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Health-related quality of life and cognitive functioning in survivors of oligodendroglioma: An international cross-sectional investigation

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Abstract

Background. Patients with oligodendroglioma have a relatively favorable prognosis. The long-term impacts of the tumor itself and its treatment on health-related quality of life (HRQOL) and cognition remain largely unclear. We investigated associations between treatment and functioning of survivors of oligodendroglioma.

Methods. In this cross-sectional observational study, patients with oligodendroglioma, isocitrate dehydrogenase-mutant and 1p/19q-codeleted, diagnosed ≥ 5 years ago, were recruited. Patients completed patient-reported outcome measures (EORTC QLQ-C30; BN20; MOS Cognitive Complaints Scale) and cognitive tests (HVLT-R, TMT, COWAT). Associations between HRQOL and cognition outcomes, and clinical variables (time since diagnosis; age at diagnosis; progression; tumor location; treatments delivered; time since treatment; current medication) were explored with regression analyses.

Results. In total, 237 patients $M = 9.9$ years postdiagnosis (SD = 4.2, range 5.0-25.8) took part from 33 sites across 9 countries. Clinically relevant levels of impairment were noted in >40% of patients on EORTC QLQ-C30 scales for cognitive functioning (56.1%), emotional functioning (49.8%), fatigue (45.1%), and physical functioning (40.5%). In individuals, cognitive impairment ranged from 17.7% for processing speed to 46.0% for episodic verbal memory (delayed recall). Among other clinical factors such as current use of antiseizure medication or antidepressants, age, disease progression, time since diagnosis and time since treatment, and radiotherapy treatment (ever received) was linked to HRQOL and cognitive functioning outcomes (posthoc analyses for cumulative radiotherapy dose: not significant).

Conclusions. In oligodendroglioma survivors, HRQOL and cognitive impairment are prevalent even years into follow-up. Supportive care and rehabilitation should be prioritized to mitigate these challenges and improve daily functioning.

Trial registration: NCT04708548

Key Points

- In oligodendroglioma patients many years postdiagnosis, quality of life issues persist.
- Cognitive, emotional, social, and physical functioning issues were reported.
- Worse quality of life and cognitive outcomes were linked to clinical factors.

Importance of the Study

Investigating late effects of treatment is a top research priority in cancer in general and neuro-oncology in particular. The emergence of new treatment options for patients with oligodendroglioma highlights the importance of studying the association between different anticancer treatments and long-term health-related quality of life and cognitive functioning. We therefore undertook this international cross-sectional study to investigate health-related quality of life and cognitive functioning of survivors of oligodendroglioma, at least 5 years since diagnosis. In 237 patients with oligodendroglioma, we identified continued issues related to cognitive, emotional, social, and physical functioning, as well as fatigue, sleep disturbances, and financial difficulties. Patients also have marked cognitive deficits on neuropsychological tests. Results can only partly be explained by treatment.

Oligodendroglioma, isocitrate dehydrogenase (IDH)-mutant, and 1p/19q-codeleted as defined by the fifth edition of the WHO Classification of Tumors of the Central Nervous System (CNS), represent rare tumor groups (~10% of gliomas in adults) with relatively favorable prognosis.[1–3] Depending on the report, median overall survival is 14 to over 20 years,[3–5] with WHO grades 2 and 3 likely reflecting a biological continuum rather than distinct entities.[6]

Current recommended therapeutic approaches for oligodendroglial tumors include surgery, radiotherapy, and chemotherapy with procarbazine, lomustine, and vincristine (PCV), or temozolomide (TMZ) if toxicity is a concern, as well as watch-and-wait strategies in younger patients (<40 years) without neurological deficits and after gross total resection.[5,7–10] However, over the last decades, treatment regimens were more heterogeneous across local centers, especially for treating tumor recurrence. Selective IDH inhibitors, such as ivosidenib and vorasidenib, represent a novel approach. The phase III INDIGO trial demonstrated promising clinical efficacy in patients with residual CNS WHO 2 IDH-mutant glioma who had undergone no previous treatment other than surgery.[11] The trial did not report detrimental effects on health-related quality of life (HRQOL) or cognitive functioning, with long-term follow-up data pending.[12] Several single-arm and multiarm RCTs are currently comparing proton to photon radiotherapy to investigate whether protons yield the same survival benefit as photons but with fewer long-term adverse effects on HRQOL and cognition,[13] as well as efforts to investigate the impact of deferring radiotherapy.[14]

In general, global HRQOL in patients with diffuse low-grade glioma can be impaired, with a recent systematic review of 22 studies reporting that patients experience functional impairment and high symptom burden, particularly related to cognitive functioning and fatigue.[15] In this review, clinical performance status and epilepsy burden were associated with HRQOL scores, with unclear contribution from respective treatments.[15] Another systematic review of 21 studies focused on long-term survivors (defined as ≥2 years after diagnosis of WHO grade 2 and 3 glioma).[16] Physical functioning issues such as motor dysfunction, fatigue, pain and changes in appearance were most marked within the first 5 years after diagnosis. Issues related to psychological, emotional and self-reported cognitive functioning were highly prevalent throughout long-term survivorship (≥10 years postdiagnosis).[16] Cognitive deficits tend to show a delayed onset,[17–21] with radiotherapy treatment associated with worse performance on tests for executive functioning, information processing and attention.[22] Indeed, radiotherapy is believed to increase the risk for cognitive deficits in the long term, although the magnitude of the risk is uncertain.[23] Associations between chemotherapy and cognitive functioning in glioma patients are even more uncertain.[23–25]

