J Neurooncol (2015) 124:185–195
DOI 10.1007/s11060-015-1821-2

CLINICAL STUDY

Health-related quality of life in patients with high-grade gliomas: a quantitative longitudinal study

K. Piil[1,2] · J. Jakobsen[3] · K. B. Christensen[4] · M. Juhler[1,5] · M. Jarden[2]

Received: 3 February 2015 / Accepted: 22 May 2015 / Published online: 31 May 2015

Abstract The diagnosis of a high-grade glioma usual is followed by functional impairment(s), cognitive decline and an impaired psycho-social well-being. This might well have a significant and negative impact on the health related quality of life. The purpose of this study was to explore physical activity levels, prevalence and severity of anxiety and depressive symptoms and health-related quality of life among patients with a highgrade glioma. This paper is based on a longitudinal mixed methods study. Patients (n = 30) completed questionnaires at 5 time points from time of diagnosis until the final follow-up after 1 year. Scores of Karnofsky Performance Status (KPS), physical activity, anxiety and depression and health-related quality of life (FACT-Br) are obtained. Patients' physical activity level and KPS decrease during the disease- and treatment trajectory. The majority of patients did not report any depressive symptoms, eight individuals (26.7 %) being depressed at various time points. Among a sub-group of participants who completed all study requirements for the entire study period the level of anxiety decreased significantly during the study. The FACT-Br sub-scale of emotional well-being increased significant, indicating a better HRQOL attend of followup. The diagnosis of a HGG leads to an ongoing functional decline measured as a decline of the KPS and a reduced physical activity during leisure time. Supportive care combined with rehabilitative and palliative approaches might well be valuable along the trajectory especially during the post-surgery period when anxiety is at its highest peak.

Keywords High-grade glioma · Quality of life · Anxiety · Depression · Physical activity

Introduction

High-grade glioma (HGG) is the most common primary cancer manifestation of the central nervous system [1]. Current treatment for HGG includes neurosurgical resection or biopsy, radiotherapy and chemotherapy [2]. Without a prospect of cure, patients experience a gradual neurological and functional decline [3, 4]. Still, the HGG prognosis has improved and long-term survival has been reported [5] which stresses the necessity of increased attention on health-related quality of life (HRQOL). For that reason it is imperative to identify and understand the mechanisms that contribute to the improvement or deterioration of HRQOL [6]. Physical deterioration has a negative impact on HRQOL, leading to anxiety and depression [7–9]. Other contributory factors that affect the level of HRQOL in patients with HGG patients are gender,

Electronic supplementary material The online version of this article (doi:10.1007/s11060-015-1821-2) contains supplementary material, which is available to authorized users.

✉ K. Piil
karin.piil@regionh.dk

1 Department of Neurosurgery, The University Hospital of Copenhagen, Rigshospitalet, UCSF 9701, Blegdamsvej 9, 2100 Copenhagen, Denmark

2 The University Hospitals Center for Health Research (UCSF) and Center for Integrated Rehabilitation of Cancer Patients (CIRE), Blegdamsvej 9, 2100 Copenhagen, Denmark

3 Neuroscience Center, The University Hospital of Copenhagen, Blegdamsvej 9, 2100 Copenhagen, Denmark

4 Section of Biostatistics, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

5 Section of Neurology, Psychiatry and Sensory Sciences, Department of Clinical Medicine, The University of Copenhagen, Nørregade 10, 1017 Copenhagen K., Denmark

tumor localisation, histological classification and reduced neuro cognitive function [10]. Further, depression is the most independent predictor of HRQOL in patients with brain tumors [11]. Symptoms of depression are found to be part of the symptom cluster that includes fatigue, sleep disturbance and cognitive impairment [12]. A higher symptom burden is associated with lower HRQOL [12, 13]. The prevalence of depression is higher among patients with brain tumors compared with other cancer patient populations [14]. D'Angelo et al. found the prevalence of depression among brain tumor patients to increase up to 1 year after surgery [15]. However, there is lack of knowledge based on longitudinal self-reported HRQOL studies including data on prevalence and severity of anxiety and depression among patients with HGG. The purpose of this study was to evaluate the physical activity level, Karnofsky Performance Status (KPS), HRQOL, prevalence and severity of anxiety and depression in a longitudinal study following patients with HGG for 1 year from the time of diagnosis. We hypothesize that KPS and functional status will decrease leading to feelings of anxiety and cases of depressions and as a result the HRQOL is expected to decrease over time. Moreover, 1-year survivors are expected to have the highest *baseline* KPS. In case of tumour progression patients are expected to have a risk of depression.

Materials and methods

Study design

The present quantitative study is based on patient reported outcome (PROs) data and is part of a larger project using mixed methods [16]. In a mixed methodology design, qualitative and quantitative data are collected in parallel and analyzed separately [17–19]. The qualitative data consist of interviews with patients and caregivers carried out at the same five test time points as the quantitative data are collected [20], the methodology being described in full elsewhere [16].

Participants and procedures

This study includes persons ≥18 years, newly diagnosed with HGG (WHO classification grade III/IV), KPS ≥60 at baseline to ensure independent responses to questionnaires and able to speak and understand Danish. The primary investigator (KP) and the clinical specialists assessed whether patients with cognitive deficits were able to participate in the study. Disease progression was not an exclusion criterion, and no patients were excluded during the study period. Patients were asked for study participation on the first postoperative day, and recruited with a consecutive sampling strategy from May to December 2012 at the Department of Neurosurgery, Rigshospitalet University of Copenhagen. All the included participants formed the *primary sample*, from which participants who completed all study requirements for the entire study period formed a *sub-sample* that allows for a complete longitudinal analysis during a 1-year follow-up. Written consent was obtained within 2 days prior to discharge from the hospital. The study is registered at the Danish Data Protection Agency (2007-58-0015/30-0758) and The Ethical Committee at the Capital Region of Denmark (H-2-2013-135) and carried out in accordance with the Declaration of Helsinki [28].

Measurements

Socio-economic conditions, KPS, disease and treatment variables were obtained at baseline from medical records and PROs. Repeated measurements were collected at 5 time points: *test 1* after surgery and diagnosis (week 1), *test 2* during radiotherapy (week 6), *test 3 and 4 after* treatment response scans and chemotherapy (week 28 and 40) and *test 5* after standard treatment and response scan (week 52). Patients received the following three validated questionnaires by mail at the five test time points (after response scan) with written instructions on how to complete and return their response in an enclosed and addressed envelope.

