European Journal of Cancer 246 (2026) 116985

Contents lists available at ScienceDirect

European Journal of Cancer

journal homepage: www.ejcancer.com

Original Research

Neurocognitive functioning in long-term survivors of glioblastoma, IDH-wildtype and astrocytoma, IDH-mutant, CNS WHO grade 4: A report from EORTC 1419 (ETERNITY)

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https://doi.org/10.1016/j.ejca.2026.116985
Received 30 May 2026; Received in revised form 30 July 2026; Accepted 31 July 2026
Available online 12 August 2026

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ARTICLE INFO

Keywords:
Glioblastoma
Neurocognitive functioning
long-term survivors

ABSTRACT

Background: ETERNITY was a retrospective and prospective cohort study investigating long-term (≥5 years) survival in patients with glioblastoma. We assessed the longitudinal course of neurocognitive function (NCF) and its determinants in a subgroup of patients with glioblastoma, IDH-wildtype, or astrocytoma, IDH-mutant, CNS WHO grade 4.

Methods: NCF was assessed at baseline and every 6 months using the Hopkins Verbal Learning Test-Revised, Controlled Oral Word Association Test, and Trail Making Test. Scores were converted to age-, sex-, and education-adjusted Z-scores and classified as impaired or unimpaired ($Z \leq -1.5$). Linear mixed models were used to analyze NCF trajectories and associations with patient and tumor characteristics.

Results: At baseline (mean 9 years post-diagnosis, range 5-21 years), 145 of 185 patients (78%) were impaired on ≥1 test outcome. Impairment rates varied between 17.4% (HVLT-R delayed recognition) and 58.7% (TMT B). NCF remained largely stable over time, with a small decline in HVLT-R delayed memory. Left-sided and temporal tumor location were negatively associated with poorer NCF (p's.01 to.03). Frontal tumor location was associated with higher psychomotor speed and cognitive flexibility (p's <.001). Patients with IDH-mutant tumors performed worse on delayed recognition, whereas IDH mutation and MGMT promoter methylation were linked to improved phonemic fluency over time.

Conclusions: The majority of long-term survivors with astrocytoma, IDH-mutant, CNS WHO grade 4, and glioblastoma IDH-wildtype show neurocognitive impairment. Nonetheless, NCF is generally stable, with tumor location and molecular features associated with specific outcomes. These insights can help guide patient counseling and personalized care.

1. Introduction

With a median survival in the range of 12 to 14 months, glioblastoma, IDH-wildtype is one of the most aggressive primary central nervous system (CNS) tumors [1,2]. Currently, around 20% of all glioblastoma patients survive for 2 years, and not more than 5% of patients survive for more than 5 years [2,3]. Patients with histological WHO grade 4 tumors that exhibit mutations in the isocitrate (IDH) 1 or 2 genes, since 2021 referred to as astrocytoma, IDH-mutant, CNS WHO grade 4, have a better prognosis than patients with glioblastoma, IDH-wildtype, as indicated by a median survival in the range of 4 years [4].

As is common with other CNS tumors, neurocognitive functioning (NCF) is negatively affected in patients with CNS WHO grade 4 glioma, with up to 56% of patients showing impairment on standardized testing in the first period after diagnosis and primary resection [5–7]. Despite these high impairment rates, patients with CNS WHO grade 4 gliomas are not prioritized for neurocognitive assessment in clinical practice [6], potentially due to their neurological symptoms and poor survival and limited practical implications [8]. Although NCF tends to appear stable at the group level, individual patients show differential cognitive trajectories over time, with some patients declining and others improving over the course of treatment, e.g, because of (temporary) relief of tumor burden [7]. Adequate neurocognitive monitoring is important, since neurocognitive deficits, even mild, not only negatively affect professional reintegration, interpersonal relationships, and leisure activities, but also hamper a primary concern of patients, which is optimization of quality of life [9–11].

Previous studies, mostly focusing on patients scheduled for neurosurgery or undergoing radiochemotherapy, have identified multiple tumor- and treatment-related factors associated with NCF in patients with grade 4 gliomas [6]. Tumor location, particularly left hemisphere, temporal and frontal location, and absence of IDH1mutation have been linked to worse NCF [12–18]. The extent to which anti-tumor treatment has acute or subacute effects on NCF in patients with gliomas seems domain-specific and may also depend on treatment type [19,20]. The long-term consequences of tumor- and treatment-related factors in patients with higher grades of gliomas is largely unknown. Research that does cover NCF in long-term survivors of grade 4 gliomas has reported impairment rates between 50-100 percent, but is based on studies with small sample sizes [21–23]. Contributing patient and disease attributes remain underexplored.

ETERNITY (EORTC 1419) was an observational study aimed at revealing prognostic indicators for longevity in patients with glioblastoma per 2016 WHO classification [24]. The first results showed that long-term survivors had a methylated MGMT promotor and frontal tumor location more often than the reference cohort of glioblastoma patients that were not long-term survivors. The absence of disease progression was affirmed as a potent indicator of prolonged survival [25].

Understanding how neurocognitive function changes over time in patients who survive more than 5 years, and the factors that influence these changes, is important for improving quality of life. This knowledge can help clinicians guide patients on expected NCF outcomes when treatment prevents tumor recurrence and support strategies that maintain daily functioning despite cognitive challenges.

The current study aims to investigate 1) longitudinal neurocognitive profiles of these long-term survivors among patients with glioblastoma, IDH-wildtype and astrocytoma, IDH-mutant, CNS WHO grade 4 who have survived over 5 years and 2) patient, tumor, and treatment characteristics associated with NCF over time.

