

# Corticosteroids use and neurocognitive functioning in patients with recurrent glioblastoma: Evidence from European Organization for Research and Treatment of Cancer (EORTC) trial 26101

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## Abstract

**Background.** In patients with recurrent glioblastoma, corticosteroids are frequently used to mitigate intracranial pressure and to improve patient neurological functioning. To date, in these patients, no systematic studies have been performed to assess neurocognitive functioning (NCF) in relation to corticosteroid treatment.

**Methods.** Using baseline data (ie, prior to randomization) of European Organization for Research and Treatment of Cancer (EORTC) trial 26101, we performed regression analysis to assess the predictive value of corticosteroid intake on performance of the EORTC brain tumor clinical trial NCF test battery. The battery is comprised of the Hopkins Verbal Learning Test—Revised (HVLT-R), Controlled Oral Word Association Test (COWA), and Trail Making Test (A and B).

**Results.** Out of 321 patients, 148 (46.1%) were not using corticosteroids, and 173 were using dexamethasone (34.3%), methylprednisolone (9.7%), or other corticosteroids (9.9%). Patients on corticosteroids had worse performance on all neurocognitive tests. Regression analyses demonstrated a negative association between corticosteroids use and the HVLT-R free recall score ( $R^2$  change = 0.034,  $F$  change (1, 272) = 13.392,  $P < .001$ ) and HVLT-R Delayed Recall score ( $R^2$  change = 0.028,  $F$  change (1, 270) = 10.623,  $P = .002$ ). No statistically significant association was found for HVLT-R Delayed recognition, COWA, TMT part A and TMT part B ( $P > .05$ ).

**Conclusions.** Glioblastoma patients prescribed with corticosteroids show poorer memory functions, expressive language, visual-motor scanning speed, and executive functioning than patients not using corticosteroids. Furthermore, we found a negative association between corticosteroid intake and memory functions. The possibility of deleterious effects of corticosteroids on NCF should be considered during clinical decision making.

**Keywords**

corticosteroids | glioblastoma | memory | neurocognitive functioning | neuroimaging

Glioblastoma is the most malignant and rapidly progressing primary brain tumor. Therefore, alleviation of symptoms, preservation of neurocognitive functioning (NCF), and healthy quality of life are important goals of treatment.<sup>1-5</sup>

Although corticosteroids are useful in treating peritumoral edema and its associated neurological symptoms, these drugs can cause arterial hypertension and immunosuppression in the short term and osteoporosis, steroid-induced diabetes, electrolyte disturbance, myopathy and cushingoid fat distribution in the long term.<sup>6</sup> Often overlooked, corticosteroids can also have profound repercussions on NCF, mood, and sleep.<sup>7,8</sup> Recent studies support the hypothesis that the duration of corticosteroid use plays a key role in determining the extent of these unwanted effects: a recent review has shown that corticosteroids have modest negative effects on executive function for acute users (up to 1 day), on recent memory for short-term (2-30 days), and chronic users (more than 31 days), and on long-term memory for acute users.<sup>9</sup> Interestingly, short-term use of corticosteroids has been related to small positive effects on language function.<sup>9</sup>

To date, little attention has been devoted to the effects of corticosteroids on NCF in glioblastoma patients. Research is limited to one small study in 44 patients with a World Health Organization (WHO) grade III tumor (16%) or glioblastoma (84%).<sup>4</sup> Correlational analyses of NCF outcomes during (N = 44) and after (N = 21) radiation therapy showed a higher dexamethasone intake to be associated with a significantly worse performance in working memory, language, and executive functioning. Considering that 59% of patients in the aforementioned study had a biopsy alone as opposed to a gross total resection prior to radiotherapy, it is conceivable that NCF deficits in these patients might also be confounded by the effects of tumor progression and/or edema during radiotherapy.

As life expectancy in patients with recurrent glioblastoma is short, maintaining NCF is a highly significant treatment goal both for patients and their caregivers.<sup>10</sup> NCF deficits are related to patients' limitations to perform activities of daily living (ADL), inability to return to work, and financial difficulties. Considering the high incidence of NCF deficits that may be mediated by corticosteroids use in glioblastoma patients, it is clinically relevant to value the effect of these drugs on NCF.<sup>2,11-13</sup>

The main aim of this cross-sectional study was to assess memory functioning, expressive language, processing speed, and executive function in patients with recurrent glioblastoma undergoing corticosteroid treatments, prior to randomization in European Organization for Research and Treatment of Cancer (EORTC) trial 26101. The secondary aim was to investigate the neurocognitive performance of patients using different types of corticosteroids.