(1) *Leisure-time physical activity level* [21–23]. Self-reported physical activity levels are rated using four response options: I Almost completely inactive: reading, TV watching, etc., II Some physical activity less than 3 h per week (h/weak): riding a bicycle or walking for pleasure, III Regular activity: heavy gardening, running, etc. for (3 h/weak, IV Regular hard physical training: running, soccer etc. for more than 4 h/weak. Additionally, at baseline, patients reported retrospectively their level of activity at 3 months prior to diagnosis.

(2) *The Hospital Anxiety and Depression Scale* (*HADS*) [24, 25]. The HADS is a validated measurement tool for detecting symptoms of anxiety and depression in patients estimating psychological well-being. The questionnaire is divided into two sub-scales for anxiety and depression with seven questions each all; 14 questions are rated on a four point scale representing the degree of distress [0 = none, 4 = unbearable]. The responses from HADS are presented as separate scores for anxiety and depression higher scores indicating greater likelihood of depression or anxiety. Recommended cut-off values for both scales are as follows: below 7 is a normal

score, scores of 8–10 indicate mild cases, scores between 11 and 15 reveal moderate cases, while 16 and above indicate severe cases of anxiety and/or depression. A score of 11 or more on either scale is considered a definite case of anxiety and/or depression.

(3) *The Functional Assessment of Cancer Therapy, General and Brain* (*FACT-G and FACT-Br*) [26, 27]. The FACT-G is a validated multidimensional questionnaire that measures HRQOL in cancer patients. FACT-Br (version 4) is a 50-item measure that includes the 27 items from FACT-G and the brain sub-scale (23 items) to assess HRQOL in brain tumor patients. It comprises 4 sub-scales: physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB) and functional well-being (FWB), on a 5-point Likert scale ranging from 0 (not at all) to 4 (very much). Moreover, the brain cancer sub-scale (BrCS) reflects issues specific for brain cancer. The highest possible score is 28 for the PWB, SWB and FWB subscales, 24 for the EWB subscale and 184 for the BrCS. FACT-Br total score is the sum of the 4 sub-scales (of the core instrument). The FACT-G total score provides a summary of the overall HRQOL across the group of patients [range 0–108] and the FACT-Br Trial Outcome Index [range 0–132] is a summary index of physical/functional outcomes. The higher the score, the better HRQOL.

Procedures for data entry and audit program were established to ensure quality control in manual keying of data [28, 29].

Statistical analyses

The KPS, the HADS sub-scales, the FACT-Br sub-scales and the responses to the ordinal items of the leisure time physical activity scale were analysed separately. Categorical variables are reported as frequencies and percentages, while continuous variables are reported as mean and standard deviations (s.d.) using a significance level of $p < 0.05$. HADS and FACT-Br data refer to the normative values [30, 31].

For the sub-sample, differences between *baseline* mean scores (anxiety, depression, FACT-Br sub-scales, FACT Br Trial Outcome Index) and 1-year follow-up assessments were examined for significance ($p < 0.05$) using paired t-tests. Further, plots of HADS and FACT-Br ($n = 30$ and $n = 18$) are presented as supplementary material.

We estimated rank correlations for the primary sample between the FACT-Br sub-scales, the sub-scales of the HADS, age, occurrence of WHO grade III tumour, and leisure time physical activity with linear mixed models using standardized dependent and independent variables providing an estimate of the correlation that takes the clustered nature of the data into account. The statistical analysis was performed with SAS statistical software, version 9.3.

Results

Sample

A total of thirty patients are included in the primary sample of the study (Fig. 1). All patients received radiotherapy and/or chemotherapy. Patients with KPS <60 were excluded [$n = 35$: aphasia ($n = 13$), severe cognitive impairment ($n = 9$) such as problems with memory, language and thinking [32], severe neurological impairment ($n = 9$) to a degree where inpatient treatment is required and psychotic/severe stress reactions ($n = 4$) requiring acute psychological treatment]. Participants who completed all study requirements during the 1-year study period form a sub-sample ($n = 18$). Medical and demographic characteristics for study patients are outlined in Table 1 according to the primary sample and the sub-group. The longitudinal response rate to the PRO questionnaires ranged from 60 to 97 %. Missing data were due to neurological decline or death.

Functional status and physical activity n = 30

At baseline, 93 % of the patients had a KPS ≥70 (Table 2).- The most profound decline (20 %) occurred during oncological treatment (between test 2 and test 3), when only 63 % of the patients had a KPS ≥70. At test five 53 % of the patients still had a KPS ≥70, and 23 % a KPS ≥90 as compared to 63 % at baseline. Most patients (75 %) were physically active more than 3 h per week (h/weak) 3 months prior to the diagnosis, and 9 % kept the same level of physically at follow-up 1 year later (Table 3).

Symptoms of anxiety and depression n = 30

According to the cut-off points of HADS *anxiety* scale, eleven patients (39 %) reported moderate or severe symptoms of anxiety at baseline (Table 4). This proportion decreased over time and at test 4 and 5 only *one* patient exceeded the cut-off level for anxiety (≥11). This trend was also seen for the mean anxiety score that was highest at baseline (mean 8.5 ± 5.2) and lowest at test 4 (mean 4.4 ± 3.5).

Concerning *depression,* the HADS scale showed moderate depression in four patients at baseline. At test 4 and 5,

