Presurgical Identification of Patients With Glioblastoma at Risk for Cognitive Impairment at 3-Month Follow-up

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BACKGROUND: Pre- and postoperative cognitive deficits have repeatedly been demonstrated in patients with glioblastoma (GBM).

OBJECTIVE: To identify presurgical risk factors that facilitate the identification of GBM patients at risk for postoperative cognitive impairment.

METHODS: Patients underwent neuropsychological assessment using Central Nervous System Vital Signs 1 d before (T0) and 3 mo after surgery (T3). Patients' standardized scores on 7 cognitive domains were compared to a normative sample using one-sample z tests. Reliable change indices with correction for practice effects were calculated to assess cognitive changes in individual patients over time. Logistic regression models were performed to assess presurgical sociodemographic, clinical, psychological, and cognitive risk factors for postoperative cognitive impairments.

RESULTS: At T0, 208 patients were assessed, and 136 patients were retested at T3. Patients showed significantly lower performance both prior to and 3 mo after surgery on all cognitive domains compared to healthy controls. Improvements and declines over time occurred respectively in 11% to 32% and 6% to 26% of the GBM patients over the domains. The regression models showed that low preoperative cognitive performance posits a significant risk factor for postoperative cognitive impairment on all domains, and female sex was a risk factor for postoperative impairments in Visual Memory.

CONCLUSION: We demonstrated preoperative cognitive risk factors that enable the identification of GBM patients who are at risk for cognitive impairment 3 mo after surgery. This information can help to inform patients and clinicians at an early stage, and emphasizes the importance of recognizing, assessing, and actively dealing with cognitive functioning in the clinical management of GBM patients.

KEY WORDS: Cognition, Glioblastoma, Individual performance, Neuropsychological assessment, Risk factors

G lioblastoma (GBM) accounts for the majority of gliomas (56.6%), and comprises the most aggressive primary brain tumors in adults.[1-4] Although the neurooncological field is evolving, GBM is still incurable and associated with overall poor outcomes: the median overall survival despite aggressive surgical resection, radiotherapy, and chemotherapy remains ~15 mo, and deteriorations in cognition and quality of life (QoL) over time are common.[5-7]

Although cognitive functioning is proven to be an independent predictor of survival in GBM patients,[8,9] it is still rarely considered (ie, assessed, monitored, or treated in rehabilitation programs) in neurooncological care. Furthermore, the literature on cognitive functioning in glioma patients is characterized by

fairly small-scale studies and strong heterogeneity in patient samples.[9,10] Previous studies show extensive preoperative, and new and worsened postoperative cognitive deficits in more than 80% of GBM patients.[6,10-17] Sociodemographic (ie, age, sex, and education),[18,19] clinical (ie, hemispheric tumor location, frontal involvement, physical health status, and tumor volume),[17-20] psychological (ie, anxiety and depression),[21] and/or cognitive (ie, preoperative neuropsychological functioning)[22] factors may play a role in predicting the outcome at 3-mo follow-up in glioma patients. However, risk factors that facilitate the identification of patients at risk for postoperative cognitive impairments already before surgery have remained unknown to date. We assessed cognitive functioning in a large sample of GBM patients using a computerized neuropsychological battery 1 d before and 3 mo after surgery. The aim of the current study was to identify patients who are at risk for postoperative cognitive impairment using preoperative factors, based on sociodemographic, clinical, psychological, and cognitive characteristics.

METHODS

Design

The present study comprised a prospective longitudinal design in which brain tumor patients admitted for surgical resection at the Elisabeth-TweeSteden hospital (Tilburg, the Netherlands) between November 2010 and November 2018 underwent neuropsychological assessment (NPA) 1 d before surgery (T0) and 3 mo after surgery (T3) as part of standard neurooncological care.

All patients provided written informed consent. Study approval was issued by the Medical Ethics Committee (file number NL41351.008.12). The patient sample of the current study includes patients who were also included in a previous study.[6]

Patients

The patients included in the current study were those who underwent initial surgical resection, and who were diagnosed with a histopathologically confirmed GBM. Patients were excluded if they (1) were younger than 18 yr, (2) had a history of intracranial neurosurgery, (3) had other major medical illnesses in the past year prior to surgery (eg, myocardial infarct), (4) lacked a basic proficiency in Dutch, (5) were unable to undergo the NPA due to severe visual, motor, or cognitive problems, and/or (6) when surgical complications occurred (eg, intracranial hematoma).

Measures and Procedure

Sociodemographic Characteristics

Patients underwent NPAs per protocol, also including a checklist and standardized interview at baseline for obtaining and verifying sociodemographic information (eg, age, educational level). The Dutch Verhage scale was used to classify the completed level of education (from unfinished elementary school to a university degree): Verhage 1 to 4 represent a low educational level (primary level education or lower), Verhage 5 a middle educational level (completion of average level secondary education), and Verhage 6 and 7 represent a high educational level (high level secondary education or university degree).[23]

Clinical Characteristics

Clinical information was retrieved from the electronic medical charts. Tumor location was classified as frontal (ie, frontal, frontal-temporal, frontal-parietal) vs nonfrontal (temporal, parietal, occipital, or a combination of these areas), and according to lesion side (ie, right, left, bilateral) by means of a standard preoperative contrast-enhanced T1 weighted magnetic resonance image. Total preoperative tumor volume was segmented semiautomatically, followed by manual adjustments, with ITK-SNAP (www.itksnap.org)[24] or BrainLab (BrainLab, Munich, Germany) software by trained researchers under supervision of the neurosurgeon. Karnofsky Performance Status (KPS) was reflected by the American Society of Anesthesiologist (ASA) score, ranging from ASA I (patient completely healthy) to ASA V (moribund patient) and considered dichotomous (ASA score I-II vs ASA score III-IV).[25] Use of psychotropic medication was defined as use of antiepileptic drugs, corticosteroid drugs, benzodiazepines, opioids, antipsychotics, stimulants, and/or antidepressants.

