



Longitudinal study of cognitive function in glioma patients treated with modern radiotherapy techniques and standard chemotherapy

Anna Rydelius^a , Jimmy Lätt^b, Sara Kinhult^c, Silke Engelholm^c, Danielle Van Westen^{b,d}, Mats Pihlgård^e , Johan Bengzon^{f,g}, Pia C. Sundgren^{b,d,h,i,*} and Åsa Lilja^{d,*}

^aDepartment of Clinical Sciences, Division of Neurology, Lund University, Lund, Sweden; ^bDepartment of Medical Imaging and Physiology, Skåne University hospital Lund University, Lund, Sweden; ^cDepartment of Clinical Sciences, Division of Oncology, Lund University, Lund, Sweden; ^dDepartment of Clinical Sciences, Division of Radiology, Lund University, Lund, Sweden; ^eDepartment of Clinical Sciences, Division of Geriatrics, Lund University, Malmö, Sweden; ^fDepartment of Clinical Sciences, Division of Neurosurgery, Lund University, Lund, Sweden; ^gStem Cell Center, BMC B10, Lund University, Lund, Sweden; ^hLund University Biomedicine Center, Lund University, Lund, Sweden; ⁱDepartment of Radiology, University of Michigan, Ann Arbor, MI, USA

ABSTRACT

Introduction: Cognitive function is an important outcome measure in patients with brain tumor, providing information about the patient's clinical situation, treatment effects and possible progressive disease. The aim of this longitudinal study was to evaluate effects of the currently used radiation and chemotherapy treatment on cognitive function and to investigate associations between cognitive function at baseline and progression as well as overall survival.

Methods: 32 patients newly diagnosed with malignant glioma were evaluated at baseline with CNS Vital Signs (CNS-VS), a computerized standardized neuropsychological test battery, prior to arc-based radiotherapy and concomitant chemotherapy with Temozolomide. CNS-VS measures the cognitive functions known to be affected in patients with brain tumor, covering nine cognitive domains. Follow-up cognitive evaluations were performed in 26 patients after 3.5 months and in 13 patients 1 year after treatment start.

Results: Overall cognitive scores were lower in the studied patient cohort at baseline compared to standardized domain scores. At 3.5 months follow-up cognitive functioning was slightly decreased, but only in 1/9 cognitive domains – visual memory – where significant changes were found compared to baseline test results. Similarly, at 12 months follow-up no significant changes in cognitive test results were seen compared to baseline examination, except for a decrease in the visual memory domain. In relation to early progression, the most significant cognitive deficits were dysfunctional visual memory and low executive functioning at baseline. Low executive function at baseline correlated most significantly with shorter overall survival.

Conclusion: The present study suggests that the currently used arc-based radiotherapy and chemotherapy might affect cognitive function less negatively than previously described during treatment and in the first year after treatment in malignant glioma patients. In general, a high cognitive test score at baseline was associated with longer time to progression and with longer survival.

ARTICLE HISTORY

Received 12 December 2019
Accepted 29 May 2020

Research gap



Longitudinal study on newly diagnosed glioblastoma patients, treated with arc-based rotation radiation and chemotherapy: descriptive data on cognitive function and clinical outcome.

Introduction

Cognitive function has long been regarded as an important outcome measure in patients with brain tumor, providing information about a patient's clinical situation and results regarding treatment effects [1,2]. Cognitive deterioration can be the first indicator of progressive disease after treatment,

as has been found in patients with low-grade gliomas [1,3] and in an early study on recurrent high-grade gliomas [4].

Cognitive function is now also recognized as an independent prognostic factor for the survival of patients with gliomas [5]. Measured by specific neuropsychological tests, cognitive impairment has been independently associated with poor prognosis in patients with newly diagnosed glioblastoma, where executive function, attention and verbal memory are the cognitive domains most closely associated with prognosis [5,6]. In patients treated for recurrent glioma, verbal memory has been independently and strongly related to overall survival after accounting for age, Karnofsky performance status score, histology and time to further tumor recurrence [7]. It has also been observed that treatment with

CONTACT Anna Rydelius  anna.rydelius@med.lu.se  Department of Clinical Sciences, Division of Neurology, Lund University, Lund, 221 84, SE, Sweden
*Shared last authors.

© 2020 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

radiotherapy plus concomitant and adjuvant temozolomide per se did not deteriorate cognition in glioblastoma patients with progression-free disease within the first 6 months of treatment [8]. Cognitive functioning may hence be important for treatment planning of individual patients and as a possible prognostic marker for tumor progression [4,9].

