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European Journal of Cancer 144 (2021) 162–168

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Objective neurocognitive functioning and neurocognitive complaints in patients with high-grade glioma: Evidence of cognitive awareness from the European Organisation for Research and Treatment of Cancer brain tumour clinical trials

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Received 27 July 2020; received in revised form 29 October 2020; accepted 29 October 2020
Available online 22 December 2020

KEYWORDS
High-grade glioma;
Neurocognitive functioning;
Cognitive awareness;

Abstract ***Background:*** Neurocognitively impaired patients with brain tumour are presumed to have reduced cognitive awareness preventing them from adequately valuing and reporting their own functioning, for instance, when providing patient-reported outcomes (PROs) such as health-related quality of life instruments. In this cross-sectional study, we aimed at assessing the concordance of neurocognitive complaints (NCCs) and objective neurocognitive

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https://doi.org/10.1016/j.ejca.2020.10.040

Health-related quality of life;
PROs

functioning (NCF) as a measure of cognitive awareness.
Methods: NCF was assessed using an internationally accepted clinical trial battery. NCC was assessed using the cognitive functioning questionnaire from the Medical Outcome Study (MOS) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire cognitive functioning subscale. Patients were divided in cognitively impaired and unimpaired groups, based on their NCF performance. Pearson's correlation coefficients between NCF and NCCs were calculated. The same procedure was used to evaluate the correlation of NCF and QLQ-C30 CF subscale.
Results: Data from EORTC trials 26091 and 26101 were pooled into a data set of 546 patients. Twenty percent of patients could be characterised as unimpaired (109) and 80% as impaired (437). Impaired patients reported more cognitive complaints on the MOS scale than unimpaired patients. Correlations between NCF and NCCs were weak but significant for impaired patients and non-significant for unimpaired ones. Similar results were found for the correlation between NCF test performance and the QLQ-C30 CF subscale.
Conclusion: Correlations between NCF test scores and complaints were weak but suggesting that neurocognitive impairment in patients with HGG does not preclude cognitive awareness. However, considering the findings of this study, we would suggest not to use PROs as a surrogate of performance-based neurocognitive evaluation.

1. Introduction

Because patients with high-grade gliomas (World Health Organisation [WHO] grades III–IV) cannot be cured, palliation of symptoms and maintenance or even improvement of physical functioning and health-related quality of life (HRQoL) are important goals of treatment. However, what makes patients with brain tumour fundamentally different from patients with tumours not involving the central nervous system is the neurocognitive deterioration most of them will face somewhere in the disease trajectory [1].

Neurocognitive functioning (NCF) in patients with glioma is well documented in the literature [2], with information about incidence, nature, severity and causes [3,4].

Neurocognitive deficits, even mild, are known to negatively affect HRQoL [5], professional reintegration, interpersonal relationships and leisure activities.

Furthermore, they may also hamper adequate patient self-reporting, as patients' neurocognitive deficits may render patient-reported outcomes (PROs) through questionnaires unreliable [6]. Exclusion of these patients at the lower end of the neurocognitive spectrum from analyses introduces undesirable bias in the evaluation of PROs during experimental treatments. Moreover, neurocognitively impaired patients may be less compliant regarding questionnaire-based monitoring, thereby introducing another source of bias.

While the incorporation of estimates of the partner or another close relative or friend (denominated as 'proxy' or 'caregiver') might solve this problem to a certain extent, it remains difficult to determine whether assessment by proxy really reflects the status of patients. Studies on the impact of NCF on patient-proxy agreement regarding HRQoL ratings show less agreement between proxies and neurocognitively impaired patients than proxies and cognitively intact patients [6].

Looking at it in more detail, there seems to be agreement between patients and proxy concerning objective signs of neurocognitive deterioration effects on quality of life [7]. Unfortunately, not the same can be said about aspects such as mood and emotional functioning [8]. Dorothee Van Der Linden *et al.* [9] 'tested the influence of executive functioning (EF) impairment on patients and proxy assessment agreement in patients with brain tumour. Patient-proxy agreement was found to be moderate; however, they did not find any association between reported EF and test performance [9].