Psychological Characteristics

The Hospital Anxiety and Depression Scale (HADS; Dutch translation) was used to assess self-reported symptoms of anxiety and depression.[26,27] The HADS comprises 14 items: both subscales (ie, anxiety and depression) include 7 items resulting in a score from 0 to 21 for both subscales. Higher scores represent more anxiety/depression symptoms, and in addition, the cut-off for clinical significance was set at 8 for each subscale.

Cognitive Performance

Cognitive functioning was assessed using the computerized battery Central Nervous System Vital Signs (CNS VS, Dutch translation).[28,29] CNS VS includes 7 neuropsychological tests that reflect performance on the domains of Verbal Memory, Visual Memory, Processing Speed, Psychomotor Speed, Reaction Time, Complex Attention, and Cognitive Flexiblity.[30] Raw domain scores were converted into sociodemographically adjusted z scores, and scores at T3 were additionally corrected for effects of practice, since both sociodemographic and practice effects were demonstrated in a Dutch normative sample (age ranging from 20 to 80 yr, education ranging from 10 to 26 yr), assessed using CNS VS at baseline (n = 158), and 3-mo (n = 136) follow-up.[28,29]

It takes 30 to 40 min to complete CNS VS. Assessments were performed using the CNS VSX local software app, on a laptop computer running a 64-bit operating system. A well-trained test technician was present during each assessment.

Statistical Analyses

Patients' Characteristics

Descriptive and comparative analyses (ie, between the patient sample that completed only T0 and the patients who completed both T0 and T3) of baseline sociodemographic, clinical, and psychological characteristics were performed using one-sample z tests and chi-square tests of independence.

Cognitive Performance and Changes on the Group Level

To examine potential differences in mean CNS VS performance on the 7 cognitive domains between GBM patients and the normative sample, 1-tailed one-sample z tests were performed for T0 and T3 (test values: mean (M) $z = 0$, standard deviation (SD) = 1). The mean

z score is comparable to the effect size (ES) Glass's Δ when calculated as follows: $M_{patients} - M_{controls}/SD_{controls}$. Therefore, mean z scores ≤ 0.50 were considered to represent small ES, between 0.51 and 0.79 medium ES, and ≥ 0.80 large ES.[31]

We conducted 2-tailed paired samples t tests to assess changes in cognitive performance over time on the group level from T0 to T3. ESs were calculated and expressed as Cohen's d as follows: $M_{difference}/SD_{difference}$ ($d \leq 0.50 =$ small, d between 0.51 and 0.80 = medium, $d \geq 0.80 =$ large).[31,32]

Cognitive Performance and Changes on the Individual Patient Level

We counted the numbers and percentages of patients scoring impaired (ie, defined as a z score of ≤ 1.50)[33] for all cognitive domains at both time points.

Furthermore, we assessed changes in performance of individual patients over time by calculating reliable change indices (RCI) for each cognitive domain.[29] RCI values exceeding ± 1.645 represented changes, whereby positive and negative values respectively represented improved and declined performance. Also, we counted the numbers of patients within every change category (improved, stable, and declined performance) for each domain.

Risk Factors for Postoperative Cognitive Impairment

Several potential preoperative risk factors were assessed: sociodemographic (age, sex, educational level), clinical (tumor location in terms of hemisphere and frontal vs nonfrontal, ASA score, tumor volume), psychological (HADS anxiety and depression), and cognitive (T0 performance for each relevant cognitive domain) variables. A binominal logistic regression analysis was performed for each cognitive domain to examine the effect of these factors on the likelihood that patients scored impaired after surgery. Linearity of the continuous predictors with respect to the logit of the dependent variable was assessed via the Box-Tidwell procedure.[34] For every cognitive domain, the explained variance Nagelkerke R square (R^2),[35] the percentage accuracy in classification (PAC), sensitivity (ie, true positive rate), and specificity (ie, true negative rate) were presented. In addition, the receiver operating characteristic (ROC) curves including area under the curve values (AUC) were shown, representing the ability of a model to discriminate between patients with and without cognitive impairment.[36] Data on the risk factors were presented as B coefficients and associated standard errors (SE). Odds ratios (ORs), representing the change in odds of scoring impaired after surgery for each increase in an unit of the predictor, are presented as well.[37]

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 24.0 (IBM Corporate Headquarters, Armonk, New York). To reduce the false discovery rate due to multiple statistical testing, P-values were set against a corrected alpha, using the Benjamini-Hochberg (BH) procedure.[38,39]

RESULTS

Patients' Characteristics

Figure 1 shows the flow of GBM patients through the study. At T0, 208 patients were included. Thirty-five percent of the patients dropped out before T3 (mostly due to clinical deterioration or decease), resulting in 136 patients at T3. Table 1 shows

patients' characteristics. There were no significant differences with regard to baseline sociodemographic, clinical, or psychological characteristics of the T0-only and T3 samples (P-values $> .133$). In order to include a preoperative predictor reflecting functional status, we looked into KPS scores of the patients.[40] Yet, out of the 208 included patients, only 51 patients were found to have a preoperatively determined KPS score recorded in their electronic patient file. Of these patients, only 3 patients had a KPS score of <80. Given the amount of missing data, and the limited spread in scores, we chose not to include KPS score as a predictor in our analysis.