Documentation on cognitive functioning in patients with high-grade glioma more than 6 months after diagnosis has, until now, been scarcely found. This may be explained by the severity of the disease, with a short expected overall survival and even shorter time to tumor progression, which strongly limits the possibility of follow-up with cognitive testing even at 12 months from diagnosis.

Recent development of novel techniques such as volumetric-modulated arc therapy (VMAT) as well as helical tomotherapy (HT) have altered the conventional treatment paradigm in radiation treatment of patients with high-grade gliomas. These arc-based radiotherapies may reduce peak radiation doses in critical regions such as the hippocampus without compromising tumor control. Data on these new techniques is limited to planning and feasibility studies [10,11].

In this longitudinal prospective study, we studied the role of cognitive function in patients newly diagnosed with primary high-grade glioma before and up to 12 months after chemo- and radiotherapy. Our major aim was to explore the effects of treatment on cognitive function and to describe clinical parameters such as tumor site, radiation dose, age and gender, depressive symptoms, operation method, steroid intake and antiepileptic medication and to investigate if these parameters are associated with cognitive function. The second aim was to explore if there are possible correlations between cognitive function at baseline before adjuvant treatment and time to tumor progression (TTP) and overall survival.

We hypothesize that chemotherapy and modern arc-based rotation radiation therapy per se have less adverse effects on cognitive function than previously described [1,2] in glioblastoma patients within the first year after radiotherapy, and that specific cognitive metrics at baseline before treatment might be a prognostic marker for TTP and survival.

Material and methods

Patients and study procedure

In this prospective study, 32 patients, (mean age of 59 years, range 35–68 years), newly diagnosed with malignant glioma were enrolled for cognitive testing from October 2013 to October 2017 at the Departments of Neurology and Oncology at Skåne University Hospital in Lund, Sweden. Patients' inclusion criteria were age >18 years, primary surgery with histopathologically confirmed diagnosis of World Health Organization (WHO) grade III or IV malignant glioma, standard postoperative oncological therapy plan, patient's consent for study participation in imaging monitoring and neurocognitive testing, including all patients admitted at the neuro oncological unit for standard postoperative treatment during the predefined study period who agreed to study participation. Cognitive examination was performed at baseline approximately four weeks after surgery but before starting

chemo-radiotherapy according to the Stupp protocol [12], after 3.5 months and, if patients were alive and testing still feasible, after 12 months.

Information regarding survival, TTP and radiological response of the tumor lesion were collected until 1 October 2017, which was the predefined endpoint for this study. Evaluation of quality of life using the EORTC QLQ C-30 [13] questionnaire, for psychiatric symptoms according to the Hospital Anxiety and Depression Scale [14] and for neurological and clinical conditions were carried out on all three test occasions. Patient characteristics and treatment parameters are presented in Table 1.

Assessment of cognitive function, neurological function and quality of life parameters

Cognitive assessment was performed using CNS Vital Signs (CNS-VS), a computerized standardized test battery measuring nine basic cognitive functions, known to be impaired in patients with brain tumor. CNS-VS has been tested and validated in brain tumor patients [15], in traumatic brain injury, dementia, attention deficit/hyperactivity disorders [16,17] and in multiple sclerosis [18]. The CNS-VS test battery comprises seven conventional neuropsychological tests: verbal and visual memory, finger tapping, symbol digit coding, the Stroop Test, a test of shifting attention and a continuous performance test. These seven tests in turn cover nine cognitive

Table 1. Patients' characteristics, tumor characteristics and treatment parameters.

	N = 32	%
Male	23	72
Female	9	28
Tumor localization		
Left	18	56
Right	10	31
Bilateral	4	13
Frontal	14	44
Non-frontal	18	56
Surgery		
Gross total resection	8	25
Partial resection	16	5
Stereotactic biopsy	8	25
Histopathology		
Glioblastoma WHO IV	31	97
Oligodendroglioma WHO III	1	3
Steroid medication		
Baseline	22	69
Antiepileptic medication		
Baseline	14	44
Total	20	62
Chemotherapy		
Temozolomide (TMZ)	13	41
TMZ + followed by 2nd line therapy	19	59
Total radiation dose		
60 Gy	30	94
<60 Gy	2	6
Median equivalent biological radiation doses (Gy)		
Left hippocampus	11	
Right hippocampus	13	
Left amygdala	11	
Right amygdala	11	

Description of included patients, i.e. number, sex and percentage of patients, tumor localization, type of surgery, histopathological diagnosis according to the 2007 WHO (World Health Organization) classification, symptomatic and oncological parameters. The lower part describes the biological radiation dose obtained to risk structures in Gray (Gy).

