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Factors associated with health-related quality of life (HRQoL) deterioration in glioma patients during the progression-free survival period

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Abstract

Background. Maintenance of functioning and well-being during the progression-free survival (PFS) period is important for glioma patients. This study aimed to determine whether health-related quality of life (HRQoL) can be maintained during progression-free time, and factors associated with HRQoL deterioration in this period.

Methods. We included longitudinal HRQoL data from previously published clinical trials in glioma. The percentage of patients with stable HRQoL until progression was determined per scale and at the individual patient level (i.e. considering all scales simultaneously). We assessed time to a clinically relevant deterioration in HRQoL, expressed in deterioration-free survival and time-to-deterioration (the first including progression as an event). We also determined the association between sociodemographic and clinical factors and HRQoL deterioration in the progression-free period.

Results. Five thousand five hundred and thirty-nine patients with at least baseline HRQoL scores had a median time from randomization to progression of 7.6 months. Between 9–29% of the patients deteriorated before disease progression on the evaluated HRQoL scales. When considering all scales simultaneously, 47% of patients deteriorated on ≥1 scale. Median deterioration-free survival period ranged between 3.8–5.4 months, and median

time-to-deterioration between 8.2–11.9 months. For most scales, only poor performance status was independently associated with clinically relevant HRQoL deterioration in the progression-free period.

Conclusions. HRQoL was maintained in only 53% of patients in their progression-free period, and treatment was not independently associated with this deterioration in HRQoL. Routine monitoring of the patients' functioning and well-being during the entire disease course is therefore important, so that interventions can be initiated when problems are signaled.

Key Points

- Almost half of the included patients experienced a deterioration in HRQoL during their progression-free survival time.
- Only WHO PS was associated with HRQoL deterioration at a statistically significant and clinically relevant level.
- Allocated treatment was not independently associated with HRQoL deterioration during the progression-free period.

Importance of the Study

Although the results of most randomized controlled trials performed in glioma patients indicate that new treatments do not improve overall survival, they have shown to prolong the period of progression-free survival. For patients, it is crucial that their level of functioning and well-being is maintained during that progression-free period. Results of our study showed that almost half of the 5539 included patients experienced a deterioration in health-related quality of life during their progression-free survival time. Only WHO performance status was found to be associated with health-related quality of life deterioration at a statistically significant and clinically relevant level, whereas allocated treatment was not independently associated with health-related quality of life deterioration during the progression-free period. In addition, we used two time-to-event models (deterioration-free survival and time-to-deterioration), that can be used to gain insight into the role of progression as a cause of HRQoL deterioration

Adult patients with a malignant glioma are confronted with the outlook of a limited survival span, along with an increasing symptom burden.[1] The incurable nature of gliomas has led to the recognition that maintenance or improvement of health-related quality of life (HRQoL) is one of the main treatment goals in this patient group. Although the results of most randomized controlled trials (RCTs) performed in glioma patients indicate that new treatments do not improve overall survival, they have shown to prolong the period of progression-free survival.[2–6] For patients, it is crucial that their level of functioning and well-being is maintained during that progression-free period, as it is important that patients can spend the limited time they have in good quality.

Although the HRQoL of glioma patients is often already impaired at diagnosis when compared to the general population,[7–9] both treatment and disease progression may cause a further deterioration in HRQoL.[8,10,11] For various stakeholders, including drug developers, regulatory agencies, and physicians, it is important to be able to understand the impact of the treatment under investigation (possible adverse effects) on the patients' functioning and well-being, independent of the effect of the disease. In recent years, several statistical models such as time-to-event models have been proposed to better evaluate the impact of treatment on HRQoL in oncology trials.[12,13] For HRQoL outcomes, the concepts "deterioration-free survival" and "time-to-deterioration" have been used to describe the time to HRQoL deterioration. In this case, deterioration-free survival reflects the time to deterioration in HRQoL, disease progression, or death, whereas the concept time-to-deterioration excludes progressive disease as an event, and thus better reflects the possible impact of the adverse effects caused by the treatment on aspects of HRQoL (see Figure 1 for an illustration of the concepts).

The primary aim of the current study was to determine whether the HRQoL of glioma patients can be maintained during the progression-free period. In addition, we investigated which sociodemographic and clinical factors were independently associated with a deterioration in HRQoL during the progression-free period.

Methods

Study Population

This study is part of the CODAGLIO (i.e. *CO*mbining clinical trial *DA*tasets in *GLIO*ma) project, in which a database was created that included HRQoL data of individual glioma patients from previously published phase II and III RCTs (Supplementary Table 1). Sociodemographic and