Cognitive Performance and Changes on the Group Level

GBM patients demonstrated significantly lower performance compared to normative controls on all cognitive domains at T0 and T3 ($ps <$ BH-corrected alpha .05) (Table 2). Worst performance (at both T0 and T3) was found for Reaction Time (ES -2.10 and -1.88, respectively) and Complex Attention (ES -2.26 and -1.60, respectively).

Paired-samples t tests revealed no significant changes in cognitive performance on the group level between T0 and T3, except for Complex Attention, for which performance improved significantly ($t(111) = -2.85$, $P = .005$) (see Table 2). With Glass' Δ ranging from 0.04 to 0.27, ESs were small for all domains.

Cognitive Performance and Changes on the Individual Patient Level

Impaired performance occurred in 29% up to 55% of the patients across different domains at T0. At T3, 23% to 49% of the patients showed impaired scores across the 7 cognitive domains (Figure 2).

Changes in performance of individual patients over time are shown in Figure 3. Improvements occurred in 11% (both Verbal Memory and Visual Memory) up to 32% (Cognitive Flexibility) of the patients across the domains. A total of 6% (Processing Speed) to 26% (Reaction Time) of the patients showed declined performance between T0 and T3.

With up to 56% and 47% of the patients showing changed performance, improvements and declines were most frequent on Reaction Time and Cognitive Flexibility. Fewest changes were observed for the memory domains, with 81% and 80% of the patients demonstrating stable performance over time on Verbal and Visual Memory, respectively.

Risk Factors for Postoperative Cognitive Impairment

The logistic regression models reached statistical significance for all cognitive domains ($ps <$ BH-corrected .05). The explained variance Nagelkerke R^2 ranged from 35% (Psychomotor Speed) up to 52% (Cognitive Flexibility), and the models correctly classified 72% (Reaction Time) to 83% (Visual Memory) of the patients (Table 3). Figure 4 demonstrates ROC curves for the 7 cognitive domains: AUC values ranged from 0.81 (Verbal Memory) to 0.88 (Cognitive Flexibility). Sensitivity and
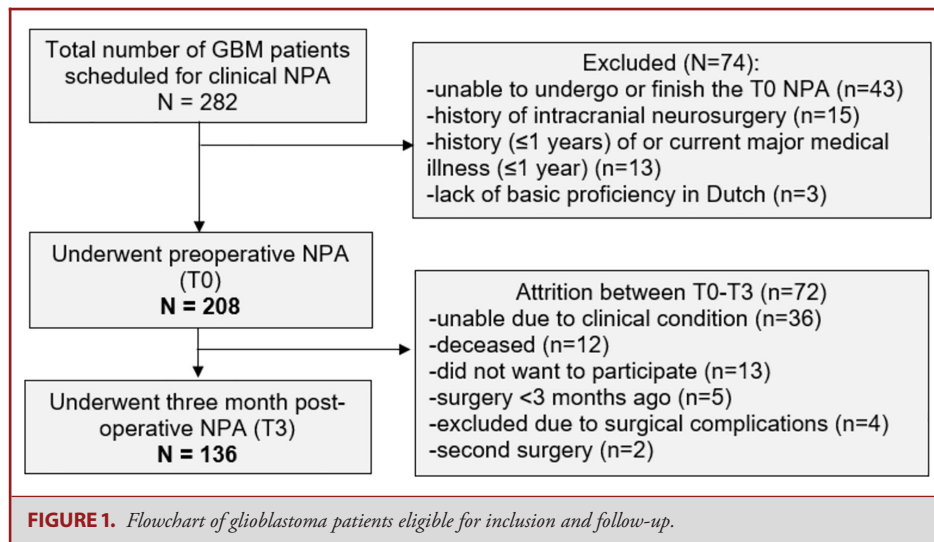
FIGURE 1. *Flowchart of glioblastoma patients eligible for inclusion and follow-up.*

TABLE 1. Baseline Characteristics of Glioblastoma Patients at T0 and T3

	T0 (n = 208)	T3 (n = 136)	z/χ^2	P
Sociodemographic characteristics				
Age (yr): mean ± SD (range)	58.5 ± 11.4 (18-81)	57.2 ± 11.9 (18-80)	− 1.33	.184
Education (yr): mean ± SD (range)	14.0 ± 3.6 (4-25)	14.2 ± 3.6 (4-25)	0.65	.517
Sex: female/male, n (%)	61 (29)/147 (71)	41 (30)/95 (70)	0.09	.768
Clinical characteristics at T0				
Hemisphere: left/right/bilateral n(%)	73 (35)/134 (64)/1 (1)	50 (37)/85 (62)/1 (1)	0.26	.876
Frontal/non-frontal, n(%)	66 (32)/142 (68)	44 (32)/92 (68)	1.89	.170
Tumor volume (cm³): median (range)	36.7 (0.7-435.4)	35.3 (0.7-163.4)	− 0.14	.889
ASA score: I/II/III n(%)	79 (38)/114 (55)/15 (7)	56 (41)/70 (52)/10 (7)	0.69	.707
Psychotropic medication: yes/no, n(%)	196 (94)/12 (6)	132 (97)/4 (3)	2.26	.133
Adjuvant therapy at T3				
Concomitant RT + ChT/RT/ChT/none	–	114 (84)/17 (13)/2 (1)/3 (2)		
Psychological characteristics at T0				
Anxiety HADS: mean ± SD (range)[a]	6.8 ± 4.3 (0-18)	6.8 ± 4.2 (0-16)	0.00	1.00
Above clinical cut-off n(%)	69 (39)	23 (17)		
Depression HADS: mean ± SD (range)[a]	4.8 ± 3.2 (0-13)	4.8 ± 3.0 (0-13)	0.00	1.00
Above clinical cut-off n(%)	41 (23)	25 (19)		