2. Methods

2.1. Design and ethics

The study consisted of a longitudinal observational design in which a subset of patients that were included in the EORTC 1419 ETERNITY registry study on long-term survival in glioblastoma [25] underwent neuropsychological assessments. Patients in the registry study who were alive were approached for participation in the neurocognitive sub study. Patients were tested at study inclusion and every 6 months thereafter until tumor progression, death, or dropout. Patients provided written informed consent before participation and the study was approved by the Ethics Board of the Canton of Zurich (KEK 2014-0555).

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[2] see appendix

2.2. Participants

Patients were recruited between 2015 and 2020 in centers in Australia, Austria, Belgium, France, Germany, Greece, Italy, Netherlands, Switzerland, United Kingdom and United States. Eligibility criteria for participation to the overarching EORTC 1419 ETERNITY registry study were: (1) age =/> 18 at diagnosis, (2) histopathological diagnosis of glioblastoma according to WHO 2016 criteria, (3) survival =/>5 years after diagnosis, (4) availability of tumor tissue from initial diagnosis (formalin-fixed, paraffin-embedded or fresh frozen), and (6) signed informed consent form. Additional inclusion criterium for neuropsychological assessment was basic proficiency in the language of the country where the patient was included. For the current study, patients with at least one neurocognitive assessment were included.

2.3. Outcome measures

2.3.1. Neurocognitive functioning

NCF was assessed by standardized tests conducted by healthcare personnel (i.e. nurse, physician, or neuropsychologist) trained on the testing protocol. The following tests yielding six outcome measures were included: Hopkins Verbal Learning Test- revised (HVLT-R) [26], Controlled Oral Word Association test (COWAT) [27], and the Trail Making Test (TMT) A and B [28], for details see supplemental Table 1.

2.3.2. Patient, tumor, and treatment characteristics

Information on age, sex, and educational level was available for all patients. The diagnosis was centrally confirmed by histological review for all patients. Baseline data on tumor and treatment characteristics were available for a subset of patients, including IDH mutation and *MGMT* promotor methylation status at central pathology review after inclusion, tumor location (classified as frontal, temporal, occipital, parietal, cerebellum, brain stem, or other), tumor lateralization (classified as left, right, or bilateral), number of recurrences (no, one or multiple), time since diagnosis (in years), initial treatment at diagnosis.

2.4. Statistical analyses

2.4.1. Patient characteristics

Descriptive statistics were used to analyze patient characteristics. To evaluate whether the subgroup of patients with only complete data on sex, education level, and age was comparable to the subgroup for whom additional clinical data was available, we performed Chi-square tests of independence (sex, educational level) and Mann–Whitney U tests (age), two-sided with $\alpha = 0.05$.

2.4.2. Standardization of test scores

Standardized Z-scores for all tests were derived using a regression-based approach, based on cognitive test data from normative controls recruited as part of a registered clinical trial (CAR Study A, ClinicalTrials.gov reference NCT02953756) [29,30]. Follow-up scores were corrected for potential practice effects using norms based on follow-up scores in healthy controls.

2.4.3. Neurocognitive functioning at baseline

Continuous neurocognitive outcome variables were summarized using means and standard deviations. We evaluated the prevalence of impairment at baseline, employing a cut-off of 1.5 SD below the mean performance of healthy controls, as indicative of cognitive impairment. The prevalence of cognitive impairment at baseline was reported as the number and percentage of scores below the cut-off separately for each of the six test outcomes. Depending on the distribution of the data, the association between test performance and survival time at inclusion were investigated using Spearman's rank correlation coefficient or Pearson's correlation coefficient. Baseline analyses were conducted using SPSS version 28.0.1.1 (IBM®, Armonk, NY, USA).

Table 1
Baseline characteristics of patients with neuropsychological assessment available.

		Total sample (N= 185)	Patients with additional clinical data (N=163)	Patients without additional clinical data (N=22)
Sex	Male	93 (49.2%)	84 (51.5%)	9 (41%)
Age		57±11	57±11	60±13
Education level	Basic/primary education	13 (7%)	12 (7.4%)	1 (4.5%)
	Lower/general secondary education, vocational education	61 (33%)	54 (33.1%)	7 (37.8%)
	Higher secondary or tertiary education	111 (60%)	97 (59.5%)	14 (57,7%)
Overall survival time (years) at inclusion			9±3	
Treatment at first diagnosis	Temozolomide concomitant and maintenance (standard of care)		104 (63.8%)	
	Nitrosoureas (+another treatment)		3 (1.8%)	
	Other		14 (8.6%)	
	Missing		42 (25.8%)	
Affected Lobe	Frontal		60 (36.8%)	
	Temporal		27 (16.6%)	
	Parietal		23 (14.1%)	
	Occipital		9 (5.5%)	
	Cerebellum/brain stem		2 (1.2%)	
	Corpus callosum		2 (1.2%)	
	Other		22 (13.5%)	
	Missing		18 (11.0%)	
Affected Hemisphere	Left		73 (44.8%)	
	Right		69 (42.3%)	
	Both		2 (1.2%)	
	Missing		19 (11,7%)	
Number of recurrences at baseline	None		73 (44.8%)	
	1 recurrence		29 (17.8%)	
	2 or more recurrences		49 (30.1%)	
	Missing		12 (7.4%)	
IDH status	Wildtype	127 (68.6%)	109 (66.9%)	18 (81.8%)
	Mutant	58 (31.4%)	54 (33.1%)	4 (18.2%)
MGMT promotor status	Methylated	141 (76.2%)	126 (77.3%)	15 (68.2%)
	Unmethylated	44 (23.8%)	37 (22.7%)	7 (31.8%)

2.4.4. Neurocognitive functioning over time

2.4.4.1. Characteristics and functioning over time. The longitudinal analyses were conducted using R Statistical Software (v4.4.0;R Core Team 2024) [31].