Considering the heterogeneous reports on patients-proxy agreement, we decided to look at this issue under a different perspective. Cognitive awareness is a broad and rather abstract concept with no shared, multidisciplinary definition. However, it can be operationally defined as the concordance between the patients' neurocognitive complaints (NCCs) and performance-based NCF [10]. The first aim of this study was to assess the association between NCF scores and NCC (Medical Outcome Study [MOS]) in patients with and without neurocognitive impairment. The second was to test the association between NCF and the QLQ-C30 cognitive functioning subscale because this measure, despite being less exhaustive than the MOS, is widely and more often adopted in the clinical field. We hypothesise that the association between both scores is relatively high in patients who are unimpaired and is lower in patients with neurocognitive deficits.

2. Patients and methods

2.1. Participants

The association between NCF and NCCs of patients with brain tumour participating in two European Organisation for Research and Treatment of Cancer (EORTC) clinical trials was analysed as a measure of cognitive awareness.

The trial sample which originally consisted of 731 patients was filtered to 509 with first recurrence of glioblastoma (EORTC 26101) and 37 patients with first recurrence of a locally diagnosed WHO grade II or III glioma without 1p/19q co-deletion (EORTC 26091) (EudraCT number 2009-017422-39 and 2010-023218-30) for a total of 546 patients. Most patients had prior chemotherapy and radiotherapy treatment, and, in both trials, evaluation before randomisation included neurocognitive and full clinical assessment.

Exclusion criteria adopted in the two trials can be found in the relative publications [11,12]. However, for this study, further exclusion criteria have been established: only patients with high-grade glioma tumours have been selected. Because data have been collected before 2016, the 2007 WHO tumour classification has been used, selecting only WHO grade III and IV tumours [13]. In addition, patients for which not enough NCF, NCC or QLQ-C30 CF data were available were excluded.

2.2. Measures

2.2.1. Objective NCF

ObjectiveNCF was assessed using an internationally adopted clinical trial battery comprising the Hopkins Verbal Learning Test–Revised (HVLT-R) [14] for total recall, delayed recall and delayed recognition indexing verbal learning and memory; the Trail Making Test (TMT part A and part B) [15] which measures attention, speed and mental flexibility and the Controlled Oral Word Association Test (COWA) [16] test which evaluates the spontaneous production of words under restricted search conditions. These tests were selected based on their wide use in clinical trials and their sensitivity to the impact of tumour and tumour treatment-related variables [17,18]. The NCF tests were administered by centrally trained and certified healthcare personnel, for example, a research nurse and neuropsychologist.

2.2.2. Patients' NCCs

Patients' NCCs were measured using the cognitive functioning questionnaire from the MOS [19]. The six-item questionnaire assesses day-to-day problems in NCF, asking patients whether in the past month they became confused, reacted slowly to things, had difficulty reasoning, were forgetful, had trouble keeping attention or had difficulty concentrating.

The MOS questionnaire was part of the NCF test package to ensure concurrent collection of objective and self-perceived ratings [19].

For the present study, the EORTC Quality of Life Questionnaire cognitive functioning subscale was used [20]. This subscale is based on two questions (20,25) of the QLQ-C30. Specifically, the items are 'Have you had difficulties in concentrating on things, like reading newspapers or watching television?' and 'Have you had difficulty remembering things?'. Tests were scored using the standardised approach recommended by the EORTC [21].

2.3. Statistical analyses

Descriptive statistics of the sample were calculated. For each of the six NCF outcome measures (i.e. [1] HVLT-R total recall, [2] HVLT-R delayed recall, [3] HVLT-R delayed recognition, [4] TMT part A, [5] TMT part B and [6] COWA), raw scores (RSs) were calculated [14–16].