ASA, American Society of Anesthesiologists;[20] ChT, chemotherapy; HADS, Hospital Anxiety and Depression Scale[41]; RT, radiotherapy.
[a]Data missing T0 = 30; T3 = 18. * $P < .05$.

specificity ranged from 46% to 68% and 76% to 94% over domains, respectively. Only presurgical cognitive performances were significant risk factors for postoperative impairments on all cognitive domains, except for Visual Memory, where sex was also found to be a significant risk factor ($ps < $ BH-corrected alpha .005) (Table 3). For all domains, higher presurgical cognitive performance was associated with a decreased likelihood of postoperative cognitive impairment (ORs ranging from 0.36 to 0.70, representing 30% to 64% higher risk on cognitive impairment for each SD lower in the preoperative z score), and females had 6.50 times higher odds to exhibit postoperative Visual Memory impairments than males.

As more of half of the patients showed stable performance over time on 6 out of 7 domains that were assessed (ie, with the exception of the Reaction Time domain, where 44% of the GBM patients showed stable performance over time), these numbers were not sufficient to carry out statistical prediction analysis on group membership (ie, improvement, stable, or declined cognitive performance) at 3-mo follow-up.

DISCUSSION

We evaluated pre- and postoperative cognitive functioning in a sample of GBM patients using the computerized neuropsychological battery CNS VS, and sought to present presurgical factors that enable the identification of patients who are at risk for postoperative cognitive deficits.

TABLE 2. Cognitive Performance on CNS VS of Glioblastoma Patients Pre- and Postoperatively

Cognitive domain	Mean z score ± SD	N[a]	z test	P[b]	Glass △[c]
T0 preoperative NPA					
Verbal Memory	− 0.90 ± 1.33	197	−12.58	<.001*	−0.90
Visual Memory	− 0.86 ± 1.29	204	−12.28	<.001*	−0.86
Processing Speed	− 1.31 ± 1.46	201	−18.63	<.001*	−1.31
Psychomotor Speed	− 1.62 ± 1.82	199	−22.82	<.001*	−1.62
Reaction Time	− 2.10 ± 2.71	193	−29.08	<.001*	−2.10
Complex Attention	− 2.26 ± 2.66	186	−30.57	<.001*	−2.26
Cognitive Flexibility	− 1.97 ± 2.26	187	−26.91	<.001*	−1.97
T3 postoperative NPA					
Verbal Memory	− 1.08 ± 1.58	129	−12.31	<.001*	−1.08
Visual Memory	− 0.64 ± 1.23	132	−7.39	<.001*	−0.64
Processing Speed	− 1.10 ± 1.34	133	−12.73	<.001*	−1.10
Psychomotor Speed	− 1.23 ± 1.65	134	−14.25	<.001*	−1.23
Reaction Time	− 1.88 ± 2.51	130	−21.41	<.001*	−1.88
Complex Attention	− 1.60 ± 2.61	122	−17.73	<.001*	−1.60
Cognitive Flexibility	− 1.56 ± 1.97	125	−17.49	<.001*	−1.56
T0-T3 pairs	**Mean difference ± SD**	**N**	**t test**	**P[e]**	**Cohen's d[d]**
Verbal Memory	− 0.23 ± 1.59	120	1.56	.121	−0.14
Visual Memory	0.14 ± 1.32	129	−1.20	.232	0.04
Processing Speed	0.16 ± 1.18	128	−1.51	.133	0.10
Psychomotor Speed	0.31 ± 1.73	129	−2.06	.042	0.18
Reaction Time	0.26 ± 2.46	120	−1.14	.255	0.11
Complex Attention	0.65 ± 2.42	112	−2.85	.005*	0.27
Cognitive Flexibility	0.33 ± 1.89	117	−1.87	.064	0.17