To investigate change in NCF over time, longitudinal Linear Mixed Models (LMM) were performed with the lme package in R [32]. Separate LMM were performed, each with one of the six test outcomes as dependent variable (HVLT-R immediate recall, HVLT-R delayed recall, HVLT-R delayed recognition, TMT A, TMT B and COWAT). In the LMM, time was the level 1 variable, with its measurements nested in the patients at level 2. We first assessed whether time showed a linear vs quadratic effect, and adopted the effect that showed the best model fit

based on the Akaike information criterion (AIC). Random intercepts were specified for all models. Random slopes were adopted if they improved model fit. Model fits were compared with likelihood ratio tests. We uniformly adopted the correlation structure that showed the best fit, again according to the AIC for most of the models.

We first investigated the course of NCF over time, with time (i.e., follow-up measurement) as the main predictor in the model. Subsequently, we assessed interactions between time and several characteristics to investigate their relationship with performance over time. Tumor lateralization (right-sided as the reference category) and tumor location (frontal lobe and temporal lobe, as separate variables) were adopted based on the support for a relationship with NCF in glioma, the number of recurrences at the time of inclusion was adopted as measure of disease control (no, one, or at least two recurrences; no recurrence as the reference category) and molecular characteristics; IDH status (wildtype as reference category) and *MGMT* promotor methylation status (unmethylated as reference category) based on their prognostic and predictive value. In case of a significant interaction effect between Time and the respective characteristic, we ran the models stratified by that variable to inspect the change over time within each group. Considering the exploratory nature of these analyses, a *p*-value of 0.05 was considered statistically significant for all analyses.

2.4.4.2. Drop-out from follow-up. Dropout in longitudinal studies of patients with cancer is usually not random, but indicative of other factors such as worsening clinical condition and disease progression [33]. Our longitudinal results could therefore be biased towards patients who function relatively well. We therefore evaluated whether NCF was related to dropout with joint modeling, using the *JM* package [34]. Joint modeling is a method that combines longitudinal data (in this study: NCF over time was analyzed with LMM) and time-to-event data (here risk of drop-out was analyzed with Cox Proportional Hazards model) into one model [35]. The model returns a log Hazard Ratio, which can be exponentiated for interpretation. The resulting HR indicates the risk of dropout as a function of change in test performance over time. Patients were considered as drop-out once they did not have any neurocognitive test data on one or more subsequent follow-up measurements. We adopted the number of recurrences (see measures) as covariate in the model.

3. Results

3.1. Sample and descriptives

One-hundred-ninety-five patients were included based on availability of baseline neurocognitive data. Ten out of 195 patients had missing data on level of education, making it impossible to standardize their test scores. After exclusion of these patients, 185 patients remained for baseline analyses. Table 1 provides an overview of characteristics of the entire sample, the subset of patients for whom additional data on patient, tumor, and treatment characteristics were available (N=163), and the subset of patients for whom only data on age, sex, educational level, *MGMT* promotor methylation and IDH status were available (n=22). Patients with and without these data were not statistically different regarding sociodemographic characteristics.

3.2. Neurocognitive functioning at baseline

Table 2 and Fig. 1 show the mean z-scores and percentages of impairment on all six test outcomes. There were some extremely low z-scores, particularly for the TMT A and TMT B, but this is not uncommon when comparing patient performance to normative data from healthy controls. Therefore, no patients were removed from the analyses. 145 of 185 patients (78%) showed impairment on one or more NCF test outcomes, with cognitive flexibility and motor speed (TMT A and B) and phonemic fluency (COWAT) showing the highest impairment rates (47.8-58.7%), and recognition memory (HVLT-R recognition) the lowest (17.4%). There was no significant difference between patients with IDH-wildtype and IDH-mutant tumor on average z-score or percentage impaired (supplemental table 2). Survival time at time of study inclusion was not related to any of the test performance (*r* range 0.035—0.116, p's >.05) (Fig. 2).

Table 2
average z-scores and impairment rates for the individual test outcomes.

Test	Average Z-score (SD)	Percentage impaired
HVLT-R immediate recall	-1.08 (1.68)	39.0%
HVLT-R delayed recall	-0.80 (1.47)	30.4%
HVLT-R delayed recognition	-0.53 (1.48)	17.4%
COWAT	-1.32 (1.09)	47.8%
TMT A	-2.80 (3.70)	49.4%
TMT B	-3.19 (3.38)	58.7%

3.3. Neurocognitive functioning over time

Results of the longitudinal Linear Mixed Models can be found in Table 3.

The models showed that overall, NCF of patients remained stable over time (range *B*= -.02 to -0.24, *p*'s >.05) for all measures except the HVLT delayed recall. Time was a significant negative predictor of poorer performance on this measure (B = -0.09, SE = 0.04, p=.01), indicating that patients as a group declined slightly over time on their delayed recall of verbal information, irrespective of clinical characteristics.

3.4. Clinical predictors of neurocognitive functioning

The number of follow-up measurements in the sample ranged from 0 (i.e., baseline only; 22.7% of patients) to 13 (3.8% of patients). One-hundred-and-ten patients (60%) had at least 2 follow-up measurements (i.e., at least a 12-month follow-up). Supplemental figure 1 shows patient attrition.

3.4.1. Predictors of verbal memory (HVLT-R)

We found several associations of tumor location with memory outcomes in LMM. A negative association (i.e., main effect) between left hemispheric localization was found for the immediate and delayed recall condition of the HVLT-R (B = -0.60 and B = -0.57 respectively, p's =.01), which indicates that patients with left-sided tumors had worse overall performance on these measures compared to patients whose tumor did not involve the left hemisphere. Temporal lobe involvement (vs no temporal lobe involvement) showed a similar negative association with HVLT-R immediate recall performance (B = -0.71, p = 0.03). We found a positive interaction between temporal lobe involvement and time for the HVLT-R delayed recall (B = 0.07, p =.03), indicating different trajectories of performance over time. Stratified analyses showed that patients with and without temporal lobe tumors showed a subtle decline in this measure over time, with decline in patients without temporal lobe tumors being somewhat steeper (B = -0.09; 95% CI, -0.17 to 0.01) than in patients with temporal lobe tumors (B = -0.06; 95 % CI, -0.16 to 0.05).