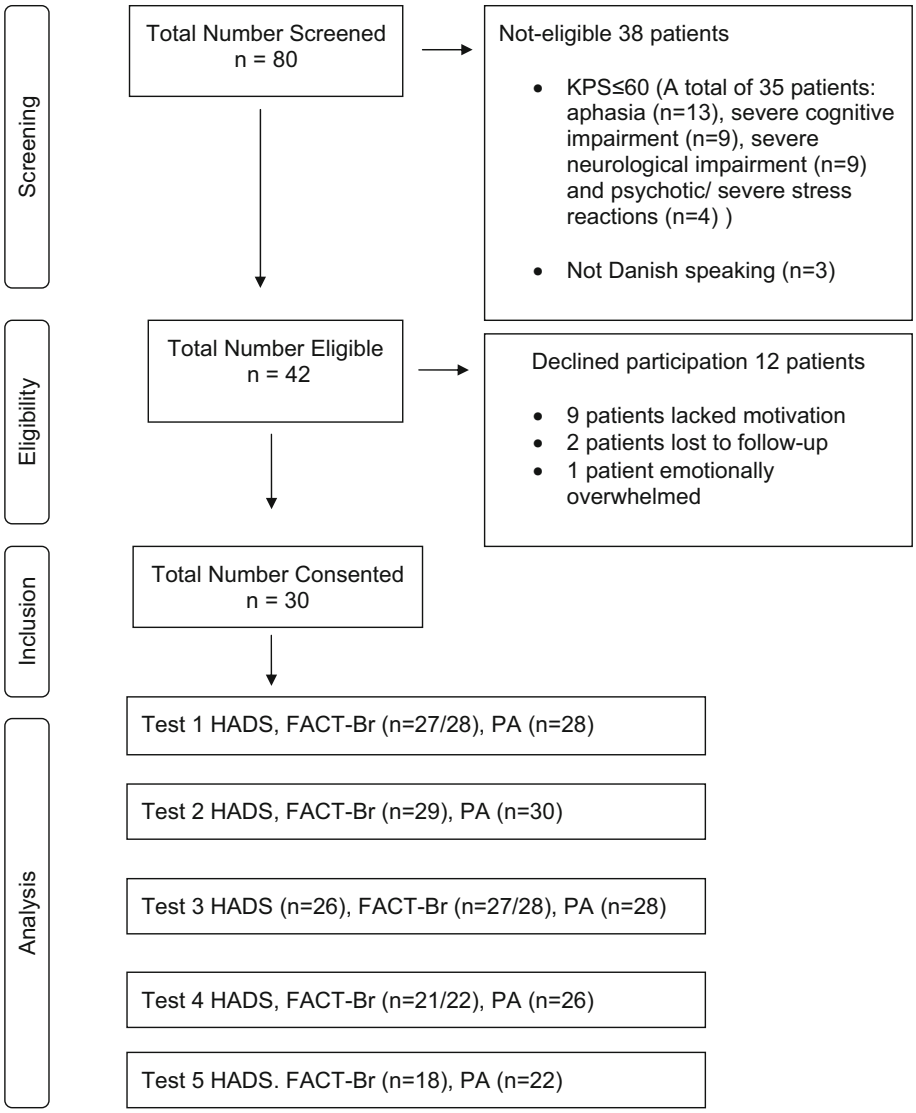

Fig. 1 Study Flow. *KPS* Karnofsky Performance Scale; *HADS* Hospital Anxiety and Depression Scale; *FACT-Br* the functional assessment of cancer therapy, brain cancer; *PA* physical activity

only one patient reported moderate depression. Mean depression scores were highest at baseline (mean 6.1 ± 3.5) and lowest at test 5 (mean 3.7 ± 3.1). A total of eight out of the 30 patients (26.6 %) reported scores indicating depression at least at one test time point during the 1-year study period (Supplementary Fig. 1), 87.5 % of them having tumor progression (see Supplementary Fig. 1 and Table 4). Compared to the normative values [30] our data were higher for anxiety (8.5 ± 5.2) at baseline compared to the normative value (of 6.14 ± 3.76) and for depression (6.0 ± 3.9) at baseline and test 3 compared to the normative value (of 3.68 ± 3.07).

Health-related quality of life n = 30

FACT-Br scores at each time point are shown in Table 5 along with normative values of the general U.S. adult population (N = 1075) [31]. FACT-G Total was lowest at baseline (71.9 ± 14.3) and highest at test 5 (83.4 ± 17.1). The same trend was seen for all sub-scales except the SWB sub-scale and the Brain Cancer sub-scale that appeared unchanged. For the SWB sub-scale the patients scored higher at baseline compared to the normative US values ($p < 0.0001$), whereas for the PWB, EWB, FWB, and the FACT-G Total the patient scores were lower than the normative sample.

Sub-sample analysis n = 18

Analysis of the development throughout the entire 1-year study period of KPS, physical activity levels, HADS and FACT-Br scores was performed in the sub-sample group of patients (n = 18) who survived until study completion.

Table 1 Medical and demographic characteristic for study patients

Characteristics	No (range) n = 30	No (range) n = 18
Age (median, range) yrs	60 (29–82)	57 (29–71)
Gender (male/female)	19/11	10/8
Diagnosis		
Glioblastoma, WHO grade IV	23	15
Primitive Neuroectodermal Tumor, WHO grade IV	1	1
Glial Cell Sarcoma, WHO grade IV	1	1
Anaplastic Astrocytoma, WHO grade III	4	1
Anaplastic Oligodendroglioma WHO grade III	1	0
Surgical procedure		
Operation/Biopsy	23/7	16/2
Unifocal/multifocal	18/12	15/3
Progression/no progression	19/11	9/9
After progression		
Stop of treatment	8	1
Re-operation and avastin/irinotecan	10	6
Re-operation and temodal	0	2
Marital status		
Married/living with partner	24	14
Single/divorced/living alone	6	4
Children living at home	9	6
Baseline BMI, median	26 (17–37)	26 (23–37)
Highest level of education		
Less than or completed municipal primary/9th or 10th grade	6	5
Training/learning	13	8
Higher education (≤4 years/≥5 years)	6/5	3/2
Employment status before diagnosis		
Full time	19	12
Sick leave/rehabilitation/flex job	1	1
Early retirement/pension	10	5
Employment status after diagnosis		
Full time/part time	3/3	3/2
Sick leave	14	7
Early retirement/pension	10	6

BMI body mass index, *WHO* World Health Organization, *Yrs* years

The KPS baseline data show that all the patients had a KPS ≥70, which also was the case 5 weeks later during radiotherapy at test 2, and 78 % still had a KPS ≥70 at the end of the study (Table 2). They reported a decrease of physical activity, where 89 % were active less than 3 h/weak at end of study (Table 3).

Mean anxiety was highest at baseline (mean 7.8 ± 5.7) and lowest at test 4 (mean 4.5 ± 3.9) (Table 4). There was a decrease in mean anxiety from test 1 to test 5 ($p = 0.0095$). No significant change in depression scores from test 1 to test 5 was identified ($p = 0.07$). Four individuals (22.2 %) obtained scores indicating depression at least at one test time point during the 1-year study period (Supplementary Fig. 1).

The EWB subscale of the FACT-Br shows a significant increase ($p = 0.0023$) from baseline (13.8 ± 6.7) to test 5 (18.4 ± 4.5). No significant changes were identified for the other sub-scales (Table 5).