[a]The number of patients differ over cognitive domains as a consequence of missing or invalid scores.
[b]*P value < BH-corrected alpha .05.
[c,d]Glass's △ and Cohen's d ES with ≤0.50 = small, 0.51-0.79 = medium, ≥ = large.[9,27]
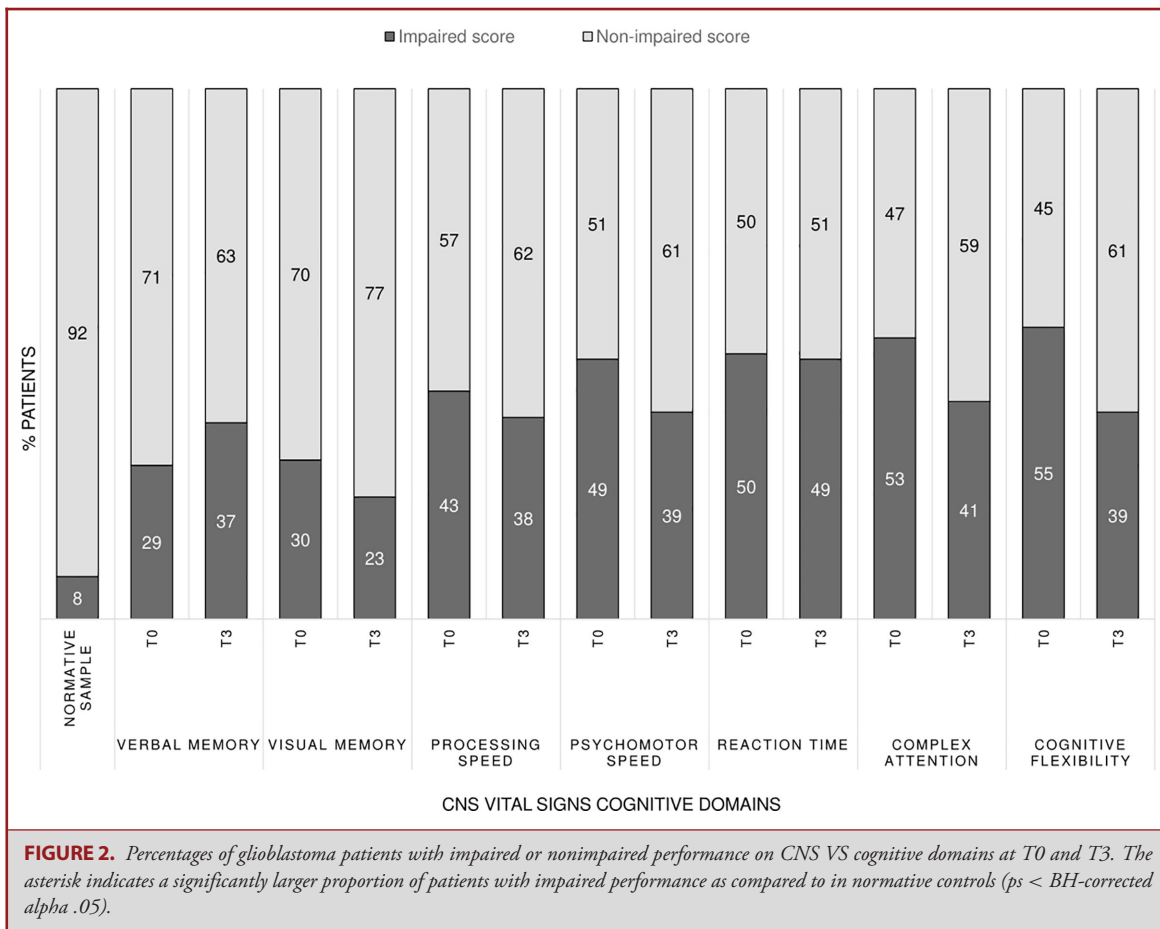[e]*P value < BH-corrected alpha .007.

Key Results

Consistent with the literature and our previous work, we found pre- and postoperative cognitive deficits to be very common in GBM patients, eg,[6,11,12,14] up to 55% and 49% of the patients showed impaired performance over the different domains prior to and after surgery, respectively. Besides very common, deficits also proved to be severe: ESs were found to be major in general (ES ranging from −0.86 to −2.26). Furthermore, our results indicate that improvements of postoperative performance are approximately as frequent as declines. Over time, only performance on Complex Attention improved significantly at the mean group level, yet postoperative group performance was still significantly and greatly impaired (with an ES of −1.60). No significant mean group changes over time were found for the other 6 cognitive domains that were assessed. Also, more than half of the patients showed stable performance over time on 6 out of the 7 domains that were assessed, suggesting that cognitive functioning does not necessarily significantly decline postsurgery. A recent meta-analysis on cognitive changes in glioma patients suggested a beneficial effect of surgery on cognitive functioning,[10] yet several studies that were excluded reported no significant declines after surgery at best, which is more in line with the current study.[12,20,41,42] Furthermore, another recent meta-analysis on cognitive functioning specifically in patients with GBM reported a consistently high risk of cognitive dysfunction and further deterioration of cognitive functioning after surgical treatment (with 7 out of 11 studies reporting static deficits or deteriorated performance).[43]

Low preoperative cognitive performance significantly increased the odds for GBM patients with regard to showing postoperative deficits on all domains. In addition, female sex was a risk factor for postoperative deficits in Visual Memory. Significant overall male advantages have been described in the literature with regard to the storage of visual and spatial information—with an increase in the magnitude of sex differences with age of participants.[44] Given the mean age of 59 yr in the current sample, the significant female disadvantage on Visual Memory in the current sample is in line with the literature. In order to further evaluate this finding, we examined potential differences between females and males in the current study: no significant differences were present with regard to age, education, hemispheric lesion side, frontal tumor involvement, ASA scores, tumor volume, anxiety,