For molecular characteristics, we found a negative association of IDH mutation with HVLT-R recognition scores (*B*= -0.50, p =.04), indicating that patients with IDH-mutant tumors performed worse overall than those with IDH-wildtype tumors. We found a significant interaction between *MGMT* promoter methylation and time for the HVLT-R delayed recall (B = 0.12, p =.01). Stratified analyses showed that patients without *MGMT* promoter methylation showed a subtle, non-significant, improvement over time in their scores (B = 0.19, 95% CI -0.15 to 0.54) while those with *MGMT* promoter-methylated tumors showed a subtle, significant, decline (*B*= -0.15; 95% CI, -0.27 to -0.04).

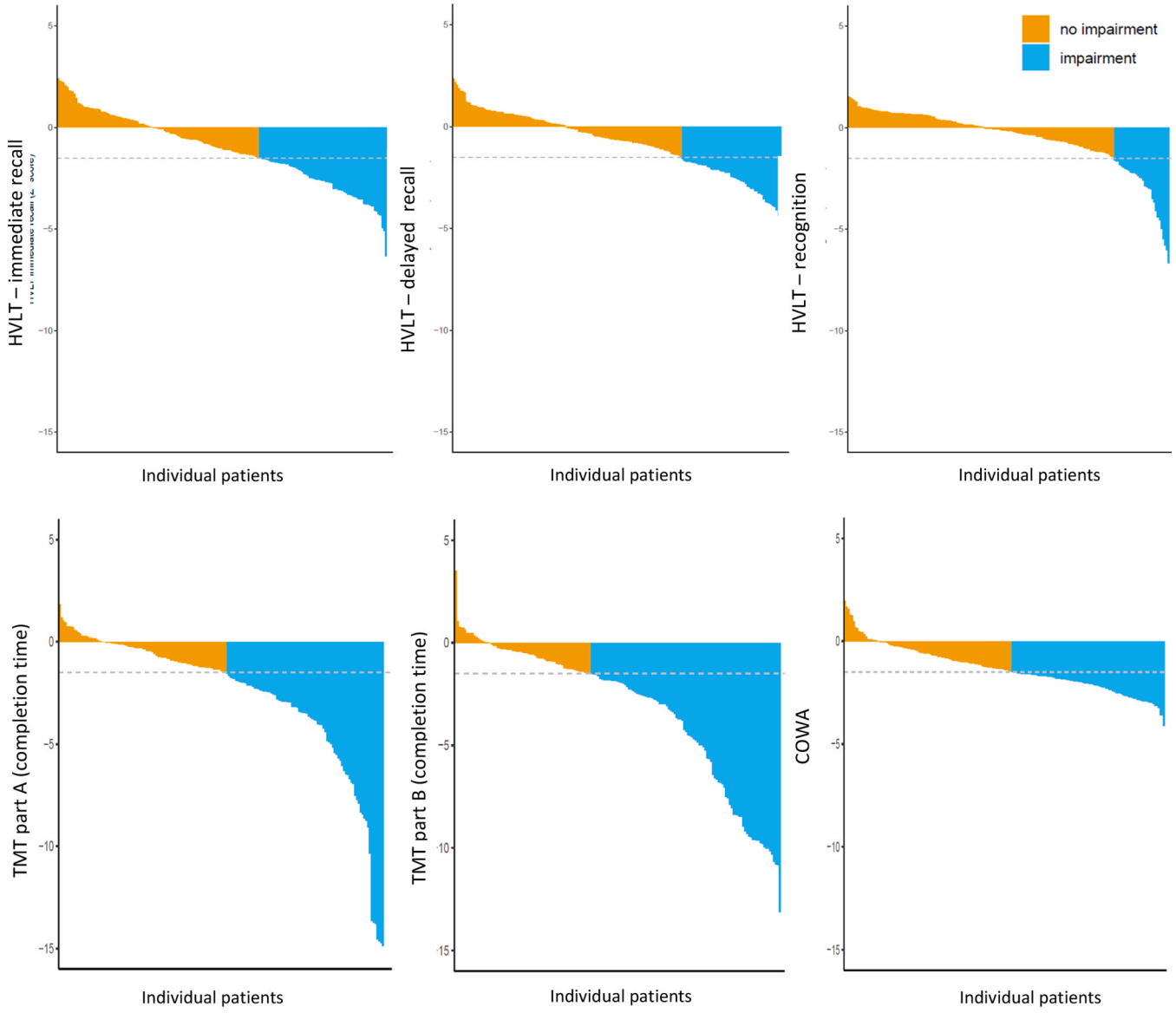

Fig. 1. Distribution of scores and impairment in the sample at baseline. The dotted line shows the cut-off for impairment (z = -1.5).