**Materials and Methods****Patients**

The sample was drawn from the EORTC trial 26101 that included 598 patients at the first recurrence of glioblastoma. EORTC 26101 is a phase III clinical trial where continuation of the randomization scheme of 2:1 (bevacizumab and lomustine or lomustine alone) was used to assess whether combination therapy yielded better overall survival.<sup>14</sup> Of relevance for the present study is that patients had to have stable or decreasing dosage of steroids for 7 days prior to the baseline MRI scan.

The trial was approved by the institutional review boards and ethics committees of all participating centers and the respective authorities. The trial (EudraCT number 2009-017422-39) was completed according to the Declaration of Helsinki, and all patients provided written informed consent. Inclusion criteria for the trial can be found in the pertinent publication.<sup>14</sup>

Furthermore, patients who had neurocognitive testing more than 3 days apart from the date of documented use of corticosteroids were excluded. This criterion was established because of corticosteroids' relatively short half-life.<sup>15</sup>

**Materials***Neurocognitive assessment*

NCF was assessed using an internationally adopted clinical trial battery recommended for brain tumor cohorts, the general cancer population, and multicenter clinical studies.<sup>16,17</sup> The selected tests are widely used standardized psychometric instruments that have proven to be sensitive to the impact of the tumor and tumor-related variables in other clinical trials.<sup>13,18</sup> The Hopkins Verbal Learning Test—Revised (HVLT-R) consists of 3 parts: free recall, delayed recall, and delayed recognition. It measures various aspects of verbal learning and memory, namely storage of verbal information as well as active and passive retrieval of this information.<sup>19</sup> The Controlled Oral Word Association Test (COWA) measures expressive language.<sup>20</sup> The Trail Making Test (TMT part A and TMT part B), part A indexes visual-motor scanning speed, while part B assesses executive functioning.<sup>21</sup> This battery takes approximately 25 minutes to complete and was administered by a trained and certified tester (eg, nurse, physician, neuropsychologist).

*Neurological evaluation*

Neurological status as a potential confounder of NCF was assessed using the five-point Medical Research Council (MRC) scale. The status ranged from "0" having no

neurological deficit to “4” no useful function—inability to make conscious responses. Lower scores correspond to fewer neurological deficits.<sup>22</sup>

### *Tumor volumetry*

The volumetric measurement of tumor volumes was performed using artificial neural networks (ANN), as described previously.<sup>23,24</sup> Briefly, this included automated ANN-based brain extraction, followed by image registration and automated ANN-based volumetric segmentation of contrast-enhanced tumor parts (CE tumor volume) and the non-enhancing T2-FLAIR hyperintense abnormality (NE/edema volume) which excludes the contrast-enhancing and necrotic portion of the tumor, resection cavity, and obvious leukoaraiosis.

### *Corticosteroid use*

Patients were divided into corticosteroid users (ie, dexamethasone, methylprednisolone, or other corticosteroids) and non-users prior to randomization in EORTC trial 26101 (N = 598). Owing to the high individual variability in corticosteroid dosage, this metric has not been taken into account in the current statistical analyses.<sup>25</sup>

## Statistical Analyses

Independent-samples *t*-tests were performed to assess whether there was a difference in NCF test scores between corticosteroid users and non-users. For each NCF test, raw scores for each of the NCF outcome measures were calculated and transformed into standardized scores, to be able to compare performance, using available normative data.<sup>19–21</sup>

Subsequently, hierarchical multiple regression was performed for each of the 6 neuropsychological test outcomes (HVLTR free recall, HVLTR delayed recall, HVLTR delayed recognition, COWA, TMT part A and TMT part B) to assess the ability of corticosteroid intake to predict neurocognitive outcome, while controlling for the influence of age, gender, tumor location, tumor hemisphere, NE/edema volume, CE tumor volume, and neurological status.<sup>26,27</sup> Raw scores were used to avoid biased projection of beta coefficients.

For the secondary aim of the study, Mann-Whitney *U* tests with *z*-scores of the neuropsychological test outcomes were performed to compare the neurocognitive performance between dexamethasone and methylprednisolone users. Non-parametrical test was used due to differences in sample size since group sizes differed.

All statistical analyses were performed in IBM SPSS Statistics for Windows, Version 26 (IBM Corp., Armonk, NY, USA), with a two-tailed significance level of 0.05.

## Human and Animal Rights

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

## Informed Consent

Informed consent was obtained from all individual participants included in the study.