function domains, i.e. composite memory, verbal memory, visual (spatial) memory, executive functioning, information processing speed, psychomotor speed, reaction time, complex attention and cognitive flexibility[19]. Further details of test description and clinical relevance are summarized in [Appendix](#). Cognitive baseline examinations were performed at the start of radiotherapy and on two additional occasions; 3.5 months after baseline (median 105 days; range 63–231 days) and at 12 months (median 378 days; range 364–490 days). Test scores (standard scores; *ss*) were retrieved for each test occasion and for each tested cognitive domain, where $ss > 109$ is defined as a result above average, $ss = 90–109$ as average, $ss = 80–89$ as low average, $ss = 70–79$ as low and $ss < 70$ as very low.

At time points corresponding to the cognitive testing, neurological performance status according to The National Institutes of Health Stroke Scale (NIH Stroke Scale (NIHSS) [20] and of clinical performance status according to The Eastern Cooperative Oncology Group (ECOG) Scale of Performance Status [21] were registered. Patients' medication including use of corticosteroids and antiepileptic drugs were noted.

Imaging

The imaging protocol included MRI examinations at baseline and at 3, 6, 12, 24 and 52 weeks after start of postoperative treatment. MRI was performed on a 3T Siemens MAGNETOM Skyra® (Erlangen, Germany), with a 20-channel head/neck coil. The MR protocol included the following sequences: axial T2 2D TSE; axial 2D FLAIR (fluid attenuated inversion recovery); T1pre- and post-Gadolinium (Gd) contrast administration with 1 mm³ isotropic resolution and dynamic susceptibility contrast perfusion MR, with the aim to distinguish treatment effects such as pseudo-progression from true tumor progression.

Additionally, conventional clinical radiological monitoring was performed at 36 weeks from baseline. Experienced neuroradiologists performed evaluation of the imaging data continuously as part of clinical routine.

Statistical analyses

Semiparametric Cox regression analyses were conducted with censoring for patients still alive/free of progression on October 1, 2017. The proportional hazards assumption was tested and appeared reasonable for all cognitive domains. In the first step, analyses adjusted for one variable at a time were performed, where $p < .05$ was considered statistically significant. Significant variables were subsequently included in the final model.

Collinearity diagnostics were carried out to investigate if several variables responded similarly using standard techniques as implemented in SAS PROC REG <https://support.sas.com/en/documentation.html>. For details, see the online SAS documentation. For the remaining analyses, standard regression techniques based on Gaussian errors were used. Intra-individual changes in cognitive domain scores were analyzed by parametric regression-based t-test. The model assumptions were tested by QQ-plotting and plotting of

standardized residuals by predicted values. A two-sided *p*-value below .05 was considered statistically significant. All analyses were carried out using SAS 9.4, Cary, NC, USA.

Results

Patient characteristics

In the study, 32 right-handed patients (23 males, 9 females) were included, all undergoing treatment with chemo- and radiotherapy. Ten patients (31%) had a tumor in the right hemisphere, 18 (56%) had a left-sided tumor localization and in 4 cases the tumors were bilaterally located. Fourteen patients (44%) had a predominantly frontal tumor localization and 18 patients (56%) had a predominantly non-frontal tumor. Eight patients (25%) had a gross total resection, 16 patients (50%) underwent a partial tumor resection and eight patients (25%) had only a biopsy for diagnosis. Histological analyses revealed glioblastoma WHO grade IV in all patients, except for one case diagnosed with anaplastic oligodendroglioma WHO grade III, ([Table 1](#)).

Thirty-one of the 32 patients underwent evaluations of cognitive function with neurocognitive examination at baseline. Follow-up cognitive evaluation was performed in 26 patients at 3.5 months after treatment start and 13 patients were also assessed at 12 months after treatment start. However, patients' clinical deterioration due to disease progression (7) or poor health, including medical side effects of therapy e. g. infections and general fatigue and deterioration in clinical performance status (ECOG Zubrod score) (2) or due to the tumor such as thromboembolism (1), or death (8) or drop out due to patients living long distance from the study center (2) limited the number of participating patients in 12 months' follow-up examinations. On the other hand, 7 patients participated at 12 months' testing despite progressive tumor disease.

