 months after surgery in patients with GBM assessed using a computerized neuropsychological battery. At the group level, only minimal changes in neuropsychological performance occurred from pre- to postsurgery, whereas substantial differences in change were found at the individual level, with 89% of the patients changing on at least 1 cognitive domain. Half of these patients showed solely improvements, a quarter showed solely declines, and another quarter of the patients showed both improvements and declines. These findings clearly demonstrate that group results mask changes on the individual level. Future studies should therefore (also) employ an individual patient approach to enhance knowledge transfer into clinical practice. Furthermore, methodological confounds, such as practice effects, should be controlled for in research and clinical settings when statements about (changes in) cognitive performance of the individual patient are at aim.

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