Neuro-Oncology 14:iv8–iv16, 2012.
doi:10.1093/neuonc/nos205

Factors influencing quality of life in adult patients with primary brain tumors

Rakesh Jalali and Debnarayan Dutta

NeuroOncology Group, Tata Memorial Hospital, Mumbai, India (R.J.); Apollo Specialty Hospital, Chennai, India (D.D.)

We performed a literature review with respect to factors influencing health-related quality of life (QOL) in adults with primary brain tumors. A comprehensive, peer-reviewed literature search was performed including studies examining QOL in adults with high-grade gliomas and low-grade gliomas and in routine neuro-oncology practice. The interpretation and implication of QOL domain scores may be different in high-grade, low-grade, and benign brain tumors. Several patient-related, treatment-related, and sociocultural factors influence QOL scores. Pretreatment baseline QOL domain scores have been shown to be a predictive parameter for survival function. Implementation of QOL scores in routine clinical practice is underused. QOL is an important outcome measure in the treatment of patients with brain tumors and should be incorporated as a surrogate end point along with traditional end points, such as disease-free and overall survival in most current trials.

Keywords: adult, primary brain tumor, quality of life, routine clinical practice.

Background

Primary brain tumors comprise 2% of all malignancies in the adult patient population.[1] Over the past few years, improvements in treatment approaches have included refinements in surgical resection, radiation therapy delivery methods, and newer systemic agents for these tumors. There have also been tremendous advances in the understanding of the molecular biology of these tumors, aiding the exploration of several new potential therapeutic avenues.[2] Such advancements have improved survival function in both benign and malignant brain tumors. Unfortunately, even with modern treatment modalities, long-term outcomes in high-grade gliomas and other such tumors remain disappointingly low, with diffuse low-grade glioma transforming to high-grade in a median duration of 5–7 years.[3,4] In benign tumors, neurological and neurocognitive function preservation is the prime concern of treatment. Therefore, preservation of normal daily activities and neurological function is being increasingly taken into consideration in the present day neuro-oncology practice, and quality of life (QOL) is considered an important end point.[5] Prospective studies evaluating the impact of disease progression and treatment on QOL domain parameters have shown disease progression to have detrimental impact on QOL domain scores.[6,7]

A meta-analysis of 30 prospective clinical trials ($n = 10{,}108$) from different primary tumor sites confirmed that pretreatment (baseline) QOL parameter scores, such as physical functioning, pain, appetite loss, and World Health Organization performance status, have prognostic significance on survival function. Age, sex, socio-demographic parameters, and distant metastasis have also been shown to influence QOL score.[8]

Treatment with aggressive surgery, radiation therapy, and chemotherapy schedules in advanced and metastatic disease impair QOL domain scores.[6–8] There is a need for caution regarding some of the potentially aggressive treatments, which may improve the clinically meaningful survival function, but may significantly impair QOL function. On the other hand, prospective clinical trials in other cancer sites have proven that early supportive care and preservation of QOL eventually improves survival function.[9] Similarly, many other prospective studies suggest that pretreatment baseline QOL domain scores are also predictive of survival function.[10]

QOL Evaluation Tools

There are various QOL and neurocognitive function assessment tools being used in clinical trials and clinical practice.[5,11–19] Functional evaluations are broad, either with objective assessment (eg, clinical examination by physician or nurse) or subjective assessment through

Corresponding Author: Rakesh Jalali, MD, Professor of Radiation Oncology and NeuroOncology, 1129, Homi Bhabha Block, Tata Memorial Hospital, Parel, Mumbai, India 400 012 (rjalali@tmc.gov.in).

questionnaire-based evaluation of well-being and QOL. Commonly used objective evaluation tools are Karnofsky performance score (KPS), neurological performance score (NPS), Barthel's activity of daily living, and others. Objective questionnaire-based QOL evaluation tools are mainly European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30), brain-specific module (BN-20), and Functional Assessment of Cancer Therapy (FACT) cancer-specific scales.[12–19] Neurocognitive function is assessed using a various battery of tests.[16] The extensive MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT) has 22 symptom items that measures affective, cognitive, focal neurologic deficit, constitutional, generalized symptom, and gastrointestinal-related factor. In the MDASI-BT, data collection tools included a patient-completed demographic data sheet, an investigator-completed clinician checklist, and a core inventory with 18 neurological symptoms.[15] In the RTOG 0525 phase-III randomized study ($n = 833$), a dose-dense temozolomide (TMZ) regimen after concomitant chemo-radiation therapy in gliobloastoma was evaluated with survival function and QOL.[20]