Investigating late effects of treatment is a top research priority in cancer in general[26] and neuro-oncology in particular.[27,28] The emergence of new treatment options highlights the importance of studying the association between different anti-cancer treatments and long-term HRQOL and cognitive functioning. The existing literature is limited particularly by the inclusion of heterogeneous glioma patient subgroups, compounded by recent changes in tumor classifications,[1,2] and variations in follow-up duration.[15,16] We therefore undertook this international cross-sectional study to investigate HRQOL and cognitive functioning of survivors of oligodendroglioma, at least 5 years since diagnosis. We also aimed to study the links between these outcomes and treatment- and disease-related factors. This endeavor might not only help patients and clinicians make better informed treatment decisions, but it may also serve as a benchmark for longer term patient outcomes for the evaluation of new treatment modalities.

Materials and Methods

Study Design

This is an international multicenter, observational cross-sectional study investigating HRQOL and cognitive functioning in long-term oligodendroglioma survivors. Clinical trial registration: NCT04708548. Sites were invited to join through the EORTC Quality of Life group, the Brain Tumor group, and several national neuro-oncology societies.

Ethics Approval

Ethical and research governance approvals were obtained at each participating center in accordance with local requirements. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Helsinki

declaration and its later amendments or comparable ethical standards.

Participants

Participants were recruited from 33 sites across 9 countries (see Acknowledgments for a full list, or Table 1 for overview of countries. Recruitment target per site was >6 patients). Patients could take part if they were diagnosed with a histologically confirmed oligodendroglioma WHO CNS grade 2 or 3 as per 2016 classification[29] in adulthood, at least 5 years ago. Patients could not take part if they were unable to complete consent and/or study procedures due to legal incompetence or insufficient proficiency of the language(s) of the country from which they were recruited. All participants signed written informed consent.

Procedure

Sociodemographic information was collected using a structured interview. Clinical data were obtained from medical records. Neuropsychological assessments were performed by a neuropsychologist or staff trained by a neuropsychologist. Questionnaires were generally completed at the same time as the neuropsychological assessment but could also be brought home and returned by post within a 14-day window. In addition to the outcome measures listed below, patient-reported outcomes for psychological distress, fatigue and information and support needs were collected. These will be reported on separately to ensure we can provide a more detailed report of these issues, known to be prevalent in glioma survivorship.[30,31] In total, study participation took patients about 60 min. Data were collected between November 2020 and April 2023.

Outcome Measures

All measures described below were offered in the official language versions relevant to the setting (English in the UK, French in France, Czech in the Czech Republic, Danish in Denmark, Italian in Italy, Swedish in Sweden, Greek in Greece, and German in Austria, Switzerland, and Germany).

Patient-reported outcome measures.

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30)[32] was used to assess HRQOL. This questionnaire yields 5 functioning scales (physical, role, cognitive, emotional, and social functioning), 9-symptom scales (fatigue, pain, nausea/vomiting, dyspnea, sleep disturbances, appetite loss, constipation, diarrhea, and financial impact; score range 1-4), and a scale for global quality of life (score range 1-7).

Disease-specific HRQOL was assessed using the EORTC Brain Cancer Module (BN20).[33] This 20-item questionnaire has 4 multiitem symptom scales (future uncertainty, visual disorders, motor dysfunction, communication deficits) and 7 single items (headaches, seizures, drowsiness, hair loss, itching skin, weakness in the legs, difficulties with bladder control; score range 1-4). Raw scores were converted into scales ranging from 0 to 100. Higher scores on the QLQ-C30 functional scales indicate better functioning, higher scores on the QLQ-C30 and BN20 symptom scales indicate higher symptom burden.

The 6-item Medical Outcomes Study cognitive functioning scale (MOS-Cog, score range 1-6) was used to assess everyday problems experienced in relation to cognitive functioning, including difficulty with reasoning and problem solving, slowed reaction time, and concentration issues.[34] Scores were converted to a 0-100 scale with lower scores indicating greater concerns.

Performance-based outcome measures.

Objective cognitive functioning was assessed using the Hopkins Verbal Learning Test-revised (HVLT-R)[35,36] to assess episodic verbal memory; the Trail Making Test (TMT)[37,38] as a measure of visuo-motor processing speed (part A) and switching executive functioning (part B); and the controlled oral word association test (COWAT)[39] to test verbal fluency (controlled initiation).

Statistical Analysis

Data were analyzed using SPSS version 28.0 for Windows (SPSS, Chicago, IL). Questionnaires were scored along the respective manuals. For cognitive data, raw test scores were converted to *Z*-scores using the mean and standard deviation (SD) from normative populations,[36,39,40] where possible correcting for age and sex. Six *Z*-scores were calculated: verbal memory recall, delayed recall, and recognition based on the HVLT-R; information processing and switching executive functioning based on the TMT A and B, respectively; and verbal fluency based on the COWAT. Impairment on each test was defined as $Z < -1.5$. Descriptive statistics were generated for sample sociodemographic and clinical characteristics and HRQOL and cognition scores. We used established thresholds for defining clinical importance on the EORTC QLQ-C30 scales.[41] EORTC QLQ-C30 reference values from the general population[42] were used to mark clinically relevant differences in scores (commonly used rule of thumb: ≥10 point difference). For MOS-Cog scores, a cutoff of ≤60 across all items was used to indicate the presence of cognitive concerns.[43] For illustrative purposes, three groups were created representing 5-10 years survival; 10-15 years survival, and 15+ years survival, with HRQOL and cognitive outcomes plotted in a bar chart.