RSs of the six NCF test outcomes were transformed into Z-scores using available normative data [14–16]. A deviation of −1.5 standard deviation (SD) or more from the Z-score mean was used as a cut-off to define NCF impairment. Based on the presence of impaired test outcomes, patients were consecutively divided in two groups. Patients who had no impairment on any of the six test outcomes were defined as unimpaired, whereas patients showing at least one impaired test were defined impaired.

The MOS and QLQ-C30 CF scores were calculated using formal guidelines [21,22].

Means of NCCs for patients with and without NCF impairment were compared using two-tailed independent sample t-tests to investigate potential systematic differences. The concordance between NCF and NCCs was assessed calculating Pearson's correlation coefficients between standardised performance scores and MOS scores for the impaired and unimpaired condition. A similar approach was used to test the concordance between NCF scores and the QLQ-C30 CF subscale.

Statistical analyses were conducted using SPSS Statistics (version 26.0, IBM corporation, Armonk, NY, USA). All statistical tests were performed at an α level of .05.

3. Results

3.1. Sample characteristics

It is important to mention that treatment course and disease duration before inclusion may have been different between patients in the two trials. All variables were measured within two weeks before randomisation. We determined a time window of ± 7 days between NCF/NCC evaluation and QLQ-C30 CF administration for reliability.

From the original patient's cohort, 82 were excluded due to complete or extensive NCF and NCC missing evaluations and 103 did not fit the histological criteria. Included patients (n = 546) had a mean age of 55.25 years, SD = 11.32 and 202 (37.%) were women. Detailed clinical information is reported in Table 1.

3.2. NCF compliance and performance

Compliance rates of NCF scores for all the participants were calculated and then performance was analysed: HVLT-R total recall had a compliance rate of 541 of 546, with M = 18.93 and SD = 7.18; HVLT-R delayed recall had a compliance rate of 536 of 546, with M = 5.68 and SD = 3.46; HVLT-R delayed recognition had a compliance rate of 527 of 546, with M = 9.24 andSD = 2.75; COWA had a compliance rate of 510 of 546, with M = *24.02* and SD = 13.63; TMT-A had a compliance rate of 521 of 546, with M = 72.91 and SD = 45.95 and TMT-B had a compliance rate of 504 of 546, with M = 173.95 and SD = 92.09.

The patients who performed less than −1.5 SD from the normalised mean were 323 of 541 for HVLT-R total recall, 330 of 536 for HVLT-R delayed recall, 164 of 527 for HVLT-R delayed recognition, 281 of 538 for COWA, 141 of 521 for TMT-A and 159 of 504 for TMT-B.

3.3. Impaired versus unimpaired standardised NCF performance

In total, 109 patients showed neurocognitively unimpaired scores, whereas 437 patients showed impaired scores. Performance of both groups is shown in Figures 1 and 2.

Table 1
Clinical characteristics.

WHO performance status				
0	196	35.9%		
1	295	54.%		
2	55	10.1%		
Histology				
Glioblastoma	473	86.4%		
Astrocytoma WHO grade III	40	6.6%		
Glioblastoma with oligodendroglial component	23	4.2%		
Gliosarcoma	8	1.5%		
Giant-cell glioblastoma	4	.7%		
Missing/unknown	3	.60%		
Tumour location				
	Hemisphere			
	Left	Bilateral	Right	
	230	24	252	
Frontal	63	6	70	25.5%
Temporal	81		86	30.6%
Parietal	20	1	21	7.7%
Occipital	21	16	22	10.8%
Other	21	1	11	6%
Multi-site	24		42	12.1%
Missing	40			7.3%

WHO, World Health Organisation.

3.4. NCC for neurocognitively impaired and unimpaired patients

An independent sample t-test was conducted to compare NCCs (MOS scores) for impaired and unimpaired conditions showing statistical significant differences in the MOS scores for the two groups: unimpaired (M = 73.73, SD = 1791) and impaired (M = 63.21, SD = 21.14); t (5.248), $p < 0.001$.