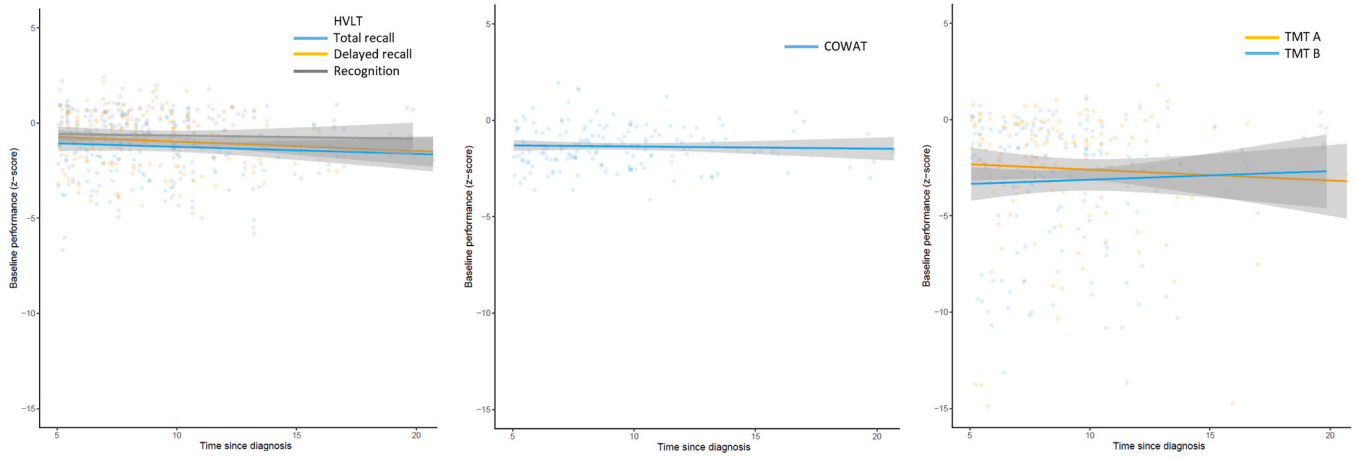

Fig. 2. Baseline performance on each NCF measure (z-score; y-axis) as a function of time since diagnosis at baseline assessment. Subtests are indicated with different colors (HVLT and TMT only). Each dot indicates an individual performance. Each line indicates the fitted regression line for that measure, including 95%CI.

Table 3
Results of the longitudinal Linear Mixed Models. Significant results are indicated in bold. # versus no or multiple recurrences, ^ versus no or single recurrence.

Parameter			HVLT immediate recall (N=182)	HVLT delayed recall (N=181)	HVLT delayed recognition (N=178)	COWAT (N=182)	TMT A (N=178)	TMT B (N=171)
Final Models (N = 185)	Time	B (*SE*)	-0.016 (0.040)	-0.092 (0.036)	-0.060 (0.042)	0.030 (0.035)	-0.205 (0.181)	-0.237 (0.132)
		p	0.70	**0.01**	0.15	0.38	0.26	0.07
	Single recurrence#	B (SE)	-0.667 (0.330)	0.533 (0.300)	0.375 (0.312)	-0.094 (0.273)	0.339 (0.831)	-0.225 (0.758)
		p	0.05	0.08	0.23	0.73	0.68	0.77
	Multiple recurrences^	B (SE)	-0.192 (0.282)	-0.183 (0.257)	0.172 (0.250)	-0.405 (0.238)	-0.371 (0.727)	-1.441 (0.666)
		p	0.50	0.48	0.49	0.09	0.61	**0.03**
	MGMT promoter-unmethylated	B (SE)	-0.179 (0.325)	-0.421 (0.296)	-0.262 (0.290)	-0.305 (0.273)	0.377 (0.831)	-0.578 (0.772)
		p	0.58	0.16	0.37	0.27	0.65	0.46
	IDH-mutant	B (SE)	-0.250 (0.275)	-0.229 (0.251)	-0.496 (0.242)	-0.400 (0.230)	-1.116 (0.695)	-0.932 (0.646)
		p	0.36	0.36	**0.04**	0.08	0.11	0.15
	Left-sided	B (SE)	-0.597 (0.239)	-0.573 (0.218)	0.369 (0.211)	-0.442 (0.201	-0.060 (0.612)	-0.572 (0.562)
		p	**0.01**	**0.01**	0.08	**0.03**	0.92	0.31
	Frontal location	B (SE)	0.578 (0.287)	0.465 (0.262)	0.233 (0.252)	0.118 (0.241)	3.147 (0.732)	2.283 (0.672)
		p	0.05	0.08	0.36	0.63	**<0.001**	**<0.001**
	Temporal location	B (SE)	-0.706 (0.320)	-0.424 (0.292)	-0.720 (0.284)	-0.193 (0.270)	0.593 (0.822)	0.194 (0.762)
		p	**0.03**	0.15	**0.01**	0.48	0.47	0.80
	Time*single recurrence	B (SE)	-0.016 (0.033)	-0.009 (0.029)	0.058 (0.040)	0.028 (0.029)	-0.221 (0.164)	0.149 (0.117)
		p	0.62	0.77	0.14	0.33	0.18	0.20
	Time*multiple recurrences	B (SE)	-0.014 (0.035)	0.029 (0.031)	0.057 (0.037)	-0.008 (0.030)	-0.276 (0.166)	-0.047 (0.118)
		p	0.69	0.36	0.13	0.80	0.10	0.69
	Time* *MGMT* promoter-unmethylated	B (SE)	0.084 (0.048)	0.119 (0.044)	0.070 (0.052)	0.122 (0.042)	-0.325 (0.199)	0.059 (0.143)
		p	0.08	**0.01**	0.18	**<0.001**	0.10	0.68
	Time*IDH-mutant	B (SE)	0.006 (0.034)	0.035 (0.030)	0.041 (0.036)	0.062 (0.029)	0.249 (0.151)	0.193 (0.109)
		p	0.87	0.25	0.25	**0.04**	0.10	0.08
	Time*Left-sided	B (SE)	0.030 (0.028)	-0.006 (0.025)	-0.014 (0.030)	-0.059 (0.024)	-0.026 (0.134)	0.005 (0.096)
		p	0.28	0.82	0.65	**0.01**	0.85	0.96
	Time*Frontal Location	B (SE)	0.015 (0.036)	0.039 (0.032)	0.003 (0.038)	-0.007 (0.031)	-0.024 (0.161)	-0.026 (0.117)
		p	0.68	0.22	0.93	0.83	0.88	0.82
	Time*Temporal Location	B (SE)	0.066 (0.035)	0.067 (0.031)	-0.033 (0.037)	0.008 (0.030)	0.077 (0.172)	0.07 (0.125)
		p	0.06	**0.03**	0.39	0.78	0.65	0.58