To explore associations between HRQOL (global HRQOL plus 5 EORTC QLQ-C30 and 4 BN20 multiitem scale scores) and cognitive functioning (6 *Z*-scores as described above) as dependent variables, and independent clinical variables (time since diagnosis), age at diagnosis, number of recurrences, current disease status (stable, no treatment/active, undergoing or planning for treatment), tumor location (left/right), treatments delivered [radiotherapy (ever), chemotherapy (ever)], time since last treatment, current medication (antiseizure medication, antidepressants), univariate regression analyses were run. Significant

associations at $P < 0.10$ between HRQOL or cognitive outcomes and clinical variables were used to determine inclusion in multivariable regression analyses. Posthoc analyses were run for cumulative (total) radiotherapy dose (continuous variable) and type of chemotherapy (PCV or temozolomide). Using backward selection, the models with best fit (fewest number or variables, most variance explained) were selected. $P < 0.05$ was considered statistically significant.

Results

Participants

In total, 237 patients with confirmed histopathological and molecular features of oligodendroglioma (IDH mutant, 1p/19q codeletion) took part (male, 60.8%), see Table 1 for basic sociodemographic and clinical characteristics. Participants were on average 9.9 years postdiagnosis (SD = 4.2, range 5.0-25.8), and 52.2 years old (SD = 11.8, range 23-78) at the time of assessment.

Patient-reported Outcome Measures

HRQOL scores are described in Table 2 and Figure 1. Impairment to a clinically important degree[41] was most commonly observed in cognitive functioning ($n = 133$, 56.1%), emotional functioning ($n = 118$, 49.8 %), fatigue ($n = 107$, 45.1%), and physical functioning ($n = 96$, 40.5%). On group level, compared to general population norms,[42] patients with oligodendroglioma have worse cognitive and social functioning, and higher levels of fatigue, and financial impact, to a clinically relevant degree (≥10 point difference).

Associations between patient-reported outcome measures and clinical factors.

Table 3 displays the associations found between HRQOL scale scores and clinical factors. Regarding generic HRQOL as assessed with the EORTC QLQ-C30, univariable analyses (Supplementary Table 1) revealed that patients' global health status score was worse in those who had ever received radiotherapy treatment or currently used antidepressant ($P < 0.10$), and both variables were retained in the multivariable model ($r^2 = 0.025$, $P < 0.01$). Physical functioning was worse in patients who were older at diagnosis, those who had ever been treated with radiotherapy, those currently on antiseizure medication, and those with active versus stable disease status (univariable analyses, $P < 0.10$). The associations between worse physical functioning and age at diagnosis, radiotherapy treatment, and antiseizure medication remained in the multivariable model ($r^2 = 0.119$, $P < 0.01$). For role functioning, worse outcomes were observed in those older at diagnosis, those treated with radiotherapy and those currently on antidepressants ($P < 0.10$). These variables remained associated in the multivariable model ($r^2 = 0.0.081$, $P < 0.01$). Cognitive functioning was worse in patients who were older at diagnosis and those with active versus stable disease status (univariable analyses, $P < 0.10$). Both variables were retained in the multivariable model ($r^2 = 0.040$, $P < 0.001$). Emotional functioning was worse in those using antidepressants and those with active versus stable disease status (univariable analyses, $P < 0.10$), with both variables retained in the multivariable model ($r^2 = 0.048$, $P < 0.01$). Social functioning was worse in patients who had ever been treated with radiotherapy, and those currently on antidepressant drugs (univariable analyses, $P < 0.10$). In the multivariable model both variables remained associated with worse social functioning ($r^2 = 0.028$, $P < 0.01$). For all associations with radiotherapy described above, posthoc analyses for cumulative dose of radiotherapy were not statistically significantly relevant.

For disease-specific HRQOL as assessed with the EORTC BN20 scales, patients had worse future uncertainty when they had experienced more recurrences ($r^2 = 0.032$, $P = 0.007$). Visual deficits were worse in patients with active versus stable disease status, though not to a statistically significant level ($r^2 = 0.015$, $P = 0.070$). Motor dysfunction was worse in patients who had a longer disease course and who were treated longer ago, those with active versus stable disease status, those ever treated with radiotherapy, and those on antidepressants or antiseizure medication (univariable analyses, $P < 0.10$). The association between worse motor dysfunction and time since diagnosis, disease status, and radiotherapy, remained significant ($P < 0.05$) in the multivariable model which also included antidepressants ($r^2 = 0.105$, $P = 0.029$; posthoc test for cumulative radiotherapy dose P = n.s.). Patients had worse communication deficits when they had been treated longer ago, when they had active versus stable disease status and when they were current antidepressant users (all retained in the multivariable model: $r^2 = 0.084$, $P < 0.001$).

For cognitive complaints as measured with the MOS-Cog scale, younger age at diagnosis and active versus stable disease status were associated with fewer complaints. The final model only includes age at diagnosis ($r^2 = 0.040$, $P = 0.003$).

Performance-based Outcome Measures

Domain scores for objective cognitive test scores are displayed in Table 4 and Figure 2. In individuals, impairment according to cognitive testing (<–1.5 SD below norms) ranged from 17.7% ($n = 42$) for processing speed to 46.0% ($n = 109$) for delayed recall. On a group level, patients with oligodendroglioma had clinically relevant impairment ($Z \leq -1.5$) in verbal episodic memory (free recall and delayed recall). Checked against a tool which uses Monte Carlo simulation to estimate false positive rates in cognitive impairment research,[44] these impairment rates are greater than expected based on chance.