Factors Influencing QOL Score

QOL scores depend on various patient-, tumor-, and treatment-related factors.[11,12,20–32] There may be differential importance of various factors influencing QOL scores in high-grade gliomas (HGGs) and low-grade gliomas (LGGs). In both in HGGs and LGGs, the tumor appears to be one of the major factors influencing cognitive function and QOL domain scores.[4,21,22,33,34] Patients with controlled disease have the most preserved QOL domain scores, whereas there are impairments on progression.[4,22] Other tumor-related factors influencing QOL scores are tumor site, laterality, size, hypothalamic involvement, hormonal deficiencies, and epilepsy.[23–29] Anticonvulsants, corticosteroids, new neurological deficit, higher dose of radiation therapy, and chemotherapy all have detrimental effects on QOL scores.[29–32] Complete surgical resection, radiation therapy in HGGs, or low dose per fraction radiation therapy in LGGs with loco-regional control will improve or maintain QOL domain scores.[4,22,23,28] Different socioeconomic and cultural factors also play a role in QOL domain scores.[11]

QOL Issues in HGGs

Patients with HGGs often present with convulsion disorders, headache, and neurological deficit.[18] These symptoms lead to definite impairment of functional abilities and QOL. Impairment of cognitive function domains in HGG depends on tumor size and location of the tumor.[21,23–26,33,34] Surgical excision of the tumors reduces the mass effect, mainly improving motor function and related QOL domains. On the other hand, injury due to aggressive surgical intervention may also induce further neurological deficit and, thus, impair QOL and survival.[32] In a non-randomized prospective study, safe surgical resection improved neurological function and QOL domain scores.[35] It seems that safe surgical resection with no additional neurological deficit after surgery leads to optimal survival function improvement and preservation of QOL.

In HGG, postoperative radiotherapy (RT) has been shown to improve survival.[4,22] Median survival even after treatment is relatively short (12–17 months), and therefore, preservation of neurological function and QOL is an important end point. RT may decrease QOL scores in patients with adverse effects, such as hair loss, fatigue, somnolence, and cognitive problems.[33] Early QOL studies ($n = 525$) in both newly diagnosed and recurrent HGG showed that patients with HGGs have impairment in QOL domains, particularly in fatigue, uncertainty about the future, motor difficulties, drowsiness, communication difficulties, and headache.[33] Patients with controlled disease had better QOL domain scores than did those with residual/recurrent disease.[33] Patients with recurrent disease had poorer QOL scores, compared with patients with newly diagnosed HGGs.[21,33,34] There was no significant difference in QOL domain scores in patients with anaplastic astrocytomas and those with GBMs.[33] Corticosteroid and anticonvulsant treatments have been shown to have a detrimental effect in few of the QOL domain scores (fatigue, somnolence) and may reduce neurocognitive function.[33]

Prospective, multi-centric randomized studies established the role of concomitant chemotherapy with TMZ and RT in newly diagnosed GBMs.[3] Patients with GBM ($n = 583$) treated with TMZ+RT had statistically significant improvement in survival function (2 months overall survival benefit with RT + TMZ; $P = .001$).[3] Long-term follow-up in the same study confirmed the superiority of TMZ+RT as the new standard of care in newly diagnosed GBMs.[36] Although there was evidence of improvement with TMZ + RT in GBMs, the main apprehension was with regard to QOL and toxicity profile with TMZ when prescribed along with RT. TMZ is known to have mainly hematological (thrombocytopenia) and gastrointestinal (nausea) toxicities.[37] Prospective QOL study in the same cohort of patients established that there was no significant detrimental effect of TMZ along with RT.[21] The RT + TMZ arm had poorer nausea and vomiting scores after RT completion, although there was no statistically significant difference compared with the RT alone arm.[21] There was improvement in global QOL score after RT + TMZ that was maintained until there was clinical or radiological progression. The TMZ + RT arm had worse social functioning score ($P = .0052$).[21]

Dose escalation study with conformal irradiation (dose levels, 66, 72, 78, and 84 Gy) were evaluated prospectively, and QOL was assessed with the Spitzer Quality of Life Index (RTOG 93–03).[38] Patients with tumor control had shown preservation of QOL

scores.[38] Dose escalation was not shown to be a significant detrimental factor for QOL.[38] However, there is a need for a larger study to evaluate the impact of dose escalation on QOL. Dose escalation with brachytherapy in HGGs has been shown to have a detrimental impact on both survival function and QOL.[32]