FIGURE 2. *Percentages of glioblastoma patients with impaired or nonimpaired performance on CNS VS cognitive domains at T0 and T3. The asterisk indicates a significantly larger proportion of patients with impaired performance as compared to in normative controls (ps < BH-corrected alpha .05).*
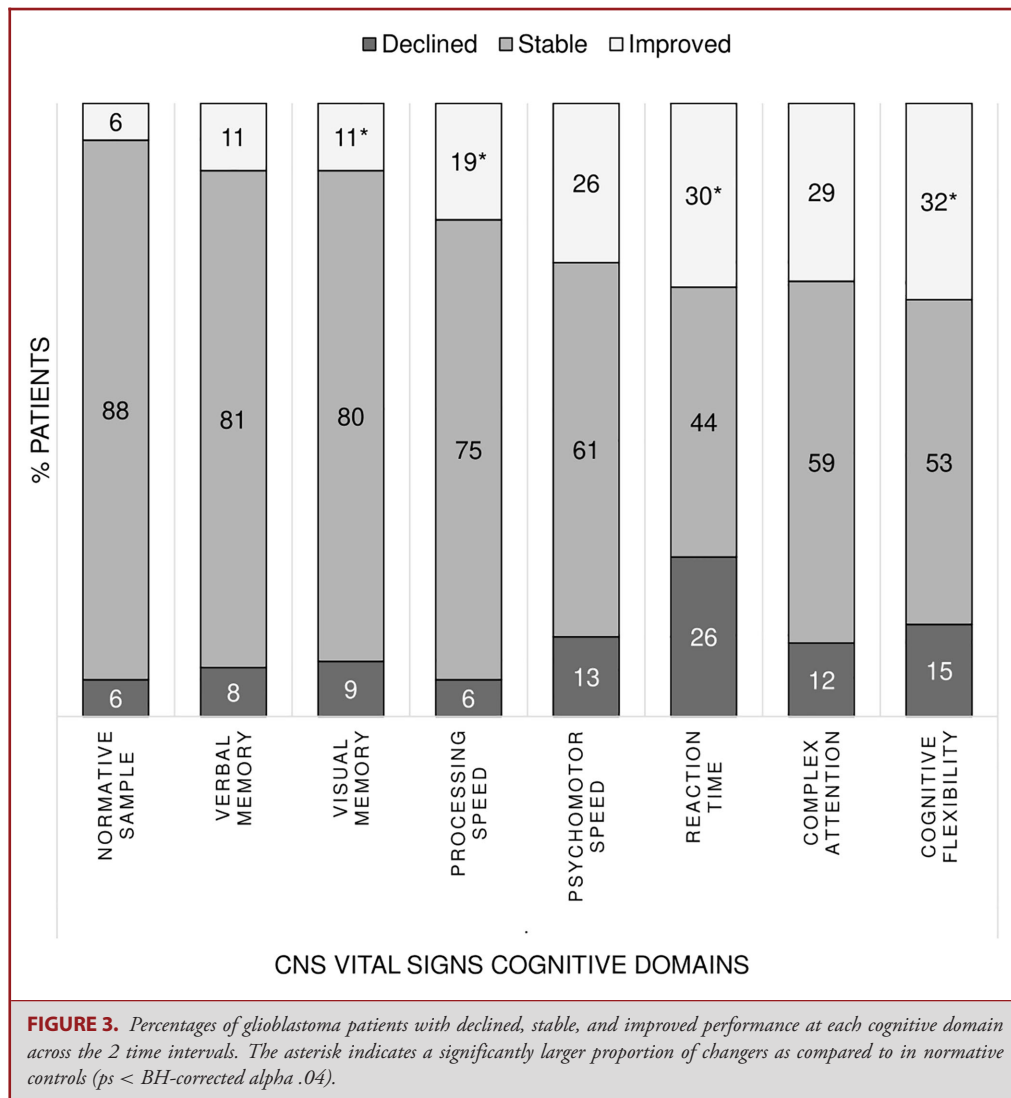
and depression (data not shown), whereby it is unlikely that these variables explain the elevated risk on postoperative visual memory impairments in females. No other sociodemographic, clinical, or psychological factors were found to increase the risk of postoperative cognitive dysfunction. The literature on cognitive functioning in glioma patients with regard to the predictive value of lesion location and volume is not clear cut, and the finding that late cognitive outcomes do not vary by these variables is therefore not suprising.[45-48] It has been suggested that gliomas can yield both local and global effects by infiltrating healthy brain tissue, reducing functional integrity of remote brain regions, and disturbing the cerebral network as a whole.[4,9] Recently, even functional connectivity within the contralesional hemisphere has been found to play a role in determining the severity of cognitive impairments.[47] Taken together, this may explain why tumor-related characteristics (ie, hemisphere, location, and volume) did not specifically predict outcomes for cognitive domains.

Interpretation

Various neuropsychological instruments have been used across studies to assess cognitive performance in GBM patients. Results

of the current and our previous study on cognitive impairments in GBM patients using a standardized computerized neuropsychological test battery (ie, CNS VS[30]) are very similar to the results of studies that examined patients using conventional paper-and-pencil tests.[5,14,16,17] Therefore, computerized batteries could be useful tools both for research and clinical purposes, providing pre- and postoperative neuropsychological information on a fairly wide range of cognitive functions in a relatively short time. Yet, it should be mentioned that CNS VS is somewhat limited in terms of covering all relevant cognitive domains, as for example language and visuospatial abilities are not evaluated by its tests. Also, the CNS VS battery would benefit from a supplementary memory test (eg, addressing retrieval and learning efficiency), as its memory tests are constrained to recognition.

The current study shows that it is possible to identify patients at risk for postoperative cognitive impairments even before surgery. The risk of postoperative impairment over the different cognitive domains becomes 30% (Complex Attention) up to 64% (Processing Speed) higher for each unit lower (ie, in terms of SD) in the preoperative cognitive z score. Former studies have already provided evidence that cognitive performance is an important predictor of QoL and (progression

FIGURE 3. *Percentages of glioblastoma patients with declined, stable, and improved performance at each cognitive domain across the 2 time intervals. The asterisk indicates a significantly larger proportion of changers as compared to in normative controls (ps < BH-corrected alpha .04).*

free) survival.[7-9] Also, cognitive performance of glioma patients (assessed with neuropsychological tests) has been found to be generalizable to "real-world" functions and activities,[49] resulting in for example slow responses to stimuli (related to Reaction Time) and struggles with adapting to new or changing events (related to Cognitive Flexibility), thereby complicating the ability of patients to perform everyday activities such as driving a car or preparing diner. We advocate the implementation of a preoperative and 3-mo postoperative NPA into the clinical care of GBM patients to gain insight into cognitive functioning and to guide in clinical decision-making. By doing so, a referral to, for example, cognitive rehabilitation can be provided timely with the aim of maintaining or even improving QoL and daily-life autonomy of patients. Additional research will be needed to examine methods for optimal rehabilitation of cognitive functioning (eg, psychoe-

ducation, strategy training, retraining, exercise interventions, pharmacological interventions) after surgery in GBM patients further, as promising results on cognitive rehabilitation in brain tumor patients have been demonstrated already.[50]