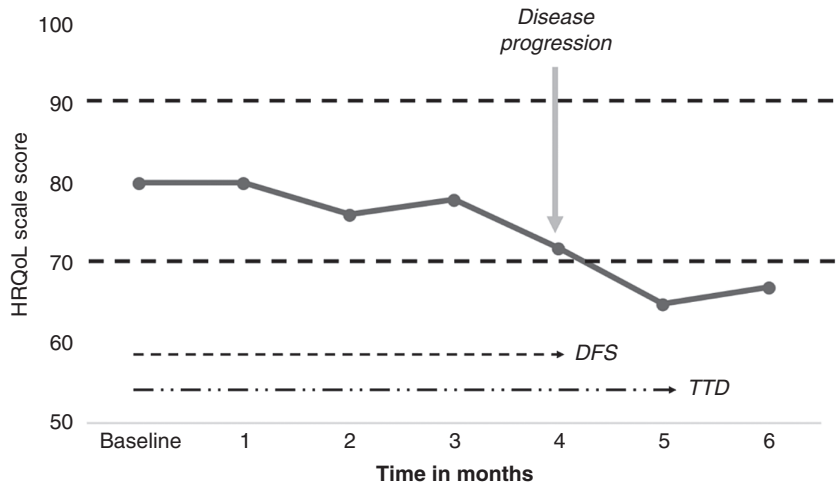

Fig. 1 Illustration of the concepts deterioration-free survival (DFS) and time-to-deterioration (TTD) for one hypothetical patient. DFS period was defined as the time to a ≥10-point deterioration (clinically meaningful change) in the HRQoL score from baseline without a subsequent ≥10-point improvement in score compared with baseline, *or* progressive disease, *or* death in the absence of a previous definitive deterioration before the next assessment. TTD was defined similarly to deterioration-free survival, with the exception that progressive disease was excluded as an event. For this hypothetical patient, HRQoL was measured monthly. At month 4, the patient had disease progression, resulting in a DFS period of 4 months. Since the HRQoL score was not ≥10 points below the baseline score of 80 at the time of progression (i.e. dashed line at 70), TTD was not yet reached. The TTD period in this example was 5 months, when the HRQoL score was below 70 points, a more than 10 point decrease compared to baseline, without a subsequent improvement. For this patient, these findings indicate that the treatment under investigation was not the main reason for HRQoL deterioration.

clinical variables that were available in all RCTs included: tumor type (World Health Organisation [WHO] grade II or III astrocytoma, oligodendroglioma, and oligoastrocytoma [all classified as non-glioblastoma], or grade IV [classified as glioblastoma]), age, sex, disease stage (newly diagnosed versus recurrent), WHO Performance Status (PS; 0 versus 1 versus 2), and prior resection (yes versus no).

HRQoL

In all included trials, HRQoL was assessed with the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) version 3.0,[14] and the EORTC brain cancer-specific QLQ-BN20.[15,16] The EORTC QLQ-C30 questionnaire consists of 30 items, comprising five functional scales, three symptom scales, a global health status scale, and six single-item scales. The QLQ-BN20 consists of 20 items, comprising four symptom scales and seven single-item symptoms. Raw item scores are linearly transformed to a 0 to 100 scale.[17] A clinically relevant change in HRQoL was defined as a change of ≥10 points on a scale, which is generally considered to reflect the minimum clinically important difference.[18] All evaluated scales were included in the analysis. Patients who completed at least one HRQoL scale at baseline were included in the study sample.

Descriptive Statistics

Descriptive statistics were used to report HRQoL scores as well as the sociodemographic and clinical characteristics of the eligible patients. Adherence to HRQoL assessments over time was calculated as the number of forms received divided by the number of forms expected at every assessment point. Importantly, patients who completed the assessments at the time of disease progression were included in the analysis. In the included RCTs, disease progression was defined by means of the Response Assessment in Neuro-Oncology (RANO) Criteria or MacDonald criteria.[19,20]

Maintenance of HRQoL During the Progression-Free Period

To evaluate if HRQoL was maintained during the progression-free period, the percentage of patients with a clinically meaningful deterioration in HRQoL scores during this period (i.e., any deterioration of ≥10 points on any scale at any follow-up assessment before disease progression) was calculated both at the scale level (i.e., the percentage of patients with HRQoL deterioration per scale) and at the individual patient level (percentage of patients with HRQoL deterioration on at least one scale, considering all 26 scales simultaneously).

Factors Associated With HRQoL Deterioration

We used linear mixed models (LMMs) with a first-order factor analytic covariance structure to evaluate which factors were independently associated with HRQoL deterioration during the progression-free survival period. LMM assumptions were assessed graphically, and potential

multicollinearity was investigated with Spearman-rank correlation coefficients and Variance inflation factor (VIF) analysis. HRQoL assessments were included until the moment more than 40% of the expected HRQoL questionnaires was missing. The factors considered in the LMMs were: age, WHO PS, sex, surgery, tumor type, and allocated treatment (radiotherapy [RT monotherapy], chemotherapy [chemo monotherapy], radiotherapy and chemotherapy combined [RT and chemo], radiotherapy and angiogenesis inhibitors combined [RT and angio], radiotherapy combined with chemotherapy and angiogenesis inhibitors [RT and chemo and angio], chemotherapy and angiogenesis inhibitors combined (CT and angio), and chemotherapy and TFF combined [CT and TTF]). LMM results are presented for the global health scale and two commonly preselected functioning scales in the original RCTs (physical functioning and role functioning), as well as the three most prevalent symptoms in this sample. Results of the other scales are described in the Supplementary Material.