Postoperative treatment parameters

All patients were treated with postoperative arc-based rotation radiotherapy by using volumetric modulated arc therapy (VMAT) or helical tomotherapy (HT), all patients receiving concomitant temozolomide (TMZ). Twenty-nine patients received 60 Gray (Gy), two patients received 34 Gy due to massive tumor burden and one patient received 10 Gy + 56 Gy with interruption due to wound infection. Median equivalent biological radiation doses were: to left hippocampus 11 Gy, right hippocampus 13 Gy, left amygdala 11 Gy, right amygdala 11 Gy. After radiotherapy all patients were treated with adjuvant temozolomide. If tumor progression occurred during the study, second line therapy was offered, including, if feasible, reoperation, otherwise renewed TMZ therapy if recurrence occurred > 6 months after ending adjuvant TMZ, or CCNU (Lomustine) if recurrence occurred earlier. In summary, the treatment was in accordance with routine management and Swedish national guidelines for malignant glioma.

Among the 32 patients, 22 patients were medicated with corticosteroids at baseline and 20 patients received

antiepileptic medication (carbamazepine, levetiracetam, valproic acid) at any time point during their participation in the study. A more detailed description of the patient characteristics, treatment and additional medication is presented in Table 1.

Survival and tumor progression (TTP)

For the complete patient cohort, the median survival was 608 days (range 83–1524 days) and the median TTP was 271 days (range 83–930 days) after diagnosis. Out of the 32 included patients, 21 patients died during the time of the study. Among these 21 patients, the median survival was 468 days (range 134–1052 days) with a median TTP of 257 days (range 133–662 days). The 11 patients who were still alive at the end of the study on 1 October 2017, had lived a median of 881 days (range 83–1524 days) after primary surgery and had a median TTP of 388 days (range 83–930 days).

Survival was negatively correlated with age, ($p = .0005$), but showed no correlation with the sex of the patient in the Cox regression analysis. There was no correlation between TTP and the age or gender of the patients in the Cox regression analysis.

Cognitive function at baseline and follow-up cognitive examination

The results of the CNS-VS test are summarized in Table 2.

The mean standard score for the psycho motor speed domain was within the normal range, for visual memory domain within lower average, all other scores in the different

tested cognitive domains were lower at baseline compared to standardized domain scores. At follow up after 3.5 months, intra-individual scores in all nine cognitive domains had decreased. However, this was statistically significant only in the domain of visual memory ($p = .015$) analyzed by t-test. None of the other eight tested domains showed statistically significant differences between baseline examinations and 3.5 months. Nor were any statistically significant differences present in the cognitive domain scores for the tested domains, apart from visual memory ($p = .045$) at 12 months' follow-up examination, compared to baseline (Table 3).

Association between cognitive function at baseline and location of the primary tumor

Patients with frontal tumors, regardless of hemisphere, had significantly lower test scores for complex attention ($p = .03$), executive functioning ($p = .03$), visual memory ($p = .02$) and verbal memory ($p = .02$) compared to patients with non-frontal tumors, assessed by t-test. Patients with tumors in the right hemisphere performed better in the cognitive domains of executive functioning ($p = .04$) and both visual and verbal memory ($p = .05$), compared to those with tumors in the left hemisphere.

Cognitive function at baseline related to type of surgery, steroid and antiepileptic medication

There were no significant correlations at baseline between cognitive function and the type of surgical operation method used, tested by linear regression analysis. However, a

Table 2. Cognitive test score CNS Vital Signs (CNS-VS) in Standard Score* (ss) at baseline, follow up 3.5 months and 12 months.

Cognitive measur (ss)	Baseline (N=31)					Follow up 1 (3.5 months) (N=26)					Follow up 2 (12 months) (N=13)				
	M	MD	Min	Max	SD	M	MD	Min	Max	SD	M	MD	Min	Max	SD
Cognitive flexibility domain	72.9	83.0	1	121	33.2	72.6	74.0	15	110	29.2	75.0	82.0	3	119	19.5
Complex attention domain	76.0	86.0	1	117	37.0	69.5	84.5	-28	118	40.4	83.0	96.0	-1	118	37.0
Executive functioning domain	70.9	80.0	1	120	32.5	69.7	65.5	2	110	30.9	80.0	84.0	9	119	34.5
Memory domain (verb + visual)	84.6	90.0	1	130	22.7	80.0	84.5	20	118	24.4	81.3	90.0	20	114	27.6
Processing speed domain	78.0	83.0	2	128	25.5	78.6	85.5	30	114	23.6	86.7	97.0	32	130	27.5
Psychomotor speed domain	90.5	100.0	7	132	29.8	88.7	95.0	33	121	24.0	91.0	94.0	31	126	25.6
Reaction time	72.8	81.0	1	111	32.1	67.9	78.0	13	110	31.9	69.3	85.0	-21	110	42.5
Verbal memory_domain	81.6	87.0	1	122	28.3	81.4	87.5	1	119	30.4	84.7	97.0	12	121	32.0
Visual memory_domain	88.8	89.0	7	125	20.4	83.6	86.0	53	112	19.5	85.7	87.0	44	110	16.6

M: mean; MD: median; SD: standard deviation.