3.4.2. Predictors of phonemic fluency (COWAT)

We found a significant interaction between time and left-sided tumor location for phonemic fluency scores (B = -0.06, p = 0.01). Stratified analyses showed a slightly steeper decline for left-sided tumors (B=-0.06; 95% CI, -0.18 to 0.07) compared to those with right-sided tumors (B= -0.03; 95% CI, -0.23 to 0.17), although these declines were not significant.

For molecular characteristics, a significant interaction existed between *MGMT* promoter methylation and time (B= 0.12, p <.01) and between IDH mutation and time (B=0.06, p=.04). Stratification indicated that patients harboring a tumor with *MGMT* promotor methylation showed a small non-significant decline over time in their scores (B = -0.05; 95% CI, -0.16 to 0.06) while the patient group without methylation showed a modest non-significant improvement (B = 0.27, 95% CI= -0.08 to 0.63). Patients harboring an IDH-mutant tumor and those harboring an IDH-wildtype tumor showed different degrees of improvement, both not significant (B = 0.05; 95% CI, -0.04 to 0.12 and B = 0.10; 95% CI, 0.00 to 0.21 respectively).

3.4.3. Predictors of psychomotor speed and cognitive flexibility over time (TMT)

We found a strong positive association between frontal lobe involvement on both part A and part B of the TMT in the LMM, indicating that patients harboring frontal lobe tumors had substantially higher overall psychomotor speed and cognitive flexibility scores than patients with tumors outside the frontal lobe (B= 3.1 and B=2.3 respectively, p's <.01). Upon inspection of this seemingly large effect, we noticed 11 patients with very low TMT A scores (z < - 10) in the non-frontal group, while one of the patients in the frontal group had such low TMT A scores.

Furthermore, we found a negative main effect of recurrence (at least two recurrences versus no or one recurrence; B=-1.44; p=.03) on TMT part B, indicating that patients who had experienced at least two recurrences at time of study inclusion had significantly worse overall cognitive flexibility scores.

3.4.4. Neurocognitive functioning in relation to dropout

The joint models showed that neurocognitive performance was not significantly related to the risk of dropout for any of the tests; HR range 0.85 (HVLT recognition) – 1.09 (COWAT); all p's >.05.

4. Discussion

The aim of this study was to investigate NCF in patients surviving for

more than 5 years with a glioblastoma, IDH wildtype, CNS WHO grade 4, or astrocytoma, IDH-mutant, CNS WHO grade 4. We found that the large majority of patients (78%) had impairment on at least one out of six NCF outcome measures at on average 9 years after diagnosis. These impairment rates are slightly higher than those in patients with newly diagnosed CNS WHO grade 3 or 4 gliomas, where the percentage of impaired patients ranges from 59%-76% [5,35], although these studies employed larger test batteries and thus had an increased probability of finding impairment. Cognitive flexibility, psychomotor speed, and phonemic fluency were most frequently affected, while recognition of verbal material was least frequently impaired. Over time, patients showed a slight decline in delayed verbal recall, irrespective of patient, tumor, or treatment-related predictors at the group level.

While most patients demonstrated cognitive impairment at study inclusion, survival time was not associated with cognitive performance. This suggests that most cognitive decline had already occurred before study inclusion and cognitive performance in this population may be explained by the combined effects of patient, tumor and treatment characteristics. Multiple patient and tumor-related characteristics were associated with NCF outcomes. The observation that patients with tumors infiltrating the temporal lobes exhibit greater impairments in verbal memory aligns with previous studies indicating that particularly left temporal lobe tumors are associated with verbal memory deficits [12,14]. This finding suggests that the damage inflicted by the tumor, as well as the subsequent surgical and radiotherapeutic interventions, result in localized damage with lasting, irreversible effects on NCF. These effects persist even in long-term survivors, indicating that compensatory mechanisms may be limited. More surprising was the finding that patients with frontal lobe tumors showed higher psychomotor speed and cognitive flexibility than patients with tumors in other locations, while the opposite might be expected [14]. We note that the patients with a frontal tumor in our sample were significantly younger compared to the other patients, suggesting that age-related decline in the other patient group might be the explanation of this apparent positive effect of frontal lobe involvement. Even though the normative data are controlled for age, it does so for age in healthy controls, while in patients with glioblastoma the negative association of age with NCF can be accelerated by the tumor and subsequent treatment [8,36]. This phenomenon has also been demonstrated in patients with epilepsy, in whom age had an accelerating effect on decline in psychomotor speed compared to healthy individuals [37].