Limitations

The current study has some limitations that should be noted. We solely included patients who were considered acceptable candidates for surgery and capable of undergoing the NPA presurgery. Also, 35% of the patients dropped out before completion of the follow-up assessment, mainly (ie, in more than two-thirds of the patients) due to a poor clinical condition or decease of patients, which is inherent to the evolution of the disease. Consequently, results may be biased toward an overestimation of cognitive performance in GBM patients. Furthermore,

TABLE 3. Binomial Logistic Regression Predicting the Likelihood of Cognitive Impairment at T3 Based on Preoperative Sociodemographic, Clinical, Psychological, and Cognitive Variables

	Verbal Memory		Visual Memory		Processing Speed		Psychomotor Speed		Reaction Time		Complex Attention		Cognitive Flexibility	
n	106		114		112		111		107		100		102	
Nagelkerke R²[a]	39.4		37.6		45.5		35.4		42.9		44.1		52.4	
PAC[b]	81.1%		83.3%		80.4%		73.0%		72.0%		78.0%		76.5%	
Sensitivity	54.4		46.2		65.9		56.8		67.9		64.1		64.1	
Specificity	93.2		94.3		88.7		83.6		75.9		86.9		84.1	
Variables	**B(SE)[c]**	**OR[d]**	**B(SE)[c]**	**OR[d]**	**B(SE)[c]**	**OR[d]**	**B(SE)[c]**	**OR[d]**	**B(SE)[c]**	**OR[d]**	**B(SE)[c]**	**OR[d]**	**B(SE)[c]**	**OR[d]**
Age	0.02(.03)	1.02	−0.02(.03)	0.98	0.01(.02)	1.01	0.00(.02)	1.00	0.05(.02)	1.05	0.07(.03)	1.07	0.04(.03)	1.04
Sex														
Female (vs male)	0.02(.56)	1.02	**−1.87(.61)**	**6.50**	0.53(.55)	1.70	0.28(.53)	1.32	−0.07(.56)	0.94	0.47(.59)	1.60	1.12(.63)	3.07
Education														
Low (vs other)	−0.52(.65)	0.60	0.49(.67)	1.64	1.55(.64)	4.70	−0.17(.59)	0.84	−0.14(.63)	0.87	−0.70(.65)	0.50	−0.05(.67)	0.95
High (vs other)	−0.97(.63)	0.38	−0.40(.74)	0.70	1.16(.64)	3.18	−0.35(.57)	0.71	−0.03(.58)	0.97	0.32(.64)	1.38	−0.07(.69)	0.94
Hemisphere														
Right (vs left)	−0.52(.57)	0.60	−0.26(.65)	0.77	−0.53(.54)	0.59	0.05(.52)	1.05	−0.39(.53)	0.68	0.31(.57)	1.36	−0.38(.66)	0.69
Tumor volume	0.04(.01)	1.00	0.01(.01)	1.01	−0.01(.01)	0.99	−.01(0.01)	1.00	−.01(0.01)	1.00	0.02(.01)	1.02	0.02(.01)	1.02
Frontal														
Yes (vs no)	−1.09(.56)	2.99	−0.68(.60)	0.51	0.00(.56)	1.00	0.43(.51)	1.53	0.77(.54)	2.16	1.12(.57)	3.07	0.80(.58)	2.23
ASA score[e]														
>3 (vs 1 or 2)	1.38(1.24)	3.95	1.57(1.00)	4.80	1.76(1.51)	5.83	0.82(1.01)	2.27	1.24(1.40)	3.47	1.22(1.18)	3.38	0.91(1.14)	2.49
HADS A[f]	0.06(.08)	1.07	0.13(.09)	1.14	0.08(.08)	1.09	−0.03(.07)	0.97	0.12(.08)	1.13	0.01(.08)	1.01	−0.01(.08)	0.99
HADS D[f]	−0.19(.12)	0.82	0.05(.11)	1.05	−0.02(.10)	0.99	0.18(.09)	1.19	0.04(.10)	1.04	0.10(.10)	1.11	0.12(.11)	1.12
Cognitive score T0	**−0.97(.24)**	**0.38**	**−0.81(.31)**	**0.45**	**−1.02(.25)**	**0.36**	**−0.74(0.18)**	**0.48**	**−0.54(.14)**	**0.59**	**−0.36(.12)**	**0.70**	**−0.71(.16)**	**0.49**