*Test scores in standard scores (ss) >109 above average; 90–109 average; 80–89 low average; 70–79 low; <70 very low.

Table 3. Differences intra-individually in cognitive test results CNS Vital Signs (CNS-VS) in Standard Score (ss) in each tested cognitive domain at follow up 1 and at follow up 2 compared to baseline.

Cognitive domains in standard scores (ss)	Follow up 1 (3.5 months) -baseline (N = 25) ^a					Follow-up 2 (12 months) -baseline (N = 13) ^b				
	M	MD	Min	Max	SD	M	MD	Min	Max	SD
Cognitive flexibility domain	-2.68	-2	-76	59	26.8	-9.3	-2	-84	25	30.3
Complex attention domain	-7.72	-2	-74	48	29.0	-4.2	0	-98	62	42.2
Executive functioning domain	-5.32	-4	-72	35	25.2	-4.8	-1	-80	63	35.5
Memory domain(sum verbal + visual)	-5.04	-4	-53	31	19.7	-8.7	0	-43	9	17.2
Processing speed domain	-3.1	-3	-24	27	13.2	-0.5	0	-45	51	27.0
Psychomotor speed domain	-2.92	-5	-42	54	19.2	-0.9	-7	-68	71	34.2
Reaction time domain	-2.5	1	-49	36	21.3	-3.0	0	-57	59	29.9
Verbal memory_domain	-7.1	-3	-90	39	30.2	-5.7	-3	-60	15	19.3
Visual memory_domain	-6.3	-5	-26	17	12.1	-8.8	-6	-37	17	14.2

M: mean; MD: median; SD: standard deviation.

^a3.5 months test results minus baseline test results.

^b1 year test results minus baseline test results.

significant correlation between steroid medication and complex attention ($p = .05$) and executive functioning ($p = .0043$) was demonstrated, with lower scores for patients on steroid medication. Antiepileptic medication did not correlate with cognition in this material.

Association between neurological performance status, quality of life and psychiatric symptoms at baseline and cognitive function

Statistically significant correlations in the linear regression analysis were seen at baseline, between executive function and neurological (NIHSS) performance status ($p = .03$) and between verbal memory and NIHSS status ($p = .01$), where patients with good neurological function had higher scores in the executive function and verbal memory domains compared to patients with impaired neurological performance status.

Analysis of cognitive functioning at baseline and change at 3.5 and 12 months versus numerical self-assessment sum scores of health and quality of life (EORTC QLQ C-30) and measurements of anxiety and depression (HADS) at baseline did not show any statistically significant correlations. In summary the patients self-reported their health and quality of life in EORTC QLQ-C30 as average to good and their psychiatric health as average according to the HADS self-assessment test results and this did not change over time.

Association between cognitive function at baseline and TTP

The better the cognitive test results, indicated by higher scores in the visual memory domain, complex attention domain and executive functioning domain at baseline, the lower the risk for tumor progression during the time of the study according to the Cox regression analysis. When taking into account all significant domains in the model, the most significant cognitive domains associated with progression were visual memory (Hazard Ratio (HR) = 0.965; $p = .002$) and executive functioning (HR = 0.951; $p < .0001$). As revealed by collinearity diagnostics, the complex attention domain was highly intercorrelated with the executive functioning domain (Table 4).

Association between cognitive function at baseline and survival

High scores in the domains of visual memory, complex attention and executive functioning at baseline prior to radio-chemotherapy treatment lowered the risk of death, analyzed at the end of this study by Cox regression analysis, although several of the domains were intercorrelated. The Cox regression analyses included adjustment for age, since a clear association between age and survival was present. Our results suggest that high age (HR = 1.134; $p = .0005$) and low executive functioning (HR = 0.926; $p = .001$) may be associated with shorter survival (Table 5).

Table 4. Time to tumor progression (TTP) hazard ratio (HR) in relation to cognitive domains adjusted for simultaneously.

Cognitive domain	Chi-square	Pr > ChiSq	Hazard ratio (HR)
Visual memory	9.3514	0.0022	0.965
Complex attention	6.0969	0.0135	1.025
Executive_functioning	16.8265	<.0001	0.951

Table 5. Overall survival (OS) hazard ratio (HR) in relation to cognitive domains and to patients' age.