A heatmap was created to visualize the distribution of patients with and without HRQoL deterioration during their progression-free period, in relation to their sociodemographic/clinical and treatment characteristics. This heatmap allows a visual inspection of which factors were associated with a specific pattern in change in HRQoL scores during the progression-free period.

Deterioration-Free Survival and Time-to-Deterioration

The deterioration-free survival period was defined as the time to a ≥10-point deterioration (in general considered to be a clinically meaningful change[18] and chosen because minimally important differences [MIDs] are available for the EORTC QLQ-C30 scales in glioma, but not for the QLQ-BN20 scales) in a HRQoL scale score from baseline without a subsequent ≥10-point improvement in score compared with baseline *or* progressive disease, *or* death in the absence of a previous deterioration before the next assessment.[10] Data were censored at the last HRQoL assessment date for patients with a change of <10 points, for patients who did not have disease progression, or for patients who died more than 9 weeks after the last HRQoL assessment. Time-to-deterioration was defined similarly to deterioration-free survival, with the exception that progressive disease was excluded as an event (i.e., non-missing HRQoL data beyond progression, if available, were included) (Figure 1).[10]

We first computed median deterioration-free survival and time-to-deterioration for each HRQoL scale in all individual RCTs. This analysis allowed us to determine the proportion of trials in which time-to-deterioration was longer than deterioration-free survival, per HRQoL scale. Next, all studies were combined and the median deterioration-free survival and time-to-deterioration per HRQoL scale were calculated. In addition, the relative proportion of events classified as (deterioration due to) progression, HRQoL deterioration in the absence of disease progression, and death (whichever occurred first) in deterioration-free survival was calculated. This provided information on the role of progression as cause of HRQoL deterioration. Kaplan-Meier methodology was used to estimate deterioration-free survival and time-to-deterioration distributions and median times. The 95% confidence intervals (CIs) were computed using the Greenwood formula.[21]

IBM SPSS Statistics and R were used for all statistical analyses.[22,23] *P*-values <.05 were considered to be statistically significant.

Results

Out of the 6048 patients included in the CODAGLIO database, 5539 (91%) patients were eligible for the current study at baseline. Over time, compliance with HRQoL data dropped to 4473 (81%) for follow-up assessment 2 until 3076 (57%) for follow-up assessment 4 (Table 3). Because of the low compliance at later follow-up (<60%), analyses were truncated to follow-up assessment 4. In this subgroup, 64% of the patients were diagnosed with glioblastoma, the mean age was 54 years, and 89% of the patients had a relatively good (0 or 1) WHO PS (Table 1). The median time from randomization to progression was 7.6 months for all included patients and 8.9 months for newly diagnosed patients only. Median time from randomization to death was 17.2 and 17.9 months for all included patients and newly diagnosed patients only, respectively.

Maintenance of HRQoL During the Progression-Free Period

At the scale level, the proportion of patients who deteriorated to a clinically relevant extent in HRQoL during the progression-free period ranged from 9% for seizures to 29% for drowsiness (Table 2). At the individual patient level, taking all HRQoL scales into account simultaneously, most patients did not deteriorate on any scale (53%), while 15% deteriorated on 1 to 5 scales, 18% on 6–10 scales, and 13% on more than 10 scales simultaneously (see Supplementary Figure 2 for the distribution of the number of patients deteriorating on a specific number of HRQoL scales).

Factors Associated With HRQoL Deterioration During the Progression-Free Period

Results of the LMMs did not indicate any multicollinearity between the included variables, and the correlation between the clinical and treatment-related variables was low to moderate (all below 0.32). Table 3 presents the estimates for the association between the selected variables and the global health status, physical functioning, and role functioning scale scores,[24] and the three most common symptoms in this sample (fatigue, drowsiness, and motor dysfunction).

Only poor performance status (WHO PS 2 compared to WHO PS 0) showed both a statistically significant and clinically relevant association (i.e. differences ≥10 points) with HRQoL deterioration over time for the preselected and for most of the remaining exploratory HRQoL scales. Several sociodemographic and clinical characteristics were independently associated with worse HRQoL over time at a statistically significant, but not clinically

Table 1. Baseline Clinical and Sociodemographic Characteristics of the Included Patients

	All included patients ($n = 5539$)	Newly diagnosed patients only ($n = 4665$)
Male	3381 (61)	2831 (61)
Female	2155 (39)	1832 (39)
Missing	3 (0)	2 (0)
Age (mean, SD)	54 (13)	53 (13)
Glioblastoma	3565 (64)	2845 (61)
Nonglioblastoma	1974 (36)	1820 (39)
WHO 0	2143 (39)	1840 (39)
WHO 1	2755 (50)	2278 (50)
WHO 2	615 (11)	522 (11)
Missing	26 (0)	25 (0)
Resected	4033 (73)	3904 (84)
Not resected	1348 (24)	757 (16)
Missing	158 (3)	4 (0)
AED use	1271 (23)	1058 (23)
Non-AED use	1666 (30)	1583 (34)
Missing	2602 (47)	2024 (43)
Steroid use	1802 (33)	1685 (36)
Non-steroid use	2278 (41)	2099 (45)
Missing	1459 (26)	881 (19)
Allocated treatment: RT alone	1240 (23)	1267 (27)
Allocated treatment: Chemo alone	1019 (19)	626 (13)
Allocated treatment: Angio alone	116 (2)	0 (0)
Allocated treatment: RT and chemo	1494 (28)	1531 (33)
Allocated treatment: RT and chemo and angio	759 (14)	779 (17)
Allocated treatment: Chemo and angio	373 (7)	23 (1)
Allocated treatment: TTFields alone	111 (2)	67 (2)
Allocated treatment: Chemo and TTFields	427 (8)	329 (7)