In bold: $P <$ BH-corrected alpha .005.
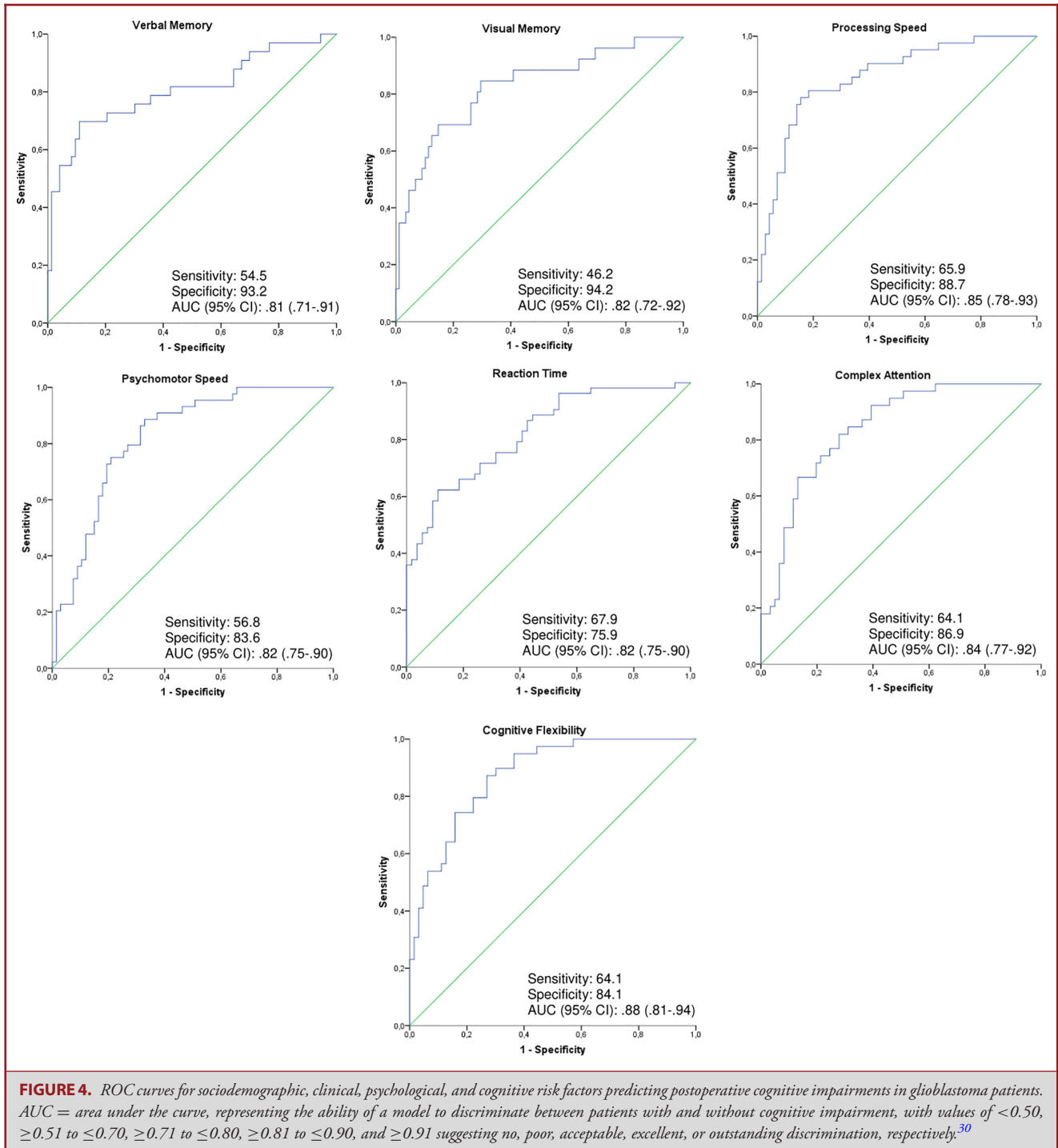[a]Nagelkerke R², larger R² values indicating more variance explained by the model, to a maximum of 1.[29]
[b]Percentage Accuracy in Classification (PAC); the percentage of the total sample that is correctly classified by the model.
[c]B coefficients and associated standard errors.
[d]OR for the predictors, OR smaller than 1.00 indicate a decreased odd of impairment for an increase in one unit of the predictor.[32]
[e]ASA, American Society of Anesthesiologists.[20]
[f]HADS, Hospital Anxiety and Depression Scale.[21]

FIGURE 4. *ROC curves for sociodemographic, clinical, psychological, and cognitive risk factors predicting postoperative cognitive impairments in glioblastoma patients. AUC = area under the curve, representing the ability of a model to discriminate between patients with and without cognitive impairment, with values of <0.50, ≥0.51 to ≤0.70, ≥0.71 to ≤0.80, ≥0.81 to ≤0.90, and ≥0.91 suggesting no, poor, acceptable, excellent, or outstanding discrimination, respectively.*[30]

patients were receiving adjuvant treatments at time of the 3-mo follow-up assessment. As this was the case in the far majority of the patients, we were unable to take effects of adjuvant radiotherapy and/or chemotherapy statistically into account in this study.

Yet, radiotherapy and chemotherapy represent an additional (ie, in addition to the tumor itself and surgical resection) risk for cognitive impairment, even with relatively well tolerated medications such as temozolomide.[51]

Future Directions

It would be desirable to be able to identify patients who are at risk for cognitive impairment on the basis of information that can be collected with relatively little effort (eg, sociodemographics, basic clinical data) at an early stage of disease. Yet, no preoperative sociodemographic (except for Visual Memory), clinical, or psychological factors were found to have significant predictive power with regard to cognitive outcomes of GBM patients at 3-mo follow-up. Future studies should aim to assess the potential added predictive value of factors that are known after surgery (eg, additional radiotherapy and/or chemotherapy, isocitrate dehydrogenase status, and disease progression) on later cognitive outcomes. By doing so, it can be determined whether cognitive outcomes of GBM patients can be predicted better if postoperative factors are added to prediction models, and moreover, risk factors for cognitive impairment that are only known postoperatively can be identified.

CONCLUSION

The current study shows that it is possible to identify patients at risk for postoperative cognitive impairments even before surgery. This information can help to inform patients and clinicians at an early stage, and emphasizes the importance of recognizing, assessing, and actively dealing with cognitive functioning in the clinical management of GBM patients.

Disclosures

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