3.5. NCF and MOS correlation for impaired and unimpaired patients

Overall, in the unimpaired group, small and non-significant correlations were observed for all NCF scores except for the HLVT-R total recall. In the impaired group, all correlation coefficients for NCF scores were significant but weak as shown in Table 2.

3.6. NCF and QLQ-C30 CF correlation for impaired and unimpaired patients

Again, in the unimpaired group, small and non-significant correlations were observed for all NCF scores. In the impaired group, except for the COWA and the TMT-A, correlations coefficients for NCF scores were significant despite being weak as shown in Table 3.

4. Discussion

The present study was performed to assess cognitive awareness in patients with and without neurocognitive impairment who have recurrent brain tumours. Patient cognitive awareness was measured as the correlation between performance-based evaluation and self-perceived evaluation scores. We also tested the correlation between performance-based evaluation and the cognitive functioning subscale of the QLQ-C30 questionnaire.

The results of our analysis seem to support the hypothesis for which cognitively impaired patients with brain tumour show awareness of their cognitive deficits. It is important to notice that the correlations, although significant, were weak. With this regard, these results should be interpreted cautiously. However, these results are counterintuitive and contradict our initial hypothesis that the concordance between NCF and NCCs would have been relatively high in unimpaired patients and lower in patients with cognitive deficits.

The role of impaired cognition as a determining factor for retainment of cognitive awareness has been

reported by a body of literature which investigated it, by mean of patient-proxy agreement. Therefore, in the present study, patients were divided in cognitively impaired and unimpaired groups, based on their cognitive performance.

To do so, we compared the cognitive performance of the participants of this study with normative data, finding that most of the patients performed poorly on at least one of the NCF tests adopted in the study (HVLT-R total recall, HVLT-R delayed recall, HVLT-R delayed recognition, COWA, TMT-A, TMT-B). These results are, for the most, coherent with what the literature concerning cognitive impairment in patients with brain tumour already reported in previous studies [2–4]. When looking at the performance of neurocognitively unimpaired patients, results for the HVLT-R tests and COWA are in line with the standardised measurements; however, the performance on the TMTs seems to be better than what we would expect in this population. This stands true for the neurocognitively impaired group as well. Indeed, impaired patients showed on the TMT-A and -B a better performance than that reported in the literature [2]. To address this, it is important to stress that these results might not be generalisable to the whole population because the data analysed in this cross-sectional study might be affected by patient and physician selection biases because it was collected in a clinical trial context.

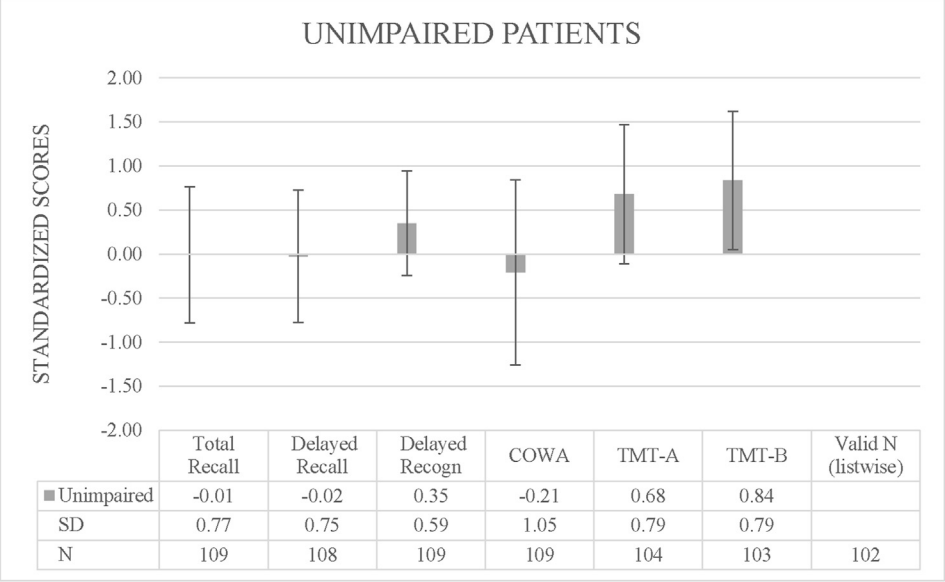
Regarding the differences in NCCs between neurocognitive impaired and unimpaired patients, we found a significant statistical difference: impaired patients showed more NCC scores than the unimpaired ones.