Associations between cognitive functioning and clinical factors.

Free recall performance was worse in patients older at diagnosis, those who had ever had radiotherapy treatment, and those who had been treated a longer time ago (univariable analyses, $P < 0.10$). The multivariable model

Sociodemographic and Clinical Characteristics	
	Participants (*N* = 237)
Age at study participation M (SD), range[A]	52.2 (11.8), 23-78
Sex *N* (%)	
Male	144 (60.8%)
Female	93 (39.2%)
Level of education *N* (%)	
Below University degree	118 (49.8%)
Above University degree	115 (48.5%)
Missing	4 (1.7%)
Marital status *N* (%)	
Married or with partner	164 (69.2%)
Single	37 (15.6%)
Divorced	26 (11.0%)
Widow(er)	2 (0.8%)
Missing	2 (0.8%)
Country *N* (%)	
France	96 (40.5%)
United Kingdom	47 (19.8%)
Germany	42 (17.7%)
Sweden	23 (9.7%)
Czech Republic	11 (4.6%)
Denmark	8 (3.4%)
Italy	5 (2.1%)
Switzerland	4 (1.7%)
Greece	1 (0.4%)
Time since diagnosis (months) Mean (SD), range	118.52 (50.90), 60-310
Age at diagnosis (years) Mean (SD), range	42.75 (11.53) 17.58-71.25
WHO CNS grade per local assessment *N* (%)	
Grade 2	118 (49.8%)
Grade 3	119 (50.2%)
Tumour lateralization *N* (%)	
Left	106 (44.5%)
Right	101 (42.6%)
Both	10 (4.2%)
Missing	9 (3.8%)
Tumour location *N* (%)	
Frontal	136 (57.4%)
Temporal	33 (13.9%)
Parietal	20 (8.4%)
Occipital	2 (0.8%)
Mix (frontal/temporal/parietal/occipital)	35 (14.8%)
Midline	3 (1.3%)
Cerebellum	1 (0.4%)
Missing	1 (0.4%)
Initial treatment *N* (%)	
Biopsy only	1 (0.4%)
Resection only	91 (38.4%)
Biopsy and chemotherapy	
Biopsy + PCV	2 (0.8%)

Continued

	Participants (*N* = 237)
Resection and chemotherapy	
Resection + temozolomide	14 (5.9%)
Resection + PCV	16 (6.8%)
Resection + temozolomide + PCV	1 (0.4%)
Biopsy and radiotherapy	
Biopsy + radiotherapy	1 (0.4%)
Resection and radiotherapy	
Resection + radiotherapy	23 (9.7%)
Biopsy, chemotherapy, and radiotherapy	
Biopsy + PCV + radiotherapy	2 (0.8%)
Resection, chemotherapy, and radiotherapy	
Resection + temozolomide + radiotherapy	23 (9.7%)
Resection + PCV + radiotherapy	51 (21.5%)
Resection + temozolomide + PCV + radiotherapy	3 (1.3%)
Chemotherapy only	
PCV	1 (0.4%)
Temozolomide	3 (1.3%)
Radiotherapy only	
Radiotherapy	2 (0.8%)
Chemotherapy and radiotherapy	
Radiotherapy + PCV	2 (0.8%)
Radiotherapy + temozolomide	1 (0.4%)
Number of recurrences *N* (%)	
0	97 (40.9%)
1	77 (32.5%)
2	56 (23.6%)
3	4 (1.7%)
4	1 (0.4%)
5	2 (0.8%)
Further treatment *N* (%)	
None	95 (40.1%)
Resection	13 (5.5%)
Radiotherapy	7 (2.9%)
Chemotherapy (any)	32 (13.5%)
Resection + chemotherapy (any)	21 (8.9%)
Resection + radiotherapy	3 (1.3%)
Radiotherapy + chemotherapy (any)	29 (12.2%)
Chemotherapy (any) + immunotherapy	1 (0.4%)
Resection + chemotherapy (any) + radiotherapy	32 (13.5%)
Chemotherapy (any) + radiotherapy + immunotherapy	1 (0.4%)
Resection + radiotherapy + chemotherapy (any) + immunotherapy	3 (1.3%)
Current treatment *N* (%)	
Chemotherapy	29 (12.2%)
Radiotherapy	3 (1.3%)
Radiotherapy + chemotherapy	2 (0.8%)
Immunotherapy/vaccine	2 (0.8%)

Continued

	Participants (***N*** = 237)
Bevacizumab	2 (0.8%)
Ever treated with radiotherapy *N* (%)	
No	63 (26.6%)
Yes	174 (73.4%)
Cumulative dose (*available from n = 140*) M (SD), range	M = 59.4 (sd = 12.01), 20-120
Ever treated with chemotherapy *N* (%)	
No	26 (11.0%)
Yes	211 (89.0%)
Temozolomide	108 (44.6%)
PCV	151 (62.4%)
Disease status at time of assessment *N* (%)	
Stable, no treatment	185 (78.1%)
Active, undergoing or planning for treatment	45 (19.0%)
Missing	7 (3.0%)
Current medication *N* (%)	
Antidepressants	24 (10.1%)
Antiseizure medication	141 (59.5%)
Dexamethasone	4 (1.7%)
Anxiolytics or sedatives	18 (7.6%)
Antipsychotic	3 (1.3%)
KPS[b] Median, range	90, 40-100