The impact of anxiety

The correlation analysis showed that level of anxiety was closely related with (1) overall HRQOL (FACT-G Total) [correlation −0.60 with 95 % confidence limits (Cl) at −0.74 to −0.45] and (2) emotional well-being (correlation −0.68 with 95 % Cl at −0.81 to −0.55). Less closely associations were established between the variables of (3) physical and functional outcomes (PWB, FWB, FACT-Br

Table 2 Karnofsky performance status

	3 mo. prior baseline n (%)	Baseline n (%)	Test 2 n (%)	Test 3 n (%)	Test 4 n (%)	Test 5 n (%)
Primary sample n = 30						
KPS						
90–100	n.o.	19 (63.3)	15 (50.0)	9 (30.0)	7 (23.3)	7 (23.3)
70–80	n.o.	9 (30.0)	10 (33.3)	10 (33.3)	9 (30.0)	9 (30.0)
50–60	n.o.	2 (6.7)	4 (13.3)	9 (30.0)	10 (33.3)	5 (16.7)
30–40	n.o.	0	1(3.3)	0	0	1 (3.3)
Dead	0	0	0	2 (6.7)	4 (13.3)	8 (26.7)
Sub-group n = 18						
KPS						
90–100	n.o	14 (77.8)	13 (72.2)	9 (50.0)	6 (33.3)	6 (33.3)
70–80	n.o	4 (22.2)	5 (27.8)	6 (33.3)	6 (33.3)	8 (44.4)
50–60	n.o	0	0	3 (16.7)	6 (33.3)	4 (22.2)
30–40	n.o	0	0	0	0	0
Dead	0	0	0	0	0	0

KPS Karnofsky performance scale, *n.o.* not obtained, *Test 2* week 6, *Test 3* week 28, *Test 4* week 40, *Test 5* week 52, *mo* months

Table 3 Physical activity levels

	3 mo. prior baseline n (%)	Baseline n (%)	Test 2 n (%)	Test 3 n (%)	Test 4 n (%)	Test 5 n (%)
Primary sample n = 30						
Leisure time physical activity						
I	3 (10.7)	13 (46.4)	9 (30.0)	14 (53.8)	9 (34.6)	7 (31.8)
II	4 (14.3)	7 (25.0)	9 (30.0)	12 (46.2)	16 (61.5)	13 (59.1)
III	16 (57.1)	8 (28.6)	11 (36.7)	0	1 (3.8)	2 (9.1)
IV	5 (17.9)	0	1 (3.3)	0	0	0
Sub-group n = 18						
Leisure time physical activity						
I	2 (11.8)	8 (50.0)	4 (22.2)	7 (43.8)	4 (22.2)	6 (33.3)
II	3 (17.6)	4 (25.0)	7 (38.9)	9 (56.3)	13 (72.2)	10 (55.6)
III	10 (58.8)	4 (25.0)	6 (33.3)	0	1 (5.6)	2 (11.1)
IV	2 (11.8)	0	1 (5.6)	0	0	0

I almost completely inactive, *II* some physical activity less than 3 h per week, *III* regular activity at least 3 h per week, *IV* regular hard physical training more than 4 h per week, *Test 2* week 6, *Test 3* week 28, *Test 4* week 40, *Test 5* week 52, *mo* months

TOI), and (4) the sum of the four sub-scales of FACT-Br (FACT-Br-Total), (5) the leisure time physical activity level and (6) the performance status (KPS) (results not shown).

The impact of depression

The depression subscale of the HADS showed close correlations to (1) the FACT-Br Trial Outcome Index (correlation −0.55 with 95 % CI at −0.69 to −0.42), (2) the FACT-G [correlation −0.64 with 95 % CI at −0.78 to −0.50], and (3) the FACT-Br total score [correlation −0.60 with 95 % CI at −0.72 to −0.48]. Regarding the individual components of the FACT-Br the association was closely to functional well-being and less close to social well-being (results not shown).

Discussion

As expected we found that KPS and physical activity levels decreased during the study period. Nonetheless anxiety and emotional well-being improved over time for 1-year survivors of HGG, with a close mutual relationship. The

Table 4 HADS: anxiety and depression

Primary sample n = 30	Baseline n = 28 (%)	Test 2 n = 29 (%)	Test 3 n = 26 (%)	Test 4 n = 21 (%)	Test 5 n = 18 (%)	Normative value mean ± SD[c]
Anxiety						
Normal 0–7	12 (42.9)	15 (51.7)	16 (64)	20 (90.9)	16 (88.9)	
Mild cases 8–10	5 (17.9)	7 (24.1)	4 (16)	1 (4.5)	1 (5.6)	
Moderate cases 11–15	7 (25)	5 (17.2)	3 (12)	0 (0)	0 (0)	
Severe cases ≥16	4 (14.3)	2 (6.9)	2 (8)	1 (4.5)	1 (5.6)	
Anxiety mean ± SD	8.5 ± 5.2	7.5 ± 4.4	7.1 ± 4.6[a]	4.4 ± 3.5[b]	4.8 ± 3.8	6.14 ± 3.76
Depression						
Normal 0–7	19 (67.9)	20 (69)	18 (69.2)	18 (81.8)	15 (83.3)	
Mild cases 8–10	5 (17.9)	6 (20.7)	4 (15.4)	3 (13.6)	2 (11.1)	
Moderate cases 11–15	4 (14.3)	2 (6.0)	4 (15.4)	1 (4.5)	1 (5.6)	
Severe cases ≥16	0 (0)	1 (3.4)	0 (0)	0 (0)	0 (0)	
Depression mean ± SD	6.1 ± 3.5	5.7 ± 4.0	6.0 ± 3.9	3.9 ± 3.3[b]	3.7 ± 3.1	3.68 ± 3.07

Sub-group n = 18	n = 18	n = 17	n = 16	n = 17	n = 18	95 % CL	P-value[d]
Anxiety							
Normal 0–7	10 (55.6)	10 (58.8)	10 (62.5)	15 (88.2)	16 (88.9)		
Mild cases 8–10	2 (11.1)	2 (11.8)	3 (18.8)	1 (5.9)	1 (5.6)		
Moderate cases 11–15	3 (16.7)	3 (17.6)	2 (12.5)	0	0		
Severe cases ≥16	3 (16.7)	2 (11.8)	1 (6.3)	1 (5.9)	1 (5.6)		
Anxiety mean ± SD	7.8 ± 5.7	7.1 ± 5.1	6.9 ± 4.4	4.5 ± 3.9	4.8 ± 3.8	−5.1643 −0.8357	p = 0.0095
Depression							
Normal 0–7	13 (72.2)	14 (82.4)	14 (87.5)	15 (88.2)	15 (83.3)		
Mild cases 8–10	3 (16.7)	2 (11.8)	1 (6.3)	1 (5.9)	1 (5.6)		
Moderate cases 11–15	2 (11.1)	1 (5.9)	1 (6.3)	1 (5.9)	1 (5.6)		
Severe cases ≥16	0	0	0	0	0		
Depression mean ± SD	5.4 ± 3.7	4.3 ± 3.5	4.7 ± 3.4	3.2 ± 3.2	3.7 ± 3.1	−3.6201 0.1757	p = 0.0725

CL confidence limit, *HADS* Hospital Anxiety and Depression Scale, *SD* standard deviation, *Test 2* week 6, *Test 3* week 28, *Test 4* week 40, *Test 5* week 52

[a] n = 25

[b] n = 22

[c] Based on 1.792 individuals representative of the general adult population in the UK (Crawford et al. 2001)

[d] One sample t-tests of average for change scores from test 5 to test 1

hypothesis that the sub-group would have a higher KPS than the primary sample was confirmed. In case of tumour progression data indicate a high prevalence of depression. Newly operated HGG patients experience early functional limitations [33], as indicated by the observation that 71 % of our study participants were completely inactive or physically active less than 3 h/weak at this time. Physical activity level did not improve among the 1-year survivors. An early and ongoing functional decline occurs, especially for the primary sample, while the sub-group had a higher KPS value. A lower tumor grade did not explain this as four out of five patients diagnosed with a WHO grade III tumor belonged to the primary sample. Exercise behaviour is found to be a strong independent predictor of survival [34]. Nevertheless, only a limited number of international intervention studies have investigated the possible benefit of physical training among HGG patients [35]. Maintaining independence for as long as possible is a priority of the patients [20] and early physical rehabilitation is recommended [36], but additional research is warranted in order to clarify the value of training in this group of patients.

This study suggests that patients with HGG report emotional distress and anxiety during the post-surgical period. This is explained by the poor prognosis and an unpredictable future [20, 37, 38]. However, the individual variations show that some patients with baseline scores

Table 5 The functional assessment of cancer therapy, brain cancer

FACT-Br sub-scales n = 30	Baseline (n = 28) mean ± SD	Test 2 (n = 29) mean ± SD	Test 3 (n = 28) mean ± SD	Test 4 (n = 22) mean ± SD	Test 5 (n = 18) mean ± SD	Normative values[c]	p-value[e]
PWB	20.0 ± 7.5	21.5 ± 6.0	20.5 ± 4.4	22.2 ± 5.3[b]	23.7 ± 8.5	22.7 ± 5.4	
SWB	23.7 ± 3.4	23.1 ± 4.6	22.0 ± 4.4	22.3 ± 6.1	23.5 ± 2.9	19.1 ± 6.8	
EWB	12.8 ± 5.8[a]	14.8 ± 5.0	16.4 ± 4.2[a]	17.1 ± 4.5	18.4 ± 4.5	19.9 ± 4.8	
FWB	14.8 ± 5.7[a]	16.7 ± 6.2	16.3 ± 5.7	17.2 ± 6.3	17.9 ± 6.0	18.5 ± 6.8	
FACT-G total	71.9 ± 14.3[a]	76.0 ± 15.2	74.7 ± 12.1[a]	78.8 ± 16.2[b]	83.4 ± 17.1	80.1 ± 18.1	
BrCS	51.4 ± 14.3	51.2 ± 15.5	49.3 ± 12.9	50.3 ± 13.7	52.5 ± 12.2		
FACT-Br TOI	87.4 ± 22.0[a]	89.3 ± 22.6	86.1 ± 19.7	90.0 ± 20.7[b]	94.1 ± 22.2		
FACT-Br total	123.9 ± 25.3[a]	127.1 ± 27.9	123.4 ± 22.7[a]	129.4 ± 27.8[b]	135.9 ± 27.1		
FACT-Br sub-scales n = 18	n = 18	n = 17	n = 18	n = 17	n = 18		
PWB	21.4 ± 7.9	21.7 ± 5.2	21.4 ± 3.4	24.0 ± 3.6	23.7 ± 8.5	22.7 ± 5.4	p = 0.1180
SWB	23.7 ± 2.9	23.9 ± 2.8	21.6 ± 4.9	22.4 ± 6.7	23.5 ± 2.9	19.1 ± 6.8	p = 0.5375
EWB	13.8 ± 6.7[d]	15.0 ± 5.8	16.8 ± 4.4	17.1 ± 4.8	18.4 ± 4.5	19.9 ± 4.8	p = 0.0023
FWB	16.3 ± 5.3[d]	17.9 ± 6.1	16.5 ± 5.9	17.8 ± 6.6	17.9 ± 6.0	18.5 ± 6.8	p = 0.0759
FACT-G total	76.4 ± 13.3[d]	78.6 ± 15.3	76.4 ± 12.1	81.3 ± 16.2	83.4 ± 17.1	80.1 ± 18.1	
BrCS	56.0 ± 13.7	78.6 ± 15.3	76.4 ± 12.1	81.3 ± 16.2	83.4 ± 17.1		p = 0.1165
FACT-Br TOI	95.8 ± 20.6[d]	55.6 ± 14.1	52.8 ± 10.7	52.3 ± 13.7	52.5 ± 12.2		
FACT-Br total	133.6 ± 24.2[d]	95.3 ± 21.6	90.8 ± 17.5	94.1 ± 20.0	94.1 ± 22.2		

FACT-Br/G the functional assessment of cancer therapy, brain cancer/general, *PWB* physical well-being, *SWB* social/family well-being, *EWB* emotional well-being, *FWB* functional well-being, *BrCS* Brain cancer subscale, *TOI* Trial Outcome Index, *Test 2* week 6, *Test 3* week 28, *Test 4* week 40, *Test 5* week 52, *SD* standard deviation

[a] n = 27

[b] n = 21

[c] Based on n = 1075 general U.S. adult population (Brucker et al. 2005)

[d] n = 17

[e] One sample t-tests of average for change scores from test 5 to baseline

within the normal range experience depression at later test time points. Fox et al. found the prevalence of depression to be 95 % at a mean of 46 months after being diagnosed with HGG [12]. Kilbride et al. identified among 13 patients, four who suffered from anxiety and five who were depressed during the interval between surgery and radiotherapy [39]. Our study found that eight [26 %] out of 30 patients [the primary sample] and four [22 %] out of 18 patients [sub-sample] reported cut-off levels indicating depression at least at one time point. Further, impairment of the physical condition and fatigue [9, 40–43] causes severe limitations of daily activities and reduce QOL [44], being followed by distressful emotional and psychological reactions such as depression [45–49].

Finally, brain tumour histology and grade of malignancy affect the production and release of biological factors that cause depressive symptoms [50]. Our study showed strong associations between depression and the variables of physical and functional outcomes suggesting that patients are at risk for unrecognised depression throughout the trajectory. In contrast, our sub-group analysis [n = 18] suggests a decreasing tendency for depression over time [p = 0.07]. This indication is supported by studies identifying patients with HGG that report an acceptable QOL during the oncological treatments [51, 52]. Still, a few cases of moderate depressions are identified at each test time point. It is difficult to distinguish between depression, 'understandable' sadness [53] or vegetative symptoms of depression such as loss of interest, emotion and energy [54]. Systematic screening and quantification for levels of depression and anxiety is imperative [55] and recommended in this group of patients, especially in case of physical decline and tumour progression. However, instruments should not be used as a substitute for in-depth conversations but rather function as guidance for clinicians that facilitate the dialogue with the patient [56].

The present results obtained with the FACT-Br identified an improved emotional well-being throughout the

HGG trajectory for the sub-sample who completed the 1-year of follow-up. There may be various explanations for this result. First, patients might adapt to their HGG illness in a way that facilitates control [5] or a better coping despite symptom progression [57]. Second, and similar to previous studies [58, 59] the SWB score was higher than the normative values at all test points showing that patients experience increased social support from friends and families, which might lead to an improvement of the HRQOL. Third, previous study confirms that hope is a source of strength that helps individuals to remain active [60, 61], brings purpose and meaning to life, encourages a positive attitude and improves psychological well-being [62]. EWB was related to the level of functional status [63], and the 1-year survivors had higher KPS values compared to the primary sample throughout the study, which could be the reason for the increase in the EWB. Our findings indicate that there is a need for interventions that improve symptom management as patients report a number of brain cancer related difficulties. It is possible that a higher level of HRQOL can be achieved and maintained among HGG patients through an early palliative approach with the aim to improve life planning [64].

Whether a prolonged survival time or improvement of HRQOL should be prioritized relies on individual preferences and needs [65, 66]. Therefore, it is crucial to involve the patients actively in the treatment decisions of depression as several therapeutical options can be provided [38]. Patient involvement has the potential to contribute to a better adaption process to the HGG illness [67]. Eventually, this can lead to a positive effect on HRQOL among terminally ill HGG patients [6].

Study limitations

The literature has identified differences in levels of anxiety, depression and HRQOL with respect to gender [68], age and KPS [10], while the role of tumor localisation is inconclusive [69–71]. Our study examined a limited number of relationships. Whether, age, gender, education and tumour progression are variables that may have an effect on the results cannot be estimated due to small sample size. Drop-out of patients was predominantly being due to neurological decline or death. A cognitive phenomenon known as *response shift* refers to a change in the meaning of the participants' values and/or perception over a period of time [72]. Therefore subjects might change their response to PROs measures over time, not only because of change in the evaluated study items, but also because they might have changed their perception of the significance of HRQOL [73].

Conclusion

Patients with HGG experience a functional and physical decline, with a negative impact on the level of physical activity. Patients' physical and functional outcomes were closely associated to the prevalence of depression. Nonetheless anxiety and emotional well-being were closely related and both improved over time for 1-year HGG survivors. Explanatory factors can be social support from friends and families and the higher performance status among the 1-year HGG survivors.

Acknowledgments We are grateful to the participants and to the physicians and nurses at the Department of Neurosurgery, University Hospital of Copenhagen who supported recruitment. The study is supported by grants from The Center for Integrated Rehabilitation of Cancer Patients [CIRE], established by The Danish Cancer Society and The Novo Nordisk Foundation, from The Neuro Centre at the University Hospital of Copenhagen, The Novo Nordisk Foundation for Clinical Nursing Research, The Capital Regional Research Foundation in Denmark, Torben and Alice Frimodts Foundation, Vera and Flemming Westerbergs Foundation, Hetland Olsen's Foundation and The Research Foundation at the University Hospital of Copenhagen.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Preusser M, de Ribaupierre S, Wohrer A, Erridge SC, Hegi M, Weller M et al (2011) Current concepts and management of glioblastoma. Ann Neurol 70(1):9–21
2. Hottinger AF, Homicsko K, Negretti L, Lhermitte B, Stupp R (2012) Decision making and management of gliomas: practical considerations. Ann Oncol 23(Suppl 10):x33–x40
3. Cavers D, Hacking B, Erridge SC, Morris PG, Kendall M, Murray SA (2013) Adjustment and support needs of glioma patients and their relatives: serial interviews. Psycho-oncology 22(6):1299–1305
4. Ostgathe C, Gaertner J, Kotterba M, Klein S, Lindena G, Nauck F et al (2010) Differential palliative care issues in patients with primary and secondary brain tumours. Support Care Cancer 18(9):1157–1163
5. Lovely MP, Stewart-Amidei C, Page M, Mogensen K, Arzbaecher J, Lupica K et al (2013) A new reality: long-term survivorship with a malignant brain tumor. Oncol Nurs Forum 40(3):267–274
6. Freire ME, Sawada NO, Franca IS, Costa SF, Oliveira CD (2014) Health-related quality of life among patients with advanced cancer: an integrative review. Rev Esc Enferm USP 48(2): 357–367
7. Giovagnoli AR (1999) Quality of life in patients with stable disease after surgery, radiotherapy, and chemotherapy for malignant brain tumour. J Neurol Neurosurg Psychiatry 67(3): 358–363
8. Litofsky NS, Farace E, Anderson Jr F, Meyers CA, Huang W, Laws Jr ER, et al. (2004) Depression in patients with high-grade glioma: results of the Glioma Outcomes Project. Neurosurgery 54(2):358–366; discussion 366–367

9. Klein M, Taphoorn MJ, Heimans JJ, van der Ploeg HM, Vandertop WP, Smit EF et al (2001) Neurobehavioral status and health-related quality of life in newly diagnosed high-grade glioma patients. J Clin Oncol 19(20):4037–4047
10. Cheng JX, Zhang X, Liu BL (2009) Health-related quality of life in patients with high-grade glioma. Neuro Oncol 11(1): 41–50
11. Pelletier G, Verhoef MJ, Khatri N, Hagen N (2002) Quality of life in brain tumor patients: the relative contributions of depression, fatigue, emotional distress, and existential issues. J Neurooncol 57(1):41–49
12. Fox SW, Lyon D, Farace E (2007) Symptom clusters in patients with high-grade glioma. J Nurs Scholarsh 39(1):61–67
13. Rooney AG, Carson A, Grant R (2011) Depression in cerebral glioma patients: a systematic review of observational studies. J Natl Cancer Inst 103(1):61–76
14. Krebber AM, Buffart LM, Kleijn G, Riepma IC, de Bree R, Leemans CR et al (2014) Prevalence of depression in cancer patients: a meta-analysis of diagnostic interviews and self-report instruments. Psychooncology 23(2):121–130
15. D'Angelo C, Mirijello A, Leggio L, Ferrulli A, Carotenuto V, Icolaro N et al (2008) State and trait anxiety and depression in patients with primary brain tumors before and after surgery: 1-year longitudinal study. J Neurosurg 108(2):281–286
16. Piil K, Jarden M, Jakobsen J, Christensen KB, Juhler M (2013) A longitudinal, qualitative and quantitative exploration of daily life and need for rehabilitation among patients with high-grade gliomas and their caregivers. BMJ Open. doi:10.1136/bmjopen-2013-003183
17. Braun V, Clarke V (2006) Using thematic analysis in psychology. Qual Res Psychol 3:77–101
18. Polit D, Beck C (eds) (2012) Nursing research. Generating and assessing evidence for nursing practice, 9th edn. Wolters Kluwer, Lippincottt Williams and Wilkins, Philadelphia
19. Creswell J, Clark V (eds) (2011) Designing and conducting mixed methods research, 2nd edn. SAGE, Thousand Oaks, California
20. Piil K, Juhler M, Jakobsen J, Jarden M (2015) Daily life experiences of patients with high-grade gliomas and their caregivers—a longitudinal exploration of rehabilitation and supportive. Neurosci Nurs (in press)
21. Saltin B, Grimby G (1968) Physiological analysis of middle-aged and old former athletes. Comparison with still active athletes of the same ages. Circulation 38(6):1104–1115
22. Adamsen L, Quist M, Andersen C, Moller T, Herrstedt J, Kronborg D et al (2009) Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial. BMJ 13(339):b3410
23. Aadahl M, Jorgensen T (2003) Validation of a new self-report instrument for measuring physical activity. Med Sci Sports Exerc 35(7):1196–1202
24. Snaith RP (2003) The hospital anxiety and depression scale. Health Qual Life Outcomes 1(1):29
25. Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. Acta Psychiatr Scand 67(6):361–370
26. Weitzner MA, Meyers CA, Gelke CK, Byrne KS, Cella DF, Levin VA (1995) The functional assessment of cancer therapy [FACT] scale. Development of a brain subscale and revalidation of the general version [FACT-G] in patients with primary brain tumors. Cancer 75(5):1151–1161
27. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A et al (1993) The functional assessment of cancer therapy scale: development and validation of the general measure. J Clin Oncol 11(3):570–579
28. Paulsen A, Overgaard S, Lauritsen JM (2012) Quality of data entry using single entry, double entry and automated forms processing—an example based on a study of patient-reported outcomes. PLoS One 7(4):e35087
29. Buchele G, Och B, Bolte G, Weiland SK (2005) Single vs. double data entry. Epidemiology 16(1):130–131
30. Crawford JR, Henry JD, Crombie C, Taylor EP (2001) Normative data for the HADS from a large non-clinical sample. Br J Clin Psychol 40(Pt 4):429–434
31. Brucker PS, Yost K, Cashy J, Webster K, Cella D (2005) General population and cancer patient norms for the functional assessment of cancer therapy-general [FACT-G]. Eval Health Prof 28(2):192–211
32. Meyers CA, Brown PD (2006) Role and relevance of neurocognitive assessment in clinical trials of patients with CNS tumors. J Clin Oncol 24(8):1305–1309
33. Keilani M, Krall C, Marosi C, Flechl B, Dieckmann K, Widhalm G et al (2012) Strength of skeletal muscle and self-reported physical performance in Austrian glioblastoma-patients. Wien Klin Wochenschr 124(11-12):377–383
34. Ruden E, Reardon DA, Coan AD, Herndon JE II, Hornsby WE, West M et al (2011) Exercise behavior, functional capacity, and survival in adults with malignant recurrent glioma. J Clin Oncol 29(21):2918–2923
35. Piil K, Juhler M, Jakobsen J, Jarden M (2014) Controlled rehabilitative and supportive care intervention trials in patients with high-grade gliomas and their caregivers: a systematic review. BMJ Support Palliat Care. doi:10.1136/bmjspcare-2013-000593
36. Bartolo M, Zucchella C, Pace A, Lanzetta G, Vecchione C, Bartolo M et al (2012) Early rehabilitation after surgery improves functional outcome in inpatients with brain tumours. J Neurooncol 107(3):537–544
37. Petruzzi A, Finocchiaro CY, Lamperti E, Salmaggi A (2013) Living with a brain tumor: reaction profiles in patients and their caregivers. Support Care Cancer 21(4):1105–1111
38. Boele FW, Verdonck-de Leeuw IM, Cuijpers P, Reijneveld JC, Heimans JJ, Klein M (2014) Internet-based guided self-help for glioma patients with depressive symptoms: design of a randomized controlled trial. BMC Neurol 14:81
39. Kilbride L, Smith G, Grant R (2007) The frequency and cause of anxiety and depression amongst patients with malignant brain tumours between surgery and radiotherapy. J Neurooncol 84(3):297–304
40. Giovagnoli AR, Silvani A, Colombo E, Boiardi A (2005) Facets and determinants of quality of life in patients with recurrent high grade glioma. J Neurol Neurosurg Psychiatry 76(4):562–568
41. Mauer M, Stupp R, Taphoorn MJ, Coens C, Osoba D, Marosi C et al (2007) The prognostic value of health-related quality-of-life data in predicting survival in glioblastoma cancer patients: results from an international randomised phase III EORTC Brain Tumour and Radiation Oncology Groups, and NCIC Clinical Trials Group study. Br J Cancer 97(3):302–307
42. Taphoorn MJ, van den Bent MJ, Mauer ME, Coens C, Delattre JY, Brandes AA et al (2007) Health-related quality of life in patients treated for anaplastic oligodendroglioma with adjuvant chemotherapy: results of a European Organisation for Research and Treatment of Cancer randomized clinical trial. J Clin Oncol 25(36):5723–5730
43. Taphoorn MJ, Stupp R, Coens C, Osoba D, Kortmann R, van den Bent MJ et al (2005) Health-related quality of life in patients with glioblastoma: a randomised controlled trial. Lancet Oncol 6(12):937–944
44. Jones LW, Friedman AH, West MJ, Mabe SK, Fraser J, Kraus WE et al (2010) Quantitative assessment of cardiorespiratory fitness, skeletal muscle function, and body composition in adults with primary malignant glioma. Cancer 116(3):695–704
45. Boele FW, Klein M, Reijneveld JC (2014) Verdonck-de Leeuw IM, Heimans JJ. Symptom management and quality of life in glioma patients. CNS Oncol 3(1):37–47