In HGGs, tumor is an important factor influencing neurocognitive function and QOL.[21,34] Disease recurrence/progression is associated with impairment of QOL domain scores.[34] Treatment modalities in recurrent HGGs also influence QOL scores. Treatment with TMZ had no significant negative effect on QOL in patients with recurrent GBM.[39] Responders to TMZ had improvement in QOL domain scores (global, motor dysfunction, emotional function, drowsiness, future uncertainty, and communication deficit) until clinical or radiological disease progression.[39]

Although TMZ and RT in GBM have not been shown to have any significant detrimental effect on QOL scores,[21] combined procarbazine, CCNU (lomustine), and vincristine (PCV) chemotherapy after RT in patients with anaplastic oligodendroglioma ($n = 368$; EORTC 26951) did show a negative impact on early QOL domain scores (nausea/vomiting, appetite loss, and drowsiness).[30,40] In longer follow-up, however, there was a significant difference between RT alone and RT+PCV.[40] In anaplastic oligodendrogliomas (RTOG 94–02), there was no progression-free survival benefit with PCV and no impact on QOL.[41] Dose escalation study in GBM with carmustine chemotherapy (RTOG 98–03) showed progressive deterioration of QOL function.[42] Few studies with small numbers of patients showed no QOL benefit with carmustine-impregnated wafers in recurrent/progressive HGGs.[43] Early studies with bevacizumab (a humanized monoclonal antibody that binds and inhibits the activity of VEGF) showed promising results in recurrent/refractory HGGs in terms of neurocognitive function preservation.[44] A randomized phase II study comparing bevacizumab alone or in combination with irinotecan ($n = 167$) in patients with recurrent/refractory GBM showed 75% reduction of corticosteroid dose at 6 months after treatment follow-up.[45] It seems that the steroid-sparing effect of bevacizumab improves neurological symptoms and may have a positive impact on QOL in recurrent/refractory HGGs. Long-term survivors with HGGs show improvement in QOL domain scores and may match healthy individuals.[45] A review of 300 patients with GBM treated with re-irradiation yielded 6-month PFS of 28%–39%; 1-year overall survival of 18%–48% and clinical improvements (QOL score) were observed in 24%–45%. Patients with KPS <70 had higher risk of early progression and lesser benefit from re-irradiation.[46]

The recently concluded RTOG-0525 study compared dose-dense TMZ to standard adjuvant TMZ in a large patient population ($n = 833$) and extensively evaluated QOL endpoints in addition to survival. QOL was overall worse in patients receiving a dose-dense TMZ schedule. Of interest, several QOL domains emerged as strong predictors of overall survival. These included baseline physical functioning (0.988; 95% confidence interval [CI], 0.977–0.999; $P = .029$), baseline delayed recognition (0.874; 95% CI, 0.771–0.991; $P = .036$), cognitive function decline (MDASI-BT; 1.82; 95% CI, 1.14–2.89; $P = .012$), cognitive function decline (QLQ-BN20; 1.95; 95% CI, 1.23–3.09; $P = .004$), deterioration of motor function (1.59; 95% CI, 1.02–2.47; $P = .041$), and deterioration of delayed recognition (1.90; 95% CI; 1.14–3.15; $P = .013$). The investigators have demonstrated that changes in QOL can act as useful markers of response and/or progression. In addition, encouragingly, collecting detailed QOL data are feasible in a large clinical trial setting.[20] This may well act as a benchmark for future clinical trials.