WHO, World Health Organisation; AED, antiepileptic drugs; RT, radiotherapy; TTFields, tumor treating fields

relevant level. For example, female sex (–5.8; 95% CI –6.9 to –4.7), and previous surgery (–3.6; 95% CI –5.1 to –2.1) were significantly associated with worse physical functioning over time at a statistically but not clinically relevant level (Table 3). For some scales, treatment other than radiotherapy only was associated with HRQoL deterioration at a statistically significant, but not clinically relevant level. For example, chemotherapy alone and chemotherapy and angiogenesis inhibitors were associated with physical functioning at a statistically significant but not clinically relevant level (Table 3).

Heatmap results showed no obvious pattern distinguishing patients with and without HRQoL deterioration before progression (Figure 2).

Deterioration-Free Survival and Time-to-Deterioration

Looking at the individual trials, time-to-deterioration was significantly longer than deterioration-free survival in 85-92% of the included trials, irrespective of the assessed HRQoL scales, whereas there was no significant difference between time-to-deterioration and deterioration-free survival times in 8-15% of the trials. When combining all RCTs, median deterioration-free survival ranged from 3.8 months for fatigue to 5.4 months for seizures, and median time-to-deterioration ranged from 8.2 months for fatigue to 11.9 months for seizures (Supplementary Table 2). For all scales, time-to-deterioration was longer than deterioration-free-survival (Figure 3), and the mean difference between the two outcomes was 5.0 months in favor of time-to-deterioration. Supplementary Figure 1 shows that progression had the largest share as event in deterioration-free survival analysis (49–82%), compared with HRQoL deterioration in the absence of disease progression (9–25%) or death (8–35%). The mean proportion of progression, HRQoL deterioration in the absence of progression, and death, whichever occurred first, in the deterioration-free survival analysis for all scales was 70%, 20%, and 10% respectively.

Table 2. Patients With Clinically Relevant Deteriorating HRQoL (i.e. ≥10 points) Before Progression Per Scale

HRQoL scale	Number (%) of patients with a deterioration in HRQoL before progression	Median time between deterioration in HRQoL and progression in days[a]
Global health status	936 (22.7)	167
Physical functioning	965 (23.4)	190
Role functioning	922 (22.3)	166
Emotional functioning	750 (18.2)	153
Cognitive functioning	921 (22.3)	161
Social functioning	895 (21.7)	151
Fatigue	1033 (25)	162
Nausea and vomiting	962 (23.3)	194
Pain	928 (22.5)	170
Dyspnea	784 (19)	175
Insomnia	805 (19.5)	188
Appetite loss	1011 (24.5)	194
Constipation	815 (19.7)	183
Diarrhea	603 (14.6)	178
Financial difficulties	671 (16.3)	175
Future uncertainty	643 (15.6)	135
Visual disorder	803 (19.5)	164
Motor dysfunctioning	922 (22.3)	144
Communication deficit	861 (20.9)	154
Hair loss	725 (17.6)	183
Seizures	372 (9)	169
Drowsiness	982 (28.8)	182
Headache	835 (20.2)	210
Itchy skin	983 (23.8)	180
Weakness of the legs	788 (19.1)	166
Bladder control	529 (2.8)	147

[a]Days from randomization to progression minus days from randomization to deterioration in HRQoL scale. Median days from randomization to pfs = 167 days.

Discussion

Using a large pooled dataset of individual HRQoL and sociodemographic/clinical data from previously conducted RCTs, the primary aim of this study was to evaluate whether glioma patients were able to maintain their level of functioning and well-being during their progression-free period. In addition, we aimed to determine which sociodemographic and clinical factors were independently associated with HRQoL deterioration during the progression-free period. First, our results showed that a small proportion of patients (9–29%) deteriorated on each specific HRQoL scale. However, when considering all scales simultaneously, we found that almost half of the patients (47%) deteriorated on at least one scale, with a mean of 5 scales. Thus, a considerable proportion of the patients experienced HRQoL deterioration during their progression-free period.

Next, we examined factors associated with HRQoL deterioration during this progression-free period. LMM analyses indicated that only baseline performance status was associated with a deterioration in HRQoL at a statistically significant and clinically relevant level. Compared to patients with a good performance status (WHO PS 0), those with poor performance status (WHO PS 2) had worse functioning and more symptoms at a statistically significant and also clinically relevant level. In addition to performance status, several other factors, including older age, male sex, and a diagnosis of glioblastoma, were independently associated with a deterioration in certain HRQoL scales. However, the degree of deterioration was not considered to be clinically relevant.