[a]Three missing.
[b]Ten missing.
[c]Two missing.
Abbreviations: CNS, central nervous system; KPS, Karnofsky performance status; PCV, procarbazine, lomustine, and vincristine; WHO, World Health Organization.

includes age at diagnosis and radiotherapy ($r^2 = 0.011$, $P = 0.050$; posthoc analysis for dose of radiotherapy $P =$ n.s.). At univariable level (Supplementary Table 1), delayed recall scores were associated with age at diagnosis, and radiotherapy treatment($P < 0.10$). The association between worse delayed recall and age at diagnosis and radiotherapy treatment remained significant ($P < 0.05$) in the multivariable model ($r^2 = 0.118$, $P = 0.022$; posthoc analyses for dose of radiotherapy and type of chemotherapy $P =$ n.s,). Delayed recognition was worse in patients who were older at diagnosis, and those who had ever had radiotherapy (univariable analyses, $P < 0.10$). The associations between worse delayed recognition and age at diagnosis and radiotherapy remained significant ($P < 0.05$) in the multivariable model ($r^2 = 0.064$, $P = 0.014$; posthoc analysis for dose of radiotherapy $P =$ n.s.). Verbal fluency was worse in those older at diagnosis, those diagnosed a longer time ago, those with left sided tumours, those treated with radiotherapy, and those longer since treatment (univariable analyses, $P < 0.10$). In the multivariable model, age at diagnosis, time since diagnosis, and radiotherapy remained associated ($r^2 = 0.121$, $P = 0.001$; post hoc analysis for dose of radiotherapy $P =$ n.s). Processing speed was worse in patients older at diagnosis and those diagnosed longer ago and those longer since treatment (univariable analyses, $P < 0.10$). Associations between processing speed and age at diagnosis, and time since diagnosis remained significant in the multivariable model ($r^2 = 0.119$, $P < 0.001$). At univariable level, switching executive functioning appeared worse in patients older at diagnosis, those diagnosed longer ago, those treated with radiotherapy and those treated longer ago ($P < 0.10$). The multivariable model with best fit included age at diagnosis, time since diagnosis, and radiotherapy ($r^2 = 0.103$, $P < 0.001$, posthoc analysis for dose of radiotherapy $P =$ n.s.).

Discussion

To date, most studies on long-term HRQOL and cognitive outcomes have reported on heterogeneous samples of patients with glioma, lacking detailed data on the subgroup of oligodendroglioma, IDH-mutant, and 1p/19q-codeleted grades 2 and 3 as defined by the fifth WHO CNS classification. For these patients, with comparably favorable prognosis and novel treatment options arising, long-term outcomes are of special importance. The results of the

Health-related Quality of Life (Impairment on EORTC QLQ-C30 Scales According to Giesinger et al.[41])		
	Participants	Outcome
Patient-reported outcome measures		
Health-related quality of life		
EORTC QLQ-C30		
Global health status	*N* = 234	*M* = 66.65, SD = 23.03
Physical functioning	*N* = 232	*M* = 81.02, SD = 20.83
Score < 83 (impaired)		*n* = 96, 40.5%
Role functioning	*N* = 233	*M* = 76.54, SD = 28.37
Score < 58 (impaired)		*n* = 52, 21.9%
Emotional functioning	*N* = 234	*M* = 68.85, SD = 24.95
Score < 71 (impaired)		*n* = 118, 49.8%
Cognitive functioning	*N* = 233	*M* = 65.81, SD = 27.75*
Score < 75 (impaired)		*n* = 133, 56.1%
Social functioning	*N* = 234	*M* = 71.94, SD = 30.03*
Score < 58 (impaired)		*n* = 67, 28.3%
Fatigue	*N* = 233	*M* = 40.34 SD = 25.92*
Score > 39 (impaired)		*n* = 107, 45.1%
Nausea/vomiting	*N* = 231	*M* = 6.20, SD = 13.27
Score > 8 (impaired)		*n* = 56, 23.6%
Pain	*N* = 233	M = 20.39, SD = 26.45
Score > 25 (impaired)		*n* = 77, 32.5%
Dyspnea	*N* = 232	*M* = 16.81, SD = 26.86
Score > 17 (impaired)		*n* = 80, 33.8%
Sleep disturbances	*N* = 233	*M* = 35.77, SD = 35.27*
Score > 50 (impaired)		*n* = 73, 30.8%
Appetite loss	*N* = 231	*M* = 10.39, SD = 23.00
Score > 50 (impaired)		*n* = 20, 8.4%
Constipation	*N* = 234	*M* = 16.67, SD = 27.67
Score > 50 (impaired)		*n* = 29, 12.2%
Diarrhoea	*N* = 233	*M* = 7.89, SD = 16.95
Score > 17 (impaired)		*n* = 47, 19.8%
Financial impact	*N* = 234	*M* = 21.08, SD = 32.71*
Score > 17 (impaired)		*n* = 82, 34.6%
EORTC BN20		
Future uncertainty	*N* = 231	*M* = 30.48, SD = 23.91
Visual deficits	*N* = 232	*M* = 11.09, SD = 18.45
Motor dysfunction	*N* = 232	*M* = 17.94, SD = 22.12
Communication deficit	*N* = 232	*M* = 26.87, SD = 27.71
Headache	*N* = 231	*M* = 22.66, SD = 30.80
Seizures	*N* = 232	*M* = 6.61, SD = 21.81
Drowsiness	*N* = 231	*M* = 31.60, SD = 31.96
Bothered by hair loss	*N* = 232	*M* = 13.65, SD = 27.40
Bothered by itching skin	*N* = 231	*M* = 13.13, SD = 25.17
Weakness of legs	*N* = 230	*M* = 13.04, SD = 25.00
Difficulty controlling bladder	*N* = 232	*M* = 15.66, SD = 28.41
MOS-Cog		
Cognitive concerns	*N* = 222	*M* = 67.62, SD = 19.87
All item scores < 60: concerns present		22 (9.3%)