46. Kim YH, Park CK, Kim TM, Choi SH, Kim YJ, Choi BS et al (2013) Seizures during the management of high-grade gliomas: clinical relevance to disease progression. J Neurooncol 113(1) :101–109
47. Klein M, Postma TJ, Taphoorn MJ, Aaronson NK, Vandertop WP, Muller M et al (2003) The prognostic value of cognitive functioning in the survival of patients with high-grade glioma. Neurology 61(12):1796–1798
48. Lovely MP, Miaskowski C, Dodd M (1999) Relationship between fatigue and quality of life in patients with glioblastoma multiformae. Oncol Nurs Forum 26(5):921–925
49. Molassiotis A, Wilson B, Brunton L, Chaudhary H, Gattamaneni R, McBain C (2010) Symptom experience in patients with primary brain tumours: a longitudinal exploratory study. Eur J Oncol Nurs 14(5):410–416
50. Starkweather AR, Sherwood P, Lyon DE, McCain NL, Bovbjerg DH, Broaddus WC (2011) A biobehavioral perspective on depressive symptoms in patients with cerebral astrocytoma. J Neurosci Nurs 43(1):17–28
51. Brown PD, Ballman KV, Rummans TA, Maurer MJ, Sloan JA, Boeve BF et al (2006) Prospective study of quality of life in adults with newly diagnosed high-grade gliomas. J Neurooncol 76(3):283–291
52. Lucchiari C, Botturi A, Silvani A, Lamperti E, Gaviani P, Innocenti A, et al. (2015) Cognitive strategies and quality of life of patients with high-grade glioma. Support Care Cancer, 1–9
53. Singer S, Brown A, Einenkel J, Hauss J, Hinz A, Klein A et al (2011) Identifying tumor patients' depression. Support Care Cancer 19(11):1697–1703
54. Weitzner MA (1999) Psychosocial and neuropsychiatric aspects of patients with primary brain tumors. Cancer Investig 17(4): 285–291; discussion 296–297
55. Rooney AG, McNamara S, Mackinnon M, Fraser M, Rampling R, Carson A et al (2013) Screening for major depressive disorder in adults with cerebral glioma: an initial validation of 3 self-report instruments. Neuro Oncol 15(1):122–129
56. Rooney AG, Brown PD, Reijneveld JC, Grant R (2014) Depression in glioma: a primer for clinicians and researchers. J Neurol Neurosurg Psychiatry 85(2):230–235
57. Brennan J (2001) Adjustment to cancer—coping or personal transition. Psychooncology 10(1):1–18
58. Halkett GK, Lobb EA, Rogers MM, Shaw T, Long AP, Wheeler HR et al (2015) Predictors of distress and poorer quality of life in high grade glioma patients. Patient Educ Couns 98(4):525–532
59. Janda M, Steginga S, Langbecker D, Dunn J, Walker D, Eakin E (2007) Quality of life among patients with a brain tumor and their carers. J Psychosom Res 63(6):617–623
60. Coolbrandt A, Sterckx W, Clement P, Borgenon S, Decruyenaere M, de Vleeschouwer S et al. (2014) Family caregivers of patients with a high-grade glioma: a qualitative study of their lived experience and needs related to professional care. Cancer Nurs. doi:10.1097/NCC.0000000000000216
61. Sterckx W, Coolbrandt A, Clement P, Borgenon S, Decruyenaere M, De Vleeschouwer S et al (2015) Living with a high-grade glioma: a qualitative study of patients' experiences and care needs. Eur J Oncol Nurs. doi:10.1016/j.ejon.2015.01.003
62. Sutton K (2013) The impact on quality of life for people with brain tumours of entering a research trial involving new anti-cancer agents. Eur J Oncol Nurs 17(4):396–401
63. Rooney AG, McNamara S, Mackinnon M, Fraser M, Rampling R, Carson A et al (2013) The frequency, longitudinal course, clinical associations, and causes of emotional distress during primary treatment of cerebral glioma. Neuro Oncol 15(5): 635–643
64. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA et al (2010) Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 363(8): 733–742
65. Johnstone M (2004) Bioethics. A nursing perspective. Churchill Livingstone, Melbourne
66. Driven L, Reijneveld JC, Taphoorn MJ (2014) Health-related quality of life or quantity of life: a difficult trade-off in primary brain tumors? Semin Oncol 41:541–552
67. Hubbard G, Kidd L, Donaghy E (2008) Preferences for involvement in treatment decision making of patients with cancer: a review of the literature. Eur J Oncol Nurs 12(4):299–318
68. Yavas C, Zorlu F, Ozyigit G, Gurkaynak M, Yavas G, Yuce D et al (2012) Health-related quality of life in high-grade glioma patients: a prospective single-center study. Support Care Cancer 20(10):2315–2325
69. Hahn CA, Dunn RH, Logue PE, King JH, Edwards CL, Halperin EC (2003) Prospective study of neuropsychologic testing and quality-of-life assessment of adults with primary malignant brain tumors. Int J Radiat Oncol Biol Phys 55(4):992–999
70. Salo J, Niemela A, Joukamaa M, Koivukangas J (2002) Effect of brain tumour laterality on patients' perceived quality of life. J Neurol Neurosurg Psychiatry 72(3):373–377
71. Rogers MP, Orav J, Black PM (2001) The use of a simple Likert scale to measure quality of life in brain tumor patients. J Neurooncol 55(2):121–131
72. Polit DF (2014) Getting serious about test-retest reliability: a critique of retest research and some recommendations. Qual Life Res 23:1713–1720
73. Ring L, Hofer S, Heuston F, Harris D, O'Boyle CA (2005) Response shift masks the treatment impact on patient reported outcomes [PROs]: the example of individual quality of life in edentulous patients. Health Qual Life Outcomes 7(3):55