An important finding was that, in general, the treatment itself was not independently associated with HRQoL deterioration during the progression-free period. Our results also indicated that time-to-deterioration was longer than deterioration-free survival in the large majority (85–92%) of the included trials, suggesting the importance of disease progression as a key event driving HRQoL decline. Indeed,

Table 3. Result of the Linear Mixed Model Analyses, Showing the Association Between Several Independent Variables and the Selected HRQoL Scales

Variable	Global health status Beta (95% CI)	Physical functioning Beta (95% CI)	Role functioning Beta (95% CI)	Fatigue Beta (95% CI)	Drowsiness Beta (95% CI)	Motor dysfunction Beta (95% CI)
Baseline (n = 5539)	Ref	Ref	Ref	Ref	Ref	Ref
FU2 (n = 4473, 81%)	.1 (–.7 to .9)	4.5 (4.1 to 5.6)*	–8 (–.3 to 1.9)	–2.4 (–3.3 to –1.5)*	–2.6 (–3.6 to 4.4)	–2.3 (–3.1 to –1.6)*
FU3 (n = 3751, 69%)	–2.0 (–2.8 to 1.1)*	.9 (.2 to 1.5)*	–1.2 (–2.3 to –.1)*	2.6 (1.7 to 3.5)*	2.5 (1.4 to 3.5)*	–.9 (–1.7 to –.2)*
FU4 (n = 3076, 57%)	–1.0 (–1.8 to –.2)	.2 (–.5 to.9)	–.2 (–1.0 to 1.3)	1.5 (.6 to 2.4)*	1.6 (.5 to 2.6)*	–.6 (–1.4 to 1.5)
Age < 41	Ref	Ref	Ref	Ref	Ref	Ref
Age 41–64	–8.3 (–10.1 to –6.5)*	–8.3 (–10.2 to –6.5)*	–9.1 (–11.6 to –6.5)*	5.9 (3.8 to 7.9)*	3.4 (1.5 to 5.3)*	3.7 (2.1 to 5.2)
Age > 64	–5.1 (–6.6 to –3.6)*	–3.6 (–5.1 to –2.1)*	–4.8 (–6.9 to –2.7)*	3.2 (1.5 to 4.9)*	6.6 (4.3 to 8.8)*	8.1 (6.2 to 9.9)*
Male	Ref	Ref	Ref	Ref	Ref	Ref
female	–1.8 (–2.9 to –.7)*	–5.8 (–6.9 to –4.7)*	–2.1 (–3.7 to –.6)*	5.4 (4.1 to 6.6)*	2.3 (1.0 to 3.7)*	2.3 (1.1 to 3.4)*
Biopsy only	Ref	Ref	Ref	Ref	Ref	Ref
Surgery	–3.2 (–4.6 to –1.7)*	–3.6 (–5.1 to –2.1)*	–4.8 (–6.9 to –2.7)*	3.9 (2.2 to 5.6)*	2.2 (.3 to 4.0)*	5.9 (4.4 to 7.5)*
WHO PS 0	Ref	Ref	Ref	Ref	Ref	Ref
WHO PS 1	–7.7 (–8.9 to –6.6)*	–9.5 (–10.7 to –8.4)*	–12.8 (–14.5 to –11.2)*	9.3 (7.9 to 10.6)*	6.9 (5.5 to 8.4)*	9.2 (8.0 to 10.4)*
WHO PS 2	–18.7 (–20.7 to –16.7)*	–28.8 (–30.8 to –26.8)*	–34.0 (–36.9 to –31.2)*	22.3 (20.0 to 24.6)*	17.1 (14.6 to 19.6)*	26.3 (24.3 to 28.4)*
Nonglioblastoma	Ref	Ref	Ref	Ref	Ref	Ref
Glioblastoma	–1.0 (–2.4 to.5)	–1.4 (–2.8 to.1)	–.5 (–2.5 to 1.6)	2.4 (.8 to 4.1)*	3.4 (1.6 to 5.2)*	1.8 (.3 to 3.3)*
Treatment: RT alone	Ref	Ref	Ref	Ref	Ref	Ref
Treatment: CT alone	–.1 (–2.3 to 2.0)	–3.4 (–5.6 to –1.6)*	.5 (–2.5 to 3.6)	.4 (–2.1 to 2.9)*	1.8 (–.9 to 4.5)	.4 (–2.7 to 1.8)
Treatment: RT and CT	.9 (–1.2 to 2.9)	–1.4 (–3.5 to.7)	–1.2 (–2.5 to 3.6)	.2 (–2.2 to 2.6)*	–1.2 (–3.8 to 1.3)	–2.2 (–4.3 to.–7)*
Treatment: RT and CT and AI	1.2 (–1.5 to 3.8)	.5 (–2.2 to 3.2)	1.5 (–2.2 to 5.3)	–2.7 (–5.7 to.4)	–2.1 (–5.4 to 1.3)	–3.1 (–5.9 to –.4)*
Treatment: CT and AI	–3.4 (–6.3 to –.4)*	–6.9 (–10.0 to –3.9)*	–5.2 (–9.4 to –.9)*	2.6 (–.8 to 6.1)	3.7 (–.1 to 7.5)	3.2 (.1 to 6.4)
Treatment: RT and AI	–6.7 (–10.9 to –2.6)*	–8.1 (–14.2 to –4.9)*	–9.3 (–15.2 to –3.4)*	8.6 (3.9 to 13.4)*	7.0 (1.8 to 12.2)	4.6 (.3 to 8.8)*
Treatment: CT and TTF	4.9 (2.2 to7.6)*	.9 (–1.8 to 3.6)	7.4 (3.6 to 11.2)*	–2.6 (–5.7 to.5)	1.1 (–2.3 to 4.4)	–4.4 (–7.2 to –1.6)*