Then, we tested the correlation between the performance-based cognitive evaluation and patient's NCCs. The correlation coefficients should be interpreted with caution because all of them were small. However, contrary to our hypothesis, all NCF test scores correlated with NCCs in the impaired group.

The same procedure was used to test the correlation between neurocognitive performance and the QLQ-C30 cognitive functioning subscale. We decided to test the correlation of NCF with both the MOS and the QLQ-C30 as the latter is often and more widely used in clinical trials. Moreover, it offered us the chance to compare the two scales even though not designed to be used as a measure of cognitive awareness. While on the one hand the MOS is more exhaustive than the QLQ-CF 30 subscale, being composed of six items rather than two, the EORTC, on the other hand, offers the chance of quicker testing which results in less burden for the patients.

Results were similar to the previous analysis, with exception for the COWA and TMT-A which did not correlate with the QLQ-C30 CF subscale even in the neurocognitively impaired group. Altogether, these results are in contrast with studies implementing patient-proxy agreement to evaluate cognitive awareness and suggest that neurocognitive impairment does not play a crucial role in patients' cognitive awareness.

It is important to mention that there are some limitations to this study. Indeed, a discrete number of patients started the TMTs but either stopped before the end or did not finish the test by the maximum time allowed. According to the scoring manual suggestions, we decided to score the performance of those who did not finish the test as the maximum time allowed unless a specific remark of the presence of sight or motor impairment was noted. In that case, the score was considered as missing.



	Total Recall	Delayed Recall	Delayed Recogn	COWA	TMT-A	TMT-B	Valid N (listwise)
Unimpaired	-0.01	-0.02	0.35	-0.21	0.68	0.84	
SD	0.77	0.75	0.59	1.05	0.79	0.79	
N	109	108	109	109	104	103	102

Fig. 1. Standardised NCF performance of neurocognitively unimpaired patients. HVLT-R, Hopkins Verbal Learning Test–Revised for total recall, delayed recall and delayed recognition; TMT, Trail Making Test; COWA, Controlled Oral Word Association; NCF, neurocognitive functioning.