Parameter	Chi-square	Pr > ChiSq	Hazard ratio (HR)
Age	12.0406	0.0005	1.134
Complex attention	5.3748	0.0204	1.032
Executive functioning	10.3768	0.0013	0.926
Verbal memory	1.0857	0.2974	1.007
Visual memory	3.4971	0.0615	0.962

Bold values indicate significant values.

Association between change in cognitive function and tumor progression

Additionally, visual boxplot estimation of change of cognitive functioning in standard scores from baseline in relation to tumor progression or stable disease at 12 months were performed for visual and verbal memory domains, complex attention and executive function domains. This showed divergent median results with more deterioration at 3.5 months in standard scores among patients with progressive disease ($n = 14/25$) at 12 months in visual and verbal memory and complex attention, but a median improvement in executive function standard scores compared to patients with stable disease at 12 months ($n = 11/25$). Among patients who were able to participate at 12 months testing ($n = 13$), median test results had less deterioration or were unchanged among patients with tumor progression ($n = 6/13$) compared to patients with stable disease ($n = 7/13$) for all four tested domains. In summary no clear association was seen between cognitive deterioration in CNS-VS and tumor progression in this cohort by visual estimation of boxplot.

Discussion

This longitudinal, descriptive study suggests that modern chemo- and radiotherapy might not negatively affect cognitive functioning in malignant glioma patients during and up to 12 months after initiated postoperative treatment. Despite a minor decrease in all cognitive domains at first follow-up at 3.5 months after initiated radiotherapy, the more refined radiation techniques currently used, with arc-based rotation radiotherapy, seem to have less neurotoxic impact on the patients, compared to previously used techniques [1,2].

Chemotherapy may have short- and long-term impacts on cognitive function of cancer patients, but in patients with a primary brain tumor this impact is assumed to be low [22].

The higher the cognitive domain scores patients had in general at baseline, the longer their TTP. Higher cognitive scores also were associated with longer overall survival. However, many of the cognitive domains were intercorrelated. The domain that significantly was associated independently with survival was the executive functioning

domain. The executive functions are ascribed to the prefrontal networks, also called the executive system. Executive dysfunction may arise with damage to or pathological conditions affecting the prefrontal networks [23].

Antiepileptic drugs and corticosteroids may influence cognitive functioning in brain tumor patients. Previous studies have demonstrated that the cognitive domains that may be sensitive to treatment-induced dysfunction include attention and executive functions, memory and psychomotor speed [24,25]. We found no influence of antiepileptic medication on cognitive functioning. We did find an association between medication of corticosteroids and impaired executive functioning. This effect may be interpreted as a result of aggressive tumor growth requiring steroid use, rather than the steroid treatment *per se*, but direct disease-driving effects of corticosteroids have also been discussed [26].

It has recently been hypothesized that properties of the tumor itself and not the anti-tumor treatment may well underlie the cognitive deficits. One study of high-grade glioma patients examined before, during and after standard chemo- and radiotherapy demonstrated no clear association between cognitive functioning and white matter hyperintensities (WMH) or cerebral atrophy (CA) [27]. Furthermore, the same study showed that the majority of patients who declined in cognitive functioning at follow-up had tumor progression within 4 months.

Standardized neuropsychological assessment should be considered an essential part of the management and care of brain tumor patients, and possibly a tool toward providing more individualized treatments. In order to ensure reproducibility and for assessment in clinical trials, it is of importance to use standardized, comparable and comprehensive testing of all patients, i.e. testing should assess the cognitive domains sensitive to tumor and treatment effects [7,28]. CNS-VS fulfills all of these criteria, which is why computerized testing in these cases may be a better option than conventional neuropsychological testing or a complement to the latter [29,30]. Since most previous studies have utilized conventional test methods, CNS-VS is suitable for use as a screening instrument, or as a serial assessment measure, but should not be regarded as replacing standard neuropsychological assessments.

This study has limitations such as the modest number of patients and that less than half of the patients could be examined at 12 months, due to death or to being too impaired, or declined to participate. With the small number of patients, the amount of statistical analyses performed may have been over-fitted. In future studies larger patient cohorts would be beneficial for more reliable observations.

Conclusion and implications for future research

This longitudinal study has demonstrated that good cognitive function in patients with primary glioblastoma, at the time of diagnosis, is one of the positive prognostic factors for prolonged TTP and survival. No significant deterioration in cognitive function was seen within 12 months following the start of therapy, possibly due to modern, less neurotoxic

radiotherapy methods. Neurocognitive examination should be regarded as an essential part of the pretreatment planning, to ensure that patients with high-grade glioma receive the best possible treatment combined with reasonable quality of life. With improved neuro-oncological treatment options, longer survival in high-grade glioma patients is expected. Further studies to evaluate the effect on neurocognitive function as a tool for therapy monitoring, including long-term follow-up in larger cohorts of patients with high-grade gliomas, are warranted.

Acknowledgments

The authors would like to acknowledge the research nurses Anna Weddig and Jan Sundberg, Department of Clinical Sciences, Division of Oncology, Lund University hospital, Lund University, Lund, Sweden and MR coordinator Inga-Lill Enochsson, Center for Medical Imaging and Physiology, Lund University hospital, Lund, Sweden and Denis Selan, RN, Ph.D. student, Department of Clinical Sciences, Malmö University, Malmö, Sweden.

Disclosure statement

The authors have no conflicts of interest to declare.

Ethical approval

The study has been approved by the ethical committee prior to inclusion of patients (#2011/598, 2011/14, 2012/188, 2014/368). All patients have given informed consent prior to being included in the study. Procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) or with the Helsinki Declaration (1964, amended in 1975 and 1983) of the World Medical Association.

Funding

This study has been supported by grants from the Swedish Research Council (K2011-52X-21737-01-3), providing research time for the AR, the Swedish Cancer Society (CAN 2016/365), providing support for the MRI examinations and, together with the Brain Foundation (FO2014-0133), for the computerized CNS-VS tests. The Regional Research Funding (ALF) (FF2014/354) provided salary support for dedicated research time for ÅL and salary support for the research nurses (JS, AW) mentioned in the acknowledgement. JB was supported by donations from Viveca Jeppsson and from Maj-Britt and Allan Johansson.

ORCID

Anna Rydelius  <http://orcid.org/0000-0002-6742-1825>
Mats Pihlsgård  <http://orcid.org/0000-0002-3934-9387>

References

- [1] Taphoorn MJB, Klein M. Review: cognitive deficits in adult patients with brain tumours [Review Article]. *Lancet Neurol.* 2004; 3(3):159–168.
- [2] Durand T, Bernier MO, Leger I, et al. Cognitive outcome after radiotherapy in brain tumor. *Curr Opin Oncol.* 2015;27(6):510–515.
- [3] Armstrong CL, Goldstein B, Shera D, et al. The predictive value of longitudinal neuropsychologic assessment in the early detection of brain tumor recurrence. *Cancer.* 2003;97(3):649–656.