*P < .05, FU, Follow-up; Ref, reference; WHO, World Health Organisation; PS, Performance status; RT, radiotherapy; CT, Chemotherapy; AI, Angiogenesis inhibitors; TTF, Tumor treating fields

in these situations, it is likely that the treatment itself did not have a negative impact on the different HRQoL aspects. In those cases where treatment had an impact on HRQoL outcomes (i.e., TTD was shorter or similar to deterioration-free survival time), the direction of the effect was not always consistent. That is, some treatment regimens had a positive impact on one HRQoL scale, and a negative impact on another scale, although typically not at a clinically relevant level. These results were not unexpected because anti-cancer treatments can simultaneously alleviate some tumor-related symptoms, while causing symptoms as side-effects of the treatment itself.

The important effect of disease progression on HRQoL outcomes is illustrated by the finding that progression was the most common event (70%) in the deterioration-free survival analyses. This finding is in line with previous research, suggesting that progression is an important factor in HRQoL deterioration in brain tumor patients.[25,26] However, not all studies reporting that progression is a key event for deterioration in a patients' functioning and well-being clearly distinguished between statistically significant and clinically relevant associations, or used multivariable models investigating the independent association between progression and HRQoL outcomes.[27–29] One difficulty in the use of progression as an outcome is that the assessment of progression is difficult, with high interobserver variability, and interpretation may be confounded by pseudoprogression.[30,31] Also, progression is typically a composite endpoint, reflecting both clinical deterioration and radiological progression. A growing tumor may cause clinical deterioration, as reflected in performance status, but may not yet be classified as progressive disease because radiologically it does not meet the criteria.[32] This means that in the period where there is radiologically no (definite) sign of disease progression, the underlying disease can still have an impact on