Contrary to most previous literature [15,17], IDH mutation status was only loosely associated with overall NCF. Patients with IDH-mutant astrocytoma, CNS WHO grade 4, showed a small improvement over time on verbal fluency (COWAT). On the other hand, patients with IDH-mutant astrocytoma, CNS WHO grade 4 performed significantly worse than those with IDH wildtype glioblastoma on recognition of verbal material (HVLT-R recognition). Moreover, though not significant, patients with IDH-mutant tumors tended to perform worse on other NCF test outcomes than those diagnosed with IDH-wildtype glioblastoma. In patients earlier in the disease trajectory, both before surgery and after chemotherapy, the presence of IDH1 mutation has been found to be relatively favorable for neurocognitive functioning [15,17]. Although a recent study in patients with diffuse gliomas found that IDH1 mutation was associated with neurocognitive deficits, when controlling for tumor grade this effect was no longer significant [38]. A possible explanation for the IDH mutation-associated impairment can be that IDH mutations are associated with the production of 2-hydroxyglutarate [39], which is associated with metabolic disruptions in the surrounding tissue and an increase of epileptogenesis in patients with gliomas [40], although a direct association with neurocognitive impairment has not been studied. Patients harboring tumors without *MGMT* promotor methylation showed better cognitive performance over time than those with *MGMT* promotor-methylated tumors on multiple measures, specifically verbal memory (delayed recall) and phonemic fluency. *MGMT* promotor methylation is a well-known predictor of prolonged survival and better treatment outcome in IDH-wildtype glioma patients [41], but has not generally been investigated for its importance for NCF. One study in patients with WHO grade 3 or 4 glioma after surgery identified an unmethylated *MGMT* promotor as a risk factor for impaired NCF, although only a brief cognitive screening tool was used to assess NCF [42]. A more comprehensive investigation into the mechanisms by which *MGMT* promoter methylation and IDH status may influence NCF is warranted. Enhanced understanding of these processes will facilitate the identification of patients at risk for neurocognitive decline.

There are several limitations to this study. First, the lack of NCF data from the time of diagnosis makes it impossible to identify changes in the period between diagnosis and 5 years later or even longer. A more in-depth comparison of available data with multiple earlier disease stages (before treatment, during and shortly after), adjusting for likely sample characteristics, could broaden our understanding of the long-term course of NCF. Although outside the scope of the current study, the adoption of a core set of commonly used NCF tests as done in some of our participating centers would facilitate this. Second, while tumor lobe involvement and lateralization were included separately in our analysis, we did not investigate a combination of location and lateralization such as 'left temporal' versus 'right temporal' tumor location due to limitations to the number of predictors we were able to fit in the statistical model. We might, therefore, have missed certain synergistic location-lateralization effects. Third, the sample size of the study was small and patient attrition was high as expected in this population, which affects statistical power especially in follow-up measurements. However, NCF was not related to drop-out, indicating that our follow-up results were not skewed towards patients with better or worse NCF. Finally, performance status at study entry and treatment specifics were not available, precluding assessment of the association between NCF and daily functioning or the effect of treatment in this population. Multiple quality of life outcomes were collected and will be reported in a subsequent publication.

Besides these limitations, there are additional issues that warrant caution for a comparison of this study's results with published literature. First, the 2021 WHO classification [43] separates IDH-mutant astrocytoma, CNS WHO grade 4 from glioblastoma, IDH-wildtype. Earlier studies on glioblastoma have included both IDH-mutant and wild-type tumors in accordance with classifications at the time. Second, we note that factors that contribute to longer survival can also affect NCF (e.g. age, IDH status and disease recurrence). When comparing the patient characteristics of studies conducted closer to the time of diagnosis with those in our study, there are some important differences. The distribution of glioblastoma in males versus females at diagnosis is 1.6/1 [3], but in our sample the number of male patients was equal to the number of female patients, as in the report of the main study [25], likely reflecting a so far not understood association of sex with outcome in glioblastoma. Our patient group was also relatively young on average at diagnosis for a grade 4 glioma cohort, which is in keeping with better prognosis for younger patients. At the same time, tumor locations in our patient cohort appear relatively similar to those in the general glioblastoma population [44], although frontal tumors were more frequent in our cohort [25]. In summary our findings are likely not generalizable to the entire population, but specific to long-time survivors.

5. Conclusion

Our study is the first to describe longitudinal NCF in a large sample of long-term survivors of glioblastoma, IDH-wildtype or astrocytoma, IDH-mutant, CNS WHO grade 4, with an average survival of 9 years after diagnosis. While most patients show impaired NCF, the severity of impairment varies between patients and functions, and NCF seems to remain mostly stable. Tumor location and characteristics are relevant for the cognitive trajectory of long-term survivors. Future studies should include neurocognitive data from earlier in the disease course, consider clinical predictors of NCF, and report by disease categories as defined in

the 2021 WHO classification. Additionally, greater emphasis should be placed on preserving NCF to support improved quality of life in this patient population.

The number of patients who survive for multiple years after diagnosis is still limited. Yet, it is not unlikely that the group of long-term survivors with IDH-wildtype or IDH-mutant gliomas of CNS WHO grade 4 will increase in the coming decades. Following diagnosis, patients wonder what their quality of life and NCF will be like if they respond to treatment. Our results suggest that although most patients will experience some impairment, NCF is similar between patients irrespective of survival time beyond 5 years.

Declaration

The author Martin van den Bent is an Editor of the EJC and was not involved in the editorial review or the decision to publish this article.

Funding

Brain Tumor Funders' Collaborative (American Brain Tumor Association, Brain Tumor Foundation of Canada, James S. McDonnell Foundation, Children's Brain Tumor Foundation, The Sontag Foundation) and by the EORTC Brain Tumor Group.