## Results

### Sociodemographic and Clinical Data

The original sample of EORTC trial 26101 consisted of 598 patients, and 277 patients (46.3%) were excluded from the analysis because of the date of neurocognitive testing and the date of documented use of corticosteroids were more than 3 days apart. Consequently, the sample for the present analyses consisted of 321 patients with a median age of 57.6 years (range 26–78); 198 males (61.7%) and 123 females (38.3%). Of these 321 patients, 173 patients used corticosteroids (53.9%) and 148 patients had no documented use of corticosteroids. Clinical information on the study sample can be found in [Table 1](#).

### NCF Performance of Corticosteroid and Non-Corticosteroid Patients

Independent-samples *t*-tests were performed to compare the results on neuropsychological tests for patients on corticosteroids (N = 173) and patients not using corticosteroids (N = 148) at baseline. There were significant differences in the scores of the HVLTR: in the free recall task, patients (N = 148) not using corticosteroids (*M* = 20.68, *SD* = 6.9; *t*(316) = 5.58, *P* = .000) performed better than those (N = 170) on corticosteroids (*M* = 16.26, *SD* = 7.1); similarly, in the delayed recall task, patients not using corticosteroids (N = 147; *M* = 6.27, *SD* = 3.3; *t*(314) = 5.14, *P* = .000) outperformed patients on corticosteroids (N = 169; *M* = 4.3, *SD* = 3.4); in the delayed recognition task, patients not using corticosteroids (N = 144; *M* = 9.37, *SD* = 2.6; *t*(307) = 3.0, *P* = .003) again showed a better performance than their counterparts undergoing corticosteroid treatment (N = 167; *M* = 8.4, *SD* = 3.2).

The COWA scores yielded a significant difference for patients on corticosteroids (N = 171; *M* = 20.71, *SD* = 13.1) and patients not using corticosteroids (N = 148; *M* = 26.53, *SD* = 14.1; *t*(317) = 3.82, *P* = .000) with the latter performing better. Furthermore, on the TMT part A, patients on corticosteroids (N = 160) took on average significantly more time to complete the test (*M* = 82.53, *SD* = 48.2) than patients not using corticosteroids (N = 145; *M* = 67.78, *SD* = 46.6; *t*(303) = −2.71, *P* = .007); this was also the case for the TMT part B, on which patients on corticosteroids (N = 153; *M* = 199.49, *SD* = 92.9) needed more time than those not using them (N = 142; *M* = 169.55, *SD* = 92.9; *t*(293) = −2.77, *P* = .006).

When comparing the scores to normative data, by mean of *z*-scores, it becomes clear that for both groups, the scores for HVLTR free recall and delayed recall deviate more than 1.5 *SD* from the mean. For HVLTR delayed recognition and COWA the corticosteroid users group deviates more than 1.5 *SD*, and the non-corticosteroid users deviate more than 1 *SD*. For TMT A and B, the corticosteroid users

group deviates around 1 SD and the non-corticosteroid users deviates around 0.5 SD from the mean.

Effect sizes ranged from small for executive functioning (TMT part B; 0.32) to medium for verbal learning and memory (HVLT-R free recall; 0.63). More detailed information can be found in [Figure 1](#).

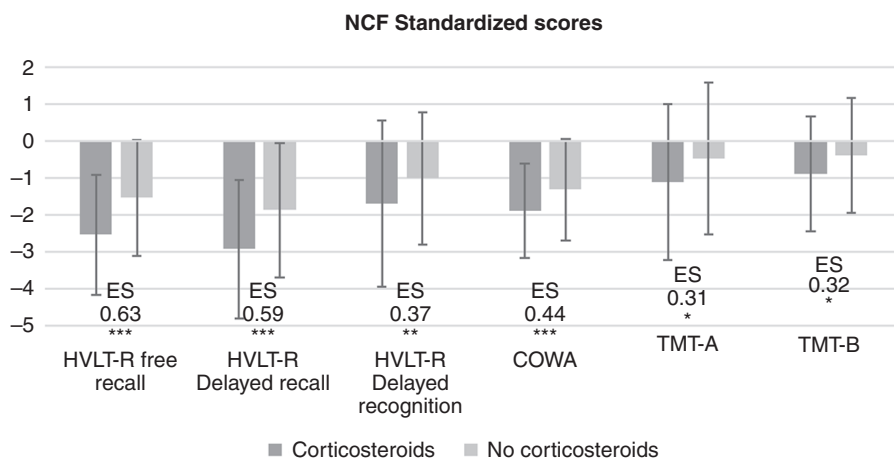
### Association Between Corticosteroid Intake and Neurocognitive Functioning

Hierarchical regression analyses were performed to test the association between corticosteroid intake and NCF after correcting for factors that could have had an impact.