- [4] Meyers CA, Hess KR. Multifaceted end points in brain tumor clinical trials: cognitive deterioration precedes MRI progression. *Neuro-Oncology*. 2003;5(2):89–95.
- [5] Johnson DR, Sawyer AM, Meyers CA, et al. Early measures of cognitive function predict survival in patients with newly diagnosed glioblastoma. *Neuro-Oncology*. 2012;14(6):808–816.
- [6] Kangas M, Tate RL, Williams JR, et al. The effects of radiotherapy on psychosocial and cognitive functioning in adults with a primary brain tumor: a prospective evaluation. *Neuro-Oncology*. 2012;14(12):1485–1502.
- [7] Meyers CA, Hess KR, Yung WK, et al. Cognitive function as a predictor of survival in patients with recurrent malignant glioma. *J Clin Oncol*. 2000;18(3):646–650.
- [8] Hilverda K, Bosma I, Heimans JJ, et al. Cognitive functioning in glioblastoma patients during radiotherapy and temozolomide treatment: initial findings. *J Neurooncol*. 2010;97(1):89–94.
- [9] Loaiza S, Carvajal S, Giraldo D, et al. Memory and attention recovery in patients with high grade glioma who completed the Stupp protocol: a before-after study. *Clin Neurol Neurosurg*. 2018;171:34–41.
- [10] Kim KS, Wee CW, Seok J-Y, et al. Hippocampus-sparing radiotherapy using volumetric modulated arc therapy (VMAT) to the primary brain tumor: the result of dosimetric study and neurocognitive function assessment. *Radiat Oncol*. 2018;13(1):29–29.
- [11] Teoh M, Clark CH, Wood K, et al. Volumetric modulated arc therapy: a review of current literature and clinical use in practice. *Br J Radiol*. 2011;84(1007):967–996.
- [12] Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987–996.
- [13] Quinten C, Coens C, Ghislain I, et al. Original research: the effects of age on health-related quality of life in cancer populations: a pooled analysis of randomized controlled trials using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 involving 6024 cancer patients [Article]. *Eur J Cancer*. 2015;51(18):2808–2819.
- [14] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361–370.
- [15] Meskal I, Gehring K, van der Linden SD, et al. Cognitive improvement in meningioma patients after surgery: clinical relevance of computerized testing. *J Neurooncol*. 2015;121(3):617–625.
- [16] Gualtieri CT, Johnson LG. A computerized test battery sensitive to mild and severe brain injury. *Medscape J Med*. 2008;10(4):90–18504479.
- [17] Littleton AC, Register-Mihalik JK, Guskiewicz KM. Test-retest reliability of a computerized concussion test: CNS vital signs. *Sports Health*. 2015;7(5):443–447.
- [18] Papathanasiou A, Messinis L, Georgiou VL, et al. Cognitive impairment in relapsing remitting and secondary progressive multiple sclerosis patients: efficacy of a computerized cognitive screening battery. *ISRN Neurol*. 2014;2014:151379.
- [19] Gualtieri CT, Johnson LG. Reliability and validity of a computerized neurocognitive test battery, CNS Vital Signs [Article]. *Arch Clin Neuropsychol*. 2006;21(7):623–643.
- [20] Goldstein LB, Samsa GP. Reliability of the National Institutes of Health Stroke Scale. Extension to non-neurologists in the context of a clinical trial. *Stroke*. 1997;28(2):307–310.
- [21] Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649–655.
- [22] Abrey L. The impact of chemotherapy on cognitive outcomes in adults with primary brain tumors. *J Neurooncol*. 2012;108(2):285–290.
- [23] Stuss DT. Functions of the frontal lobes: relation to executive functions [Article]. *J Int Neuropsychol Soc*. 2011;17(5):759–765.
- [24] Correa D. Cognition in brain tumor patients. *Curr Neurol Neurosci Rep*. 2008;8(3):242.
- [25] Douw L, Stam CJ, Klein M, et al. Neural networks and neuro-oncology: the complex interplay between brain tumour, epilepsy and cognition. In: Tosh CR, Ruxton GD, Tosh CR, et al., editors. *Modelling perception with artificial neural networks*. New York, NY, US: Cambridge University Press; 2010. p. 149–183.
- [26] Kostopoulou ON, Mohammad AA, Bartek J, et al. Glucocorticoids promote a glioma stem cell-like phenotype and resistance to chemotherapy in human glioblastoma primary cells: biological and prognostic significance. *Int J Cancer*. 2018;142(6):1266–1276.
- [27] Froklage F, Oosterbaan L, Sizoo E, et al. Central neurotoxicity of standard treatment in patients with newly-diagnosed high-grade glioma: a prospective longitudinal study. *J Neurooncol*. 2014;116(2):387–394.
- [28] Fliessbach K, Rogowski S, Hoppe C, et al. Computer-based assessment of cognitive functions in brain tumor patients. *J Neurooncol*. 2010;100(3):427–437.
- [29] Flechl B, Ackerl M, Mag CS, et al. The Association of Early Cognition Assessments and Progression-free Survival in Patients with Glioblastoma Multiforme. *J OncoPathol*. 2014;1(4):1–9.
- [30] Hoffermaun M, Bruckmann L, Mahdy Ali K, et al. Pre- and postoperative neurocognitive deficits in brain tumor patients assessed by a computer based screening test [Article]. *J Clin Neurosci*. 2017;36:31–36.

Appendix. CNS vital signs

Test Domain	Description	Clinical relevance, examples
Verbal memory	Learning a word list of 15 words with immediate and delayed recognition	Remembering appointments, taking medications etc.
Visual memory	Learning a list of 15 geometric figures with immediate and delayed recognition	Remembering a calendar of events, remembering graphic instructions, finding your way around, operating machines etc.
Psychomotor speed	Pressing a space bar with left and right index finger as many times as you can in 10 sec. Repeated trials	Driving a car, playing a musical instrument, using precision instruments etc.
Complex attention	Shifting attention from one instruction to another quickly and accurately (matching geometric objects by shape or color); shifting attention by matching color and words according to shifting rules (Stroop test); Continuous performance test responding to only one target (the letter B) among many letters shown on the screen	Sustained attention; ability to perform mental tasks requiring vigilance quickly and accurately. This function is essential for self-regulation and behavioral control
Cognitive flexibility	Shifting attention, see above	Reasoning, decision making, impulse control, attending a conversation etc.
Processing speed	Corresponding numbers and symbols shown on the screen in random order	Ability to recognize and process information, motor speed, fine motor coordination, visual-perceptual ability. Important when, for example driving a car, or in occupational issues
Executive function	Shifting attention, see above	Ability to sequence and manage multiple tasks simultaneously, tracking and responding to a set of instructions

Summarized description of test domains and clinical relevance.

Summarized and reproduced from: Gualtieri and Johnson [16], and Meskal et al. [15].