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Jaap C. Reijneveld: Writing – original draft. **Guido Reifenberger:** Writing – review & editing, Investigation. **Patrick Y. Wen:** Writing – review & editing, Investigation. **Frances Sé:** Writing – review & editing. **Thierry Gorlia:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Jörg Felsberg:** Writing – review & editing, Investigation. **Martin van den Bent:** Writing – review & editing, Investigation. **Giuseppe Lombardi:** Writing – review & editing, Investigation. **Michael W. Ronellenfitsch:** Writing – review & editing, Investigation. **Francois Ducray:** Writing – review & editing, Investigation. **Niklas Thon:** Writing – review & editing, Investigation. **Drijver Josephine:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Peter Hau:** Writing – review & editing, Investigation. **Emilie Le Rhun:** Writing – review & editing, Investigation. **Caroline Hertler:** Writing – review & editing, Investigation. **Matthias Preusser:** Writing – review & editing, Investigation. **Elke Butterbrod:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Wolfgang Wick:** Writing – review & editing, Investigation. **Oliver Schnell:** Writing – review & editing, Investigation. **Amélie Darlix:** Writing – review & editing, Investigation. **Emmie M.C. van den Dobbelsteen:** Writing – review & editing, Project administration. **Martin Klein:** Writing – original draft, Investigation, Conceptualization. **Roberta Rudà:** Writing – review & editing, Investigation. **Noor de Boer:** Writing – review & editing, Project administration. **Jennifer Clarke:** Writing – review & editing, Investigation. **Alessia Pellerino:** Writing – review & editing, Investigation. **Tabouret Emeline Tabouret:** Writing – review & editing, Investigation. **Karishma Kumar-Wessel:** Writing – review & editing, Investigation. **Michael Weller:** Writing – original draft, Investigation, Conceptualization.

Declaration of Competing Interest

The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for this journal and was not involved in the editorial review or the decision to publish this article.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Caroline Hertler reports financial support was provided by Brain Tumor Funders Collaborative. Caroline Hertler reports a relationship with Swiss Cancer League that includes: funding grants. Caroline Hertler reports a relationship with Swiss National Fond that includes: funding grants. Caroline Hertler reports a relationship with Filling the Gap Grant that includes: funding grants. Alessia Pellerino reports a relationship with Servier that includes: speaking and lecture fees. Jennifer L. Clarke reports a relationship with Servier that includes: consulting or advisory, funding grants, and travel reimbursement. Jennifer L. Clarke reports a relationship with Merck that includes: funding grants. Jennifer L. Clarke reports a relationship with Novartis that includes:. Emeline Tabouret reports a relationship with LEO Pharma that includes: funding grants. Emeline Tabouret reports a relationship with Serb that includes: funding grants. Emeline Tabouret reports a relationship with Gliocure that includes: consulting or advisory. Emeline Tabouret reports a relationship with Novocure that includes: speaking and lecture fees. Emeline Tabouret reports a relationship with Servier that includes: speaking and lecture fees. Wolfgang Wick reports a relationship with Servier that includes: consulting or advisory and speaking and lecture fees. Wolfgang Wick reports a relationship with Enterome that includes: consulting or advisory. Amelie Darlix reports a relationship with Novocure that includes: consulting or advisory and speaking and lecture fees. Amelie Darlix reports a relationship with Servier Pharmaceuticals that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Amelie Darlix reports a relationship with AstraZeneca that includes: consulting or advisory. Giuseppe Lombardi reports a relationship with Bayer that includes: board membership, consulting or advisory, funding grants, and travel reimbursement. Giuseppe Lombardi reports a relationship with Servier that includes: board membership, consulting or advisory, funding grants, and travel reimbursement. Giuseppe Lombardi reports a relationship with Chimerix that includes: funding grants. Giuseppe Lombardi reports a relationship with Novocure that includes: board membership and consulting or advisory. Martin van den Bent reports a relationship with Boehringer Ingelheim that includes: consulting or advisory and funding grants. Martin van den Bent reports a relationship with Incyte that includes: consulting or advisory. Martin van den Bent reports a relationship with Genenta that includes: consulting or advisory. Martin van den Bent reports a relationship with Servier that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Martin van den Bent reports a relationship with Symbiopharma that includes: consulting or advisory. Martin van den Bent reports a relationship with Chimerix that includes: consulting or advisory. Martin van den Bent reports a relationship with Fore biotherapeutics that includes: consulting or advisory. Martin van den Bent reports a relationship with Nuvation that includes: consulting or advisory. Martin van den Bent reports a relationship with AstraZeneca that includes: consulting or advisory. Francois Ducray reports a relationship with Novocure that includes: consulting or advisory, funding grants, paid expert testimony, and speaking and lecture fees. Francois Ducray reports a relationship with Servier that includes: consulting or advisory, funding grants, paid expert testimony, and speaking and lecture fees. Michael W. Ronellenfitsch reports a relationship with Uniscientia Foundation Vaduz that includes: funding grants. Michael W. Ronellenfitsch reports a relationship with Forum for rare diseases that includes: speaking and lecture fees. Michael W. Ronellenfitsch reports a relationship with FomF GmbH that includes: speaking and lecture fees. Peter Hau reports a relationship with Deutsche Krebshilfe that includes: funding grants. Peter Hau reports a relationship with Deutsche Forschungsgemeinschaft that includes: funding grants. Peter Hau reports a relationship with Wilhelm Sander-Stiftung that includes: funding grants. Peter Hau reports a relationship with Bayerisches Zentrum für Krebsforschung that includes: funding grants. Peter Hau reports a relationship with Novocure that includes: consulting or advisory and speaking and lecture fees. Peter Hau reports a relationship with Glaxo Smith Kline that includes: board membership and consulting or advisory. Peter Hau reports a relationship with Seagen that includes: consulting or advisory and speaking and lecture fees. Matthias Preusser reports a relationship with Bayer that includes: board membership, consulting or advisory, and speaking and lecture fees. Matthias Preusser reports a relationship

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Acknowledgments

The authors acknowledge a generous starting grant from the Brain Tumor Funders' Collaborative that made this project possible and as a donation from the University of Zurich, Switzerland, and to wish to thank all colleagues and staff at the European Organisation for Research and Treatment of Cancer (EORTC, Brussels, Belgium), at the participating sites, and finally, all patients and caregivers that supported this project.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2026.116985.

Data availability

Data are available from the European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium, and the Department of Neurology, University Hospital and University of Zurich, Zurich, Switzerland (M.W.), upon reasonable request.

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