[a]≥10 point difference compared to general population norms.[42]

Abbreviations: EORTC BN20, European Organisation for Research and Treatment of Cancer Brain Neoplasm 20; EORTC QLQ-C3, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; M = mean; Mos-Cog, Medical Outcomes Study Cognitive functioning scale; *n*, number of cases; SD, standard deviation.

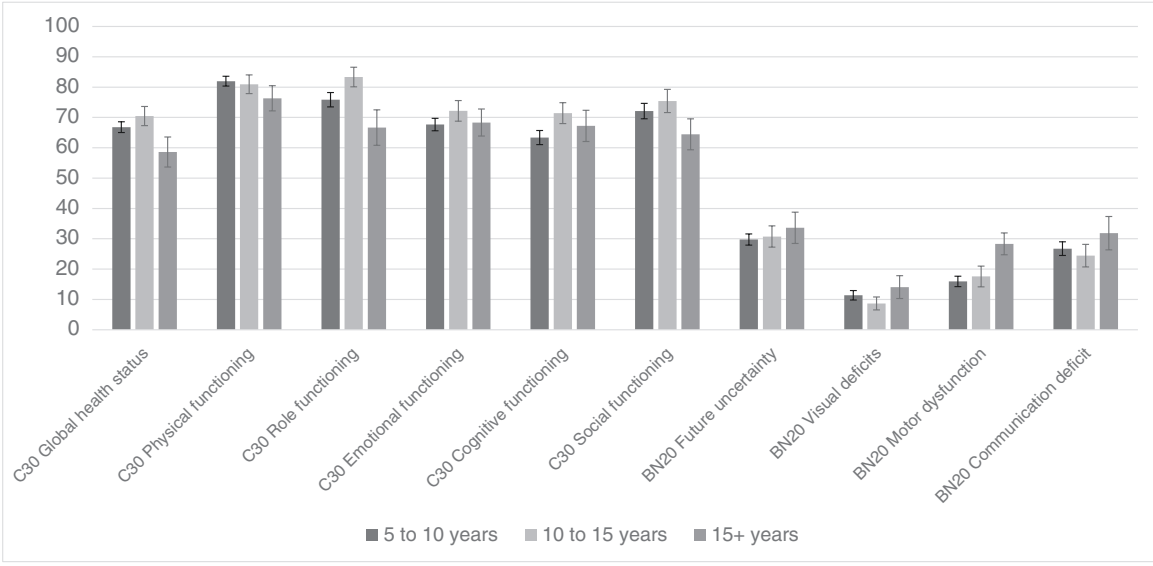
Final Regression Models Showing Associations between HRQOL and Cognitive Outcomes, and Clinical Variables

Regression models		*B*	95% CI	Model R^2	*P*-value
Dependent variable	Independent variables				
EORTC QLQ-C30					
Global health status				0.025	<0.001
	Radiotherapy	−8.247	−12.361 to 1.001		0.095
	Antidepressants	−5.680	−18.150 to 1.657		0.102
Physical functioning				0.119	<0.001
	Age at diagnosis	−0.513	−0.737 to −0.290		<0.001
	Radiotherapy	−6.887	−12.726 to −1.049		0.021
	Antiseizure medication	−7.183	−12.400 to −1.967		0.007
Role functioning				0.081	<0.001
	Age at diagnosis	−0.391	−0.705 to −0.077		0.015
	Radiotherapy	−9.868	−18.032 to −1.704		0.018
	Antidepressants	−19.672	−31.873 to −7.471		0.002
Cognitive functioning				0.040	<0.001
	Age at diagnosis	−0.278	−0.597 to 0.042		0.088
	Current disease status	10.413	1.213 to 19.614		0.027
Emotional functioning				0.048	<0.001
	Current disease status	7.929	−0.243 to 16.102		0.057
	Antidepressants	−15.946	−27.095 to −4.796		0.005
Social functioning				0.028	<0.001
	Radiotherapy	−7.661	−16.363 to 1.041		0.084
	Antidepressants	−11.501	−24.400 to 1.398		0.080
EORTC BN20					
Future uncertainty				0.032	0.007
	Number of recurrences	4.505	1.254 to 7.757		
Visual deficits				0.015	0.070
	Current disease status	−5.674	−11.820 to 0.472		
Motor dysfunction				0.105	0.029
	Time since diagnosis	0.070	0.015 to 0.125		0.013
	Current disease status	−8.778	−15.693 to −1.864		0.013
	Radiotherapy	8.246	2.005 to 14.487		0.010
	Antidepressants	9.186	−0.254 to 18.627		0.056
Communication deficits				0.084	<0.001
	Current disease status	−10.162	−20.187 to −0.137		0.047
	Antidepressants	16.256	4.064 to 28.449		0.009
	Time since last intervention (months)	0.087	0.001 to 0.173		0.048
MOS-Cog					
	Age at diagnosis	−0.345	−0.569 to −0.122	0.040	0.003
HVLT-R					
Free recall				0.110	0.050
	Age at diagnosis	−0.048	−0.068 to −0.029		<0.001
	Radiotherapy	−0.667	-1.178 to -0.156		0.011
Delayed recall				0.118	0.022
	Age at diagnosis	−0.052	-0.073 to −0.032		<0.001
	Radiotherapy	−0.705	−1.239 to −0.172		0.010
Delayed recognition				0.064	0.014
	Age at diagnosis	−0.031	−0.049 to −0.012		0.001
	Radiotherapy	−0.623	−1.108 to −0.139		0.012