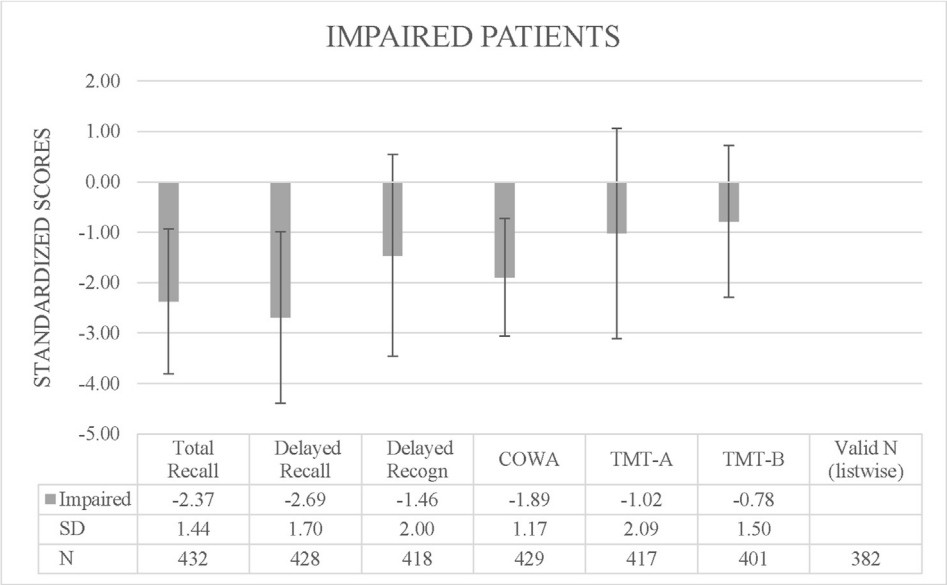


Fig. 2. Standardised NCF performance of neurocognitively impaired patients. HVLT-R, Hopkins Verbal Learning Test–Revised for total recall, delayed recall and delayed recognition; TMT, Trail Making Test; COWA, Controlled Oral Word Association; NCF, neurocognitive functioning.

The present study contributes to the body of literature investigating cognitive awareness in high-grade brain tumour with insight coming from one of the largest samples analysed to date. A better understanding of cognitive awareness could prevent biased PROs such as quality of life reports and help the clinician-patient interaction when discussing consent to treatment and research whilst affected by tumour-related disorders [23].

Additional investigation of patients' ability to evaluate their cognitive functioning is needed. Future studies should focus on long-term evaluation, as well as the effects of tumour and tumour treatment on cognitive awareness. Moreover, we believe that the lack of agreement regarding the adopted measures of cognitive awareness in the literature might play a role in the heterogeneity of the results. Testing cognitive awareness tools tailored around the neurocognitive tests implemented in the study and the comparison with patients-proxy agreement would offer more insights into this matter.

Table 2
Correlation coefficients between NCF and NCC.

Patient Group	HVLT-R total recall	HVLT-R delayed recall	HVLT-R delayed recognition	COWA	TMT-A	TMT-B
Unimpaired	.170	.089	.118	−.090	−.049	−.088
Impaired	.272**	.263**	.242**	.246**	−.190**	−.189*

MOS, Medical Outcome Study; HVLT-R, Hopkins Verbal Learning Test–Revised; TMT, Trail Making Test; COWA, Controlled Oral Word Association; NCF, neurocognitive functioning; NCC, neurocognitive complaint.
** Correlation is significant at the .01 level (2-tailed).
* Correlation is significant at the .05 level (2-tailed).

Table 3
Correlation coefficients between NCF and QLQ-C30 CF.

Patient Group	HVLT-R total recall	HVLT-R delayed recall	HVLT-R delayed recognition	COWA	TMT-A	TMT-B
Unimpaired	.079	.114	−.082	.019	.031	−.068
Impaired	.165**	.155**	.114*	.094	−.065	−.106*

MOS, Medical Outcome Study; HVLT-R, Hopkins Verbal Learning Test–Revised; TMT, Trail Making Test; COWA, Controlled Oral Word Association; NCF, neurocognitive functioning.
** Correlation is significant at the .01 level (2-tailed)
* Correlation is significant at the .05 level (2-tailed).

Altogether, correlations between NCF test scores and NCCs were small but significant, suggesting that neurocognitive impairment in patients with HGG (high grade glioma) does not preclude cognitive awareness. However, considering the findings of this study, we would suggest not to use PROs as a surrogate of performance-based neurocognitive evaluation.

Funding

This study received funding from the European Organisation for Research and Treatment of Cancer (EORTC) project: 1626 Quality of Life Group (QLG) grant number: 007/2016.

CRediT author statement

IC: Conceptualization, Methodology, Formal analysis, Writing - Original Draft, Writing - Review & Editing; AB: Supervision, Writing - Review & Editing; JD: Writing - Review & Editing; JT: Methodology,

Writing - Review & Editing; MVB: Trial design, Investigation, Writing - Review & Editing; AI: Trial design, Investigation, Writing - Review & Editing; WW: Trial design, Investigation, Writing - Review & Editing; MP: Writing - Review & Editing; MK: Conceptualization, Supervision, Writing - Review & Editing, Funding acquisition; JR: Conceptualization, Supervision, Writing - Review & Editing, Funding acquisition.

Conflict of interest statement

None declared.

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