**Table 1** Sociodemographic and Clinical Characteristics of the Recurrent Glioblastoma Patients From EORTC trial 26101 (N = 321) at Baseline

	Corticosteroids				Non-Corticosteroids			
Age, median (range)	56.42 (27-78)				58.71 (26-76)			
Gender, n								
Male	109				89			
Female	64				59			
Tumor location, n								
	L	C	R	T	L	C	R	T
Frontal	22	3	26	51	19	3	13	35
Temporal	26	–	21	47	23	–	28	51
Parietal	6	–	4	10	6	–	4	10
Occipital	10	–	10	20	3	1	4	8
Other/Multiple	23	4	15	42	11	6	12	29
Total	87	7	76	170	62	10	61	133
Missing	3				15			
Neurological status, n (%)								
No neurological deficit	41 (23.7%)				69 (46.7%)			
Some neurological deficits	84 (48.55%)				52 (35%)			
Moderate functional impairment	31 (17.95%)				20 (13.5)			
Major functional impairment	4 (2.3%)				–			
Missing	13 (7.5%)				7 (4.8%)			
Total	173				148			

**Abbreviations:** L, left; C, center; R, right; T, total.



**Figure 1.** Neurocognitive outcomes based on z-scores with effects sizes. HVLT-R (Hopkins Verbal Learning Test—Revised), COWA (Controlled Oral Word Association), TMT (Trail Making Test). \* $P < .05$ , \*\* $P < .01$ , \*\*\* $P < .001$ .

The analysis corrected for age, gender, neurological status (MRC), tumor hemisphere, tumor location, edema, and tumor volume. No correction was made for the treatment arm due to the results shown in the RTOG 0825.<sup>28</sup> Corticosteroid intake was associated with significantly poorer initial storage of verbal information (HVLTR free recall,  $\beta = -0.193$ ,  $P < .001$ ) and with poorer active retrieval of verbal information (HVLTR delayed recall,  $\beta = -0.177$ ,  $P = .002$ ). On the other hand, no significant association was found with passive retrieval of verbal information (HVLTR delayed recognition,  $P = .288$ ), with expressive language as measured by the COWA ( $P = .070$ ), with processing speed (TMT A,  $P = .140$ ) and executive functioning (TMT B,  $P = .304$ ). Additional  $\beta$ - and  $P$ -values are presented in Table 2.

### Effects of Different Types of Corticosteroids on Neurocognitive Functioning

Glioblastoma patients, with or without corticosteroids, performed worse on all neurocognitive tests than the healthy population. The EORTC trial 26101 comprised patients using different types of corticosteroids with dexamethasone ( $N = 108$ ) and methylprednisolone ( $N = 31$ ) being the most frequent. Therefore, a Mann-Whitney  $U$  test was performed to test whether there were differences in neurocognitive performance between dexamethasone and methylprednisolone. No statistically significant differences were found ( $P > .05$ ).

## Discussion

The primary aim of this study was to assess memory functioning, expressive language, processing speed, and executive functioning in patients with recurrent glioblastoma undergoing corticosteroid treatments in EORTC trial 26101. The secondary aim was to investigate the neurocognitive performance of patients using different types of corticosteroids.

The literature outside the brain tumor field indicates that corticosteroid use may be associated with lower performance in all domains of NCF and in our study, we found significant differences in neurocognitive performance between patients using corticosteroids and patients that did not. The association between corticosteroid use and verbal free recall and delayed recall is in line with outcomes of a meta-analysis of studies in healthy subjects.<sup>9</sup> Notably, the meta-analysis did not report differential effects of corticosteroids on immediate memory, while in our study, we found differences in memory performance.

A possible interpretation of the lower memory functioning in patients using corticosteroids may be related to the brain target area of corticosteroid drugs. The highest concentration of corticosteroid receptors is in the hypothalamus, pituitary gland, and hippocampus which are all parts of the hypothalamic-pituitary-adrenal (HPA) axis.<sup>29</sup> The hippocampus, an area that is critical to the processing and storage of memory, has a direct inhibitory effect on the hypothalamus and therefore on the whole HPA axis. However, corticosteroid intake increases cortisol production which leads to less inhibitory action of the hippocampus on the HPA axis.<sup>30</sup> We did not find significant differences in delayed recognition. A possible explanation is that delayed recognition is a different retention aspect of information retrieval. Recall is thought to rely heavily on retrieval of information represented in cortical areas, whereas recognition seems to be more of a dual process based on recollection and/or familiarity.<sup>31,32</sup>