Continued

Regression models		*B*	95% CI	Model R^2	*P*-value
COWAT					
Verbal fluency				0.121	0.001
	Time since diagnosis	−0.003	−0.007 to 0.000		0.051
	Age at diagnosis	−0.003	−0.051 to -0.022		<0.001
	Radiotherapy	-0.484	−0.870 to −0.098		0.014
TMT					
Processing speed				0.119	<0.001
	Time since diagnosis	−0.009	−0.013 to −0.005		<0.001
	Age at diagnosis	−0.041	−0.061 to −0.021		<0.001
Switching executive functioning				0.103	<0.001
	Time since diagnosis	−0.006	−0.010 to −0.001		0.009
	Age at diagnosis	−0.038	−0.057 to −0.019		<0.001
	Radiotherapy	−0.547	−1.048 to −0.045		0.033

Abbreviations: B, beta; CI, confidence interval; COWAT, controlled oral word association test; EORTC BN20 European Organisation for Research and Treatment of Cancer Brain Neoplasm 20; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HVLT-R, Hopkins Verbal Learning Test-Revised; KPS, Karnofsky Performance Status; Mos-Cog, Medical Outcomes Study Cognitive functioning scale; R^2, *R* square; TMT, Trail Making Test. For disease status, the reference category is "stable, no treatment.".



HRQOL Functioning Scale Scores with Standard Errors for Subgroups of Time Since Diagnosis (5-10 years: *N* = 147; 10-15 years: *N* = 57; 15+ years: *N* = 30).

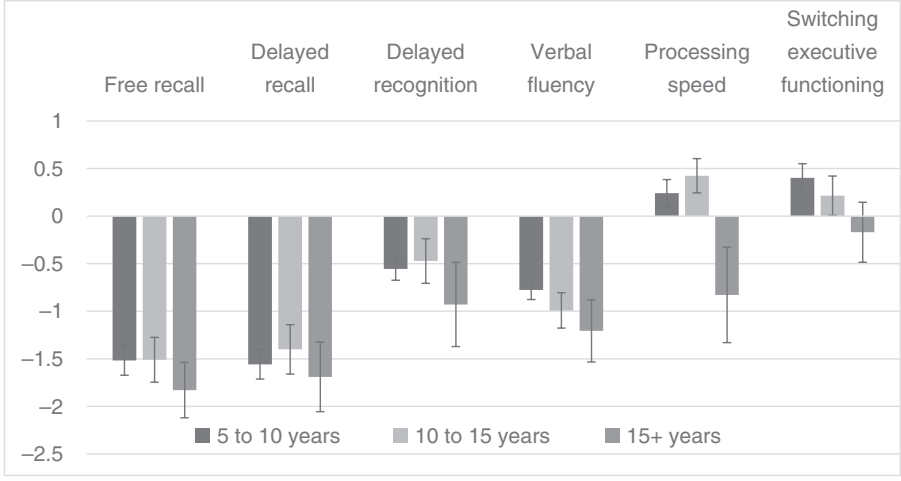
present study will provide valuable context for assessing the potential impact of new treatments on long-term functioning of patients with oligodendroglioma.

In our sample of 237 patients on average 10 years after diagnosis (range, 5-28 years), we found clinically relevant levels of HRQOL impairment related to cognitive, emotional, and physical functioning, as well as fatigue, in over 40% of patients. Patients' cognitive and social functioning, fatigue, sleep disturbances, and financial impact were poorer on a group level compared to general population norms.[42] Regarding neuropsychological test performance, objective scores on an episodic verbal memory test were impaired on a group level, and across all domains 18% to 46% of patients experienced clinically relevant impairment. Whilst there are currently no existing thresholds for defining clinical importance for disease-specific HRQOL

Cognitive Functioning Outcomes

	Participants	Outcome
Cognitive functioning		
HVLT-R (Episodic verbal memory)		
Free recall; encoding and retrieval	*N* = 223	*M* = −1.56, SD = 1.77
Score < −1.5 (impaired)		*n* = 101 (42.6%)
Delayed recall; consolidation	*N* = 221	*M* = −1.54, SD = 1.86
Score < −1.5 (impaired)		*n* = 109 (46.0%)
Delayed recognition; storing	*N* = 223	*M* = −0.59, SD = 1.64
Score < −1.5 (impaired)		*n* = 45 (19.0%)
COWAT		
Verbal fluency; initiation	*N* = 224	*M* = −0.88, SD = 1.34
Score < −1.5 (impaired)		*n* = 70 (29.5%)
TMT		
Part A: Processing speed	*N* = 218	*M* = 0.14, SD = 1.81
Score < −1.5 (impaired)		*n* = 42 (17.7%)
Part B: Switching executive functioning	*N* = 216	*M* = 0.29, SD = 1.69
Score < −1.5 (impaired)		*n* = 49 (20.7%)

Abbreviations: COWAT, controlled oral word association test; HVLT-R, Hopkins Verbal Learning Test-Revised; *M*, mean; *n*, number of cases; SD, standard deviation; TMT, Trail Making Test.