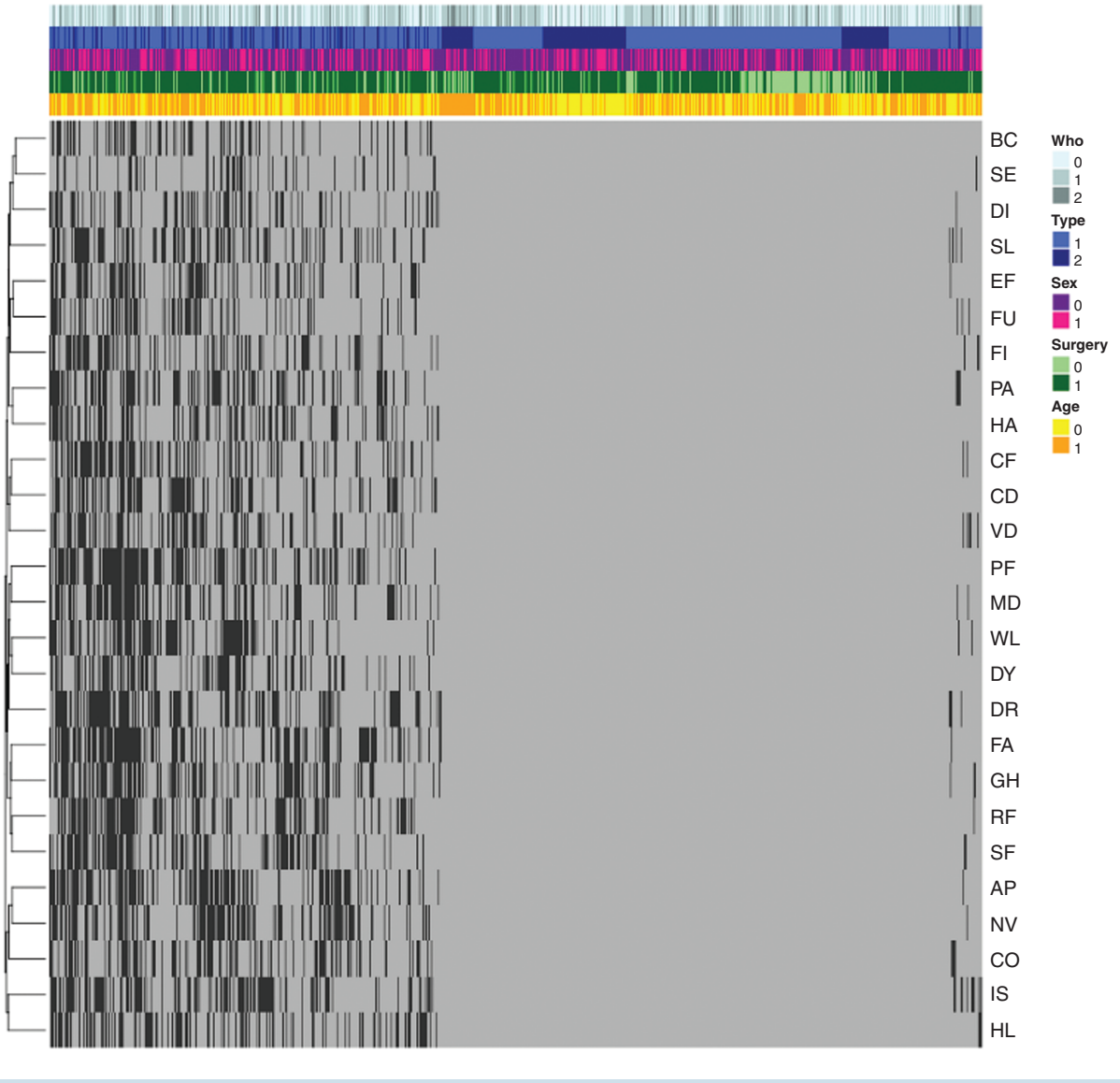

Fig. 2 Heatmap reflecting patients with and without HRQoL deterioration before progression. Patients HRQoL scales are ordered so that patients with similar scores are next to each other, using hierarchical cluster techniques. The horizontal axis represent all individual patients, HRQoL scales are represented on the vertical axis. Dark gray indicates patients with progression, light gray indicates patients without HRQoL deterioration. Annotations above the figure indicate patients' clinical characteristics: WHO PS, age, sex, tumor type, and previous surgery. WHO, World Health Organization Performance Status; type, type of tumor 1: glioblastoma, 2: non-glioblastoma); sex, 0: male, 1: female; surgery 0 resected, 1 non resected; age, age split by mean 0: 53 and younger, 54: 54 and older.

aspects of HRQoL. If HRQoL would have been assessed more frequently, which is possible in clinical practice but not in clinical trials, a deterioration of HRQoL before progression may have been detected more frequently than shown in this study. This is further illustrated by post hoc analyses showing that although the median time between HRQoL deterioration and progression in days was between 135 and 210 days, a large proportion of these patients progressed within 100 days after HRQoL deterioration (Supplementary Figure 3). Further research on the role of clinical and/or radiological disease progression in HRQoL deterioration is therefore warranted.

This study revealed that a large proportion of patients experienced a clinically relevant deterioration in aspects of HRQoL during the progression-free period, and warrants attention. One important method to prevent HRQoL deterioration is routine monitoring of the patients' functioning and well-being during the entire disease course. Routine monitoring may signal symptoms and other issues at an early stage, allowing the implementation of interventions addressing these issues.[33,34] When preventing or treating symptoms, this may subsequently have a positive impact on the patients' activities in daily life and overall quality of life. Which aspects of HRQoL are most important to a