Analyses comparing NCF between patients prescribed with dexamethasone and methylprednisolone did not show any statistically significant difference ( $P > .05$ ). The reason behind this can be ascribed to their similar high glucocorticoid and negligible mineralocorticoid potency, which is preferred in neuro-oncology.<sup>15</sup>

For future research, it might be interesting to perform a longitudinal study and look at functional impairment during treatment to separate general neurological worsening from corticosteroid effects on cognition. It

**Table 2** Standardized Beta Coefficients and  $P$ -values for Hierarchical Multiple Regression for Significant Models

	HVLTR FR	HVLTR DR
Model	$R^2$ change = 0.034, $F$ change (1, 272) = 13.392, $P < .001$	$R^2$ change = 0.028, $F$ change (1, 270) = 10.623 $P = .002$
Corticosteroid intake	$\beta = -0.193$ , $P < .001$	$\beta = -0.177$ , $P = .002$
NE/edema volume	$\beta = -0.101$ , $P = .169$	$\beta = -0.121$ , $P = .116$
CE tumor volume	$\beta = -0.059$ , $P = .421$	$\beta = -0.023$ , $P = .761$
Tumor location	$\beta = 0.013$ , $P = .793$	$\beta = -0.013$ , $P = .807$
Hemisphere	$\beta = -0.193$ , $P < .001$	$\beta = -0.279$ , $P < .001$
MRC score	$\beta = -0.197$ , $P < .001$	$\beta = -0.205$ , $P < .001$
Gender	$\beta = 0.166$ , $P = .001$	$\beta = 0.139$ , $P = .009$
Age	$\beta = -0.191$ , $P < .001$	$\beta = -0.172$ , $P = .002$

**Abbreviations:** CE, contrast-enhanced; HVLTR DR, Hopkins Verbal Learning Test—Revised delayed recall; HVLTR FR, Hopkins Verbal Learning Test—Revised free recall; MRC, Medical Research Council; NE, non-enhancing.



might also be interesting to investigate the potential interaction effects of corticosteroids and brain tumor medication, like bevacizumab (BEV), possibly in the follow-up data of EORTC trial 26101. Recently, multiple studies showed that corticosteroids use may be associated with compromised overall and progression-free survival, especially when combined with radiotherapy and/or chemotherapy.<sup>33–35</sup> BEV produces responses that result in a decreased use of glucocorticoids; therefore, the use of BEV may be associated with less corticosteroid use and likewise might prevent potential negative effects on NCF.

There are several limitations to this study. Considering the myriad of factors that might give rise to neurocognitive deficits in brain tumor patients, based on this single observation, no conclusions can be drawn as to the causal relation between corticosteroids use and NCF.

One of the inclusion criteria of the trial was the participation of glioblastoma patients with first recurrence. This implies that most patients will already have had chemoradiation and adjuvant chemotherapy and neurocognitive deficits in these patients consequently must be interpreted against the backdrop of earlier incurred neurocognitive deficits resulting from the tumor and its treatment.<sup>36</sup> The finding that patients not using corticosteroids also have impaired NCF stresses this notion. It is also important to consider that with the available data, it is not possible to separate further progression, which most likely was the indication to start corticosteroid treatment from the effect of corticosteroid. Furthermore, at study entry, it was not documented how long patients were on corticosteroids. Although it is safe to assume that most patients were on prolonged corticosteroid schedules, differences between, acute, short-term, and long-term corticosteroid users have been reported and cannot completely be ruled out in the present study.<sup>9</sup> Therefore, the results must be interpreted with caution.

Glioblastoma patients prescribed with corticosteroids show poorer memory function, expressive language, visual-motor scanning speed, and executive functioning than patients not using corticosteroids. Furthermore, corticosteroid intake is negatively associated with memory functions. A better understanding of the influence of corticosteroids on NCF could prevent both biased reports on neurocognitive outcomes in glioblastoma clinical trials as well as help the clinical decision making process and thus tailor treatment according to individual needs.

Further research is needed to investigate the long-term effects and interactions of corticosteroids and chemotherapeutic agents, including BEV. Altogether, these findings might raise awareness and discussion on the benefit of corticosteroids and alternatives, like BEV,<sup>37</sup> in balancing the survival benefits against the potential side effects on NCF, everyday life functioning, and thereby on health-related quality of life.

## Supplementary Material

Supplementary material is available at *Neuro-Oncology Practice* online.

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**Conflict of interest statement.** No authors have a potential conflict of interest.

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