Cognitive Domain *Z*-scores with Standard Errors for Subgroups of Time Since Diagnosis (5-10 years: *N* = 141; 10-15 years: *N* = 53; 15+ years: *N* = 30).

(EORTC BN20), and whilst not compared to a control group, the scores of our patient sample on future uncertainty appear high, and seizure burden appears low, compared to cohorts of low-grade glioma patients, assessed on average 6,[45,46] 12,[46] and 26 years postdiagnosis.[47] It appears that seizure burden can decrease over time,[47] possibly indicating better management with antiseizure medication or psychological adjustment to seizures. In our sample, future uncertainty increased with greater number of recurrences experienced, reflecting the psychological burden of this incurable disease on patients. Similar HRQOL issues were also noted in a systematic review of patients with grades 2 and 3 glioma, at least 2 years after diagnosis.[16]

Of the clinical factors explored, it appears that higher age at diagnosis, active disease status, radiotherapy (regardless of cumulative dose), and antidepressant medication use are associated with worse HRQOL outcomes.

Antidepressant use is known to be high in glioma populations,[48] and could be a proxy for mood issues, which are common in glioma survivorship and strongly related to HRQOL.[16,30] In our study, mood was also assessed and will be reported on separately. In this investigation, we found no clear links between chemotherapy and HRQOL or cognitive outcomes. The literature is divided on whether chemotherapy treatment in adults is associated with cognitive deficits,[49–51] although it does appear most consistently linked to impairment in memory and executive functioning.[52] There is reason to believe different chemotherapies can impact on cognitive functioning differently,[51] hence we had planned to do posthoc analyses for type of chemotherapy upon any significant univariable associations with HRQOL or cognitive outcomes. Generally, radiotherapy is more consistently associated with cognitive deficits in patients with glioma,[23,53] typically demonstrating a radiotherapy dose dependency.[22] In part, we may not have found a link to either chemotherapy or cumulative dose of radiotherapy in posthoc analyses due to the limited variation in our sample: for example, >70% had received radiotherapy, and the cumulative dose delivered remained under 60 Gy for the vast majority of participants. Only 11% of participants had never had chemotherapy, and over the years 21.5% received both temozolomide and PCV. Those older at diagnosis and treated a longer time ago, tended to perform worse on cognitive tests. Age is only inconsistently linked to cognitive performance in patients with brain tumors,[24] but our findings are in line with other studies demonstrating late cognitive effects of antitumour treatment.[23,24] It should be noted that our models explained a modest % of variance (between 1.5% and 14%), indicating limited explanatory value.

Strengths of this study include the relatively large sample size of patients with confirmed oligodendroglioma diagnosed >5 years ago, and the wealth of patient-centered and clinical outcomes collected. We were able to undertake this study because of the strong collaborative EORTC network, recruiting participants from 33 centers across 9 countries. Of note, not all 9 countries were represented equally, with >75% of the data collected from 3 countries (France, United Kingdom, Germany). To enhance feasibility of data collection (languages; participant burden) we have used a modest cognitive testing battery which presents a limitation. A limitation is the cross-sectional nature of the study precluding the investigation of changes over time. We concentrated on patients who were at least 5 years from diagnosis which may have introduced survivor bias. Some recruitment bias may exist in that patients who were not well enough to participate, may have declined—it should thus be noted that the data presented likely overestimate HRQOL and cognitive outcomes of the population. Moreover, participants generally had high education levels. In our regression models, we were unable to include all potentially relevant factors such as tumour volume, and specific tumour location. The high number of treatment modalities used in this sample, in various combinations and different timepoints in the disease trajectory, must be noted. This is partly attributed to the broad inclusion criteria which highlights the good external validity of our findings, but also the large number of sites and countries contributing data. Moreover, the lack of consensus on the best first-, second-, or third-line treatment during the decades in which the patients were treated, likely contributed to centers using their own treatment protocols based on their best practice and interpretation of the evidence-base at the time. With the current treatment guidelines of ASCO, SNO, and EANO,[8,9] future prospective studies may hopefully report on groups of patients with oligodendroglioma treated more uniformly.

In conclusion, our study demonstrates that HRQOL and cognitive issues are prevalent in patients with oligodendroglioma at least 5 years after diagnosis. In this cross-sectional investigation, where patients were recruited from 9 countries and various treatment regimens were employed, we found associations between radiotherapy treatment and long-term HRQOL outcomes, most convincingly in physical/motor functioning, and cognitive outcomes. Prospective studies remain needed, and we stress the importance of consistently assessing HRQOL and cognitive outcomes in clinical practice and treatment trials. Still, the results from the current investigation may be useful to compare against any late effects of therapies currently being trialled—or active trials that investigate the role of delaying radiotherapy. Even years into follow-up patients might benefit from proactively offered supportive care and rehabilitation, ideally as part of organised comprehensive survivorship care.

Supplementary material

Supplementary material is available online at *Neuro-Oncology* (https://academic.oup.com/neuro-oncology).

Keywords

cognition | health-related quality of life | low-grade glioma | oligodendroglioma | survivorship

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Conceptualization: FB, MW, MK
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Investigation: All authors
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Previous dissemination

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Remaining authors declared none.

Data Availability

The data that support the findings of this study are available from the corresponding author (F.W.B.) or the EORTC Quality of Life group, upon reasonable request and following appropriate agreements.

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