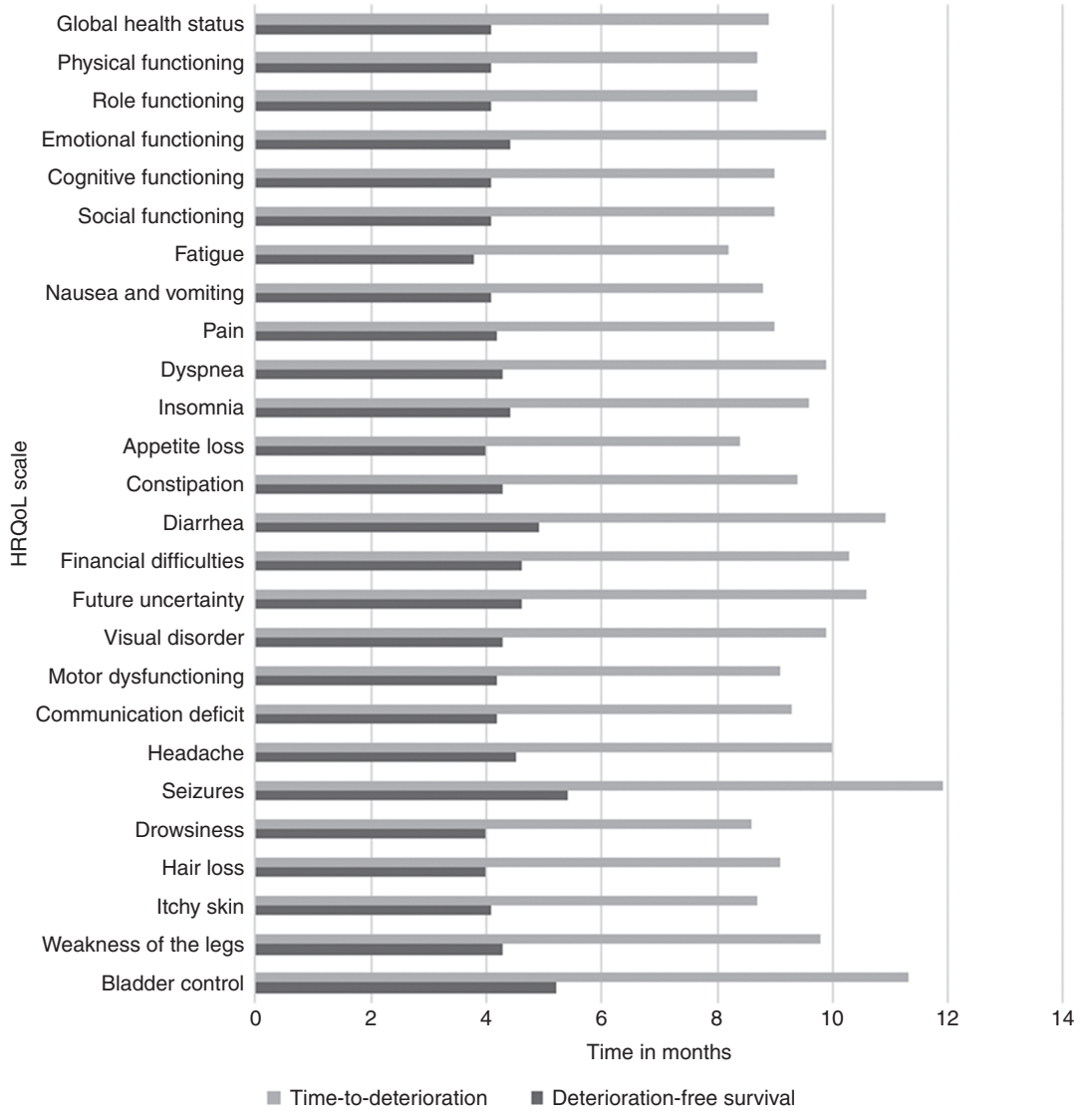

Fig. 3 Mean deterioration-free survival and time-to-deterioration in months per HRQoL scale when all included trials combined.

patient (e.g. hair loss or cognitive complaints) and need an intervention, is based on the individual patients' preferences and values and should be discussed during the consultations with the physicians. Currently, several rehabilitation programs are being developed, for example aiming at fatigue, motor symptoms, and cognitive problems, and should be considered for patients presenting with these problems.[35,36] This study has several limitations that should be noted. One important limitation, which is inherent to HRQoL research in general, is missing data during follow-up. Patients with worse health status are less likely to complete questionnaires, causing attrition bias and resulting in patients with better HRQoL being overrepresented during later follow-up assessments.[37] Additionally, we used a 10 points difference in HRQoL score over time to define a clinically relevant change. Although this cutoff has been used in many studies over the past decades, more recent studies suggest that this threshold may be too simplistic in that it does not distinguish between different HRQoL scales, the direction of change (improvement or deterioration), or between cancer types.[38] Very recently, minimally important differences (MID) for all EORTC QLQ-C30 scales for glioma patients have been determined. Applying these MIDs, which are typically smaller than the 10-point cutoff (they range between 4 and 11 points for both within-group and between-group mean difference in change in glioma patients),[39] would probably result in different median deterioration-free survival and time-to-deterioration times, and in more significant and clinically relevant associations in the linear mixed model analyses. However, because there are currently no MIDs available for the QLQ-BN20 scales, we decided to use the general 10-point cutoff in this study for all scales, including those of the EORTC QLQ-C30. Another limitation is

that not all patients in the included studies were assessed at the exact same time points with respect to the HRQoL and radiological assessments, as the duration of the intervals of assessment differed across trials (Supplementary Table 3 and Supplementary Figure 4). Since the calculation of deterioration-free survival and time-to-deterioration periods depends on the timing of these assessments, the obtained estimates may therefore be biased, as patients between trials may not be comparable. Moreover, since the timing of the HRQoL and radiological assessments is largely similar, (large) differences in the duration of TTD and deterioration-free survival are also difficult to establish in clinical trials. In daily clinical practice, where HRQoL could be monitored more frequently than radiological assessment, differences may be more significant.

In conclusion, this study suggests that almost half of the patients with glioma will experience a clinically relevant deterioration in at least one HRQOL scale during their progression-free period. While extending the progression-free period is certainly important, it is most meaningful if the patients' HRQoL is relatively good during that period. In general, treatment was not found to be independently associated with a clinically relevant deterioration in HRQoL during the progression-free period.

Supplementary Material

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

Keywords

brain tumor | deterioration-free-survival | progressive disease | time-to-deterioration

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Authorship statement. BB, MB, AAB, OC, UH, FKG, AM, RS, MW and WW were the principal investigators of the RCTs for which the data was originally collected, and were involved in data collection. In addition, JR and MT were also involved in data collection in several RCTs. All authors were involved in the conceptualization of this study. MC and LD performed the statistical analysis and wrote the first draft of the manuscript. All authors have been involved in the revision of the manuscript and have read and approved the final version.

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