QOL Issues in LGGs

LGGs include diffuse fibrillary astrocytoma, oligodendroglioma, and mixed oligo-astrocytomas, and median PFS after diagnosis is 5–7 years; 5- and 10-year PFS rates are 50% and 12%, respectively.[4] In LGG, tumor is the most important factor influencing the QOL and neurocognitive function score.[4,22] LGGs are treated with total or near-total surgical resection. Patients with LGG treated with gross surgical excision have been shown to have improved QOL domain scores.[4] In LGG, after safe surgical excision with no additional neurological deficit, peri-operative injuries do not impair QOL domain scores.[4] Patients with biopsy only had poorer QOL scores.[4,22] It appears that patients with deep seated/eloquent area LGGs are treated with biopsy only, and impaired QOL function may be mostly attributable to the location of tumor rather than surgery type.[4,11,22] Prospective evaluation of LGGs ($n = 101$) with pre- and postoperative QOL evaluation and long-term evaluation (>10 years) suggests that there is short-term impairment of cognitive and QOL domain functions after surgery.[47] However, after safe surgical resection, QOL is maintained in long-term follow up.[47] Location of the tumor has shown to influence QOL score.[24] Patients with dominant hemisphere tumor had more disability in cognitive function scores.[24] Patients treated with anti-epileptics had poor attention and execution function.[26] Right hemisphere lesions cause poor perception and psychomotor speed function.[24] Left hemisphere lesions are associated with poor attention and execution function.[24]

Two important studies have evaluated the RT dose-response relationship in LGGs.[23,48] There was a plateau in the dose-response curve after RT dose of 45 Gy (in 1.8–2 Gy/fraction). The EORTC 22845 study addressed the role of RT (early vs late) in LGGs in multi-centric, prospective, randomized setting.[23] The recent update with longer follow-up (follow-up range, 2–22 years; median, 9.3 years) of this randomized study with a large cohort of patients ($n = 311$) showed PFS benefit in the early RT arm and no difference in overall survival.[4] Thus, young patients with

seizures and near complete surgical excision are considered for late RT at progression. On the other hand, patients with higher probability of local recurrence (according to Pignatti's criteria) were considered for early RT.[49] Early RT in patients with LGG with high-risk of recurrence delays disease progression and, thus, may also preserve cognitive function. Unfortunately, in this randomized study, QOL assessment was not included; thus, the impact of early or late RT on QOL parameters was not evaluated.

A prospective study of 195 LGGs at Maastricht University with long-term follow up (median follow-up, 12 years) assessed the QOL parameters with RT in LGGs.[50,51] Patients with LGGs had poorer cognitive function scores, compared with healthy matched individuals and patients with Non-Hodgkin Lymphoma/Chronic lymphocytic leukemia.[50] It suggests that tumor impairs cognitive function and QOL. First assessment at 6 years after RT did not show any significant difference in cognitive function domains between the early RT and the no (delayed) RT arms.[50] However, at second assessment after 12 years, significant worsening of cognitive domains, such as executive functioning ($P = .03$), information processing speed ($P = .05$), and attention domain ($P = .003$), were seen in the early RT arm.[51] Higher dose per fraction (>2 Gy) may have accelerated detrimental impact on cognitive functions.[51] This study showed that even conventional RT (1.8–2 Gy per fraction) can cause additional late delayed cognitive function impairment, especially in the attention domain. Chemotherapy also has shown to impair cognitive function ("chemobrain").[29] A prospective study of TMZ in LGGs showed preserved QOL scores in patients with controlled/stable disease.[31]

QOL Issues in Benign Tumors

Benign brain tumors/lesions (eg, craniopharyngiomas, pituitary tumor) do not progress to higher grade and usually have long survival.[52–56] Reduction of mass effect with surgical intervention, prevention of progression, and preservation of neurological function are the main goals of treatment. Unfortunately, there are only few prospective cognitive function and QOL studies in adult patients with these rare benign conditions. In craniopharyngiomas and pituitary tumors, hydrocephalus, growth hormone (GH) deficiency, and hypothalamic involvement have been shown to impair cognitive function.[52–56] The transsphenoidal approach has been shown to preserve QOL domains in pituitary tumors.[55] Patients with acromegaly with controlled disease have preserved QOL scores compared to patients with uncontrolled disease.[56] GH deficiency has a detrimental impact on QOL.[54] Patients with craniopharyngiomas have impaired cognitive function scores, compared with healthy individuals.[52] It seems that conventional postoperative RT has no detrimental effect on patients with pituitary tumors or craniopharyngiomas.[52,53]

QOL Studies in Routine Clinical Practice

The majority of data on QOL in brain tumors are from western populations in which the socioeconomic and cultural backgrounds are different from those in Asian populations.[11,21,22,33,34] Interpretation and implication of QOL domain scores may be different in clinical trials with well-informed patients and comprehensive consent forms than in routine clinical practices in which patients are less informed about the outcome of the treatment.[11] Socio-cultural factors may interfere with dissemination of appropriate information regarding the disease and prognosis.[11] There are publications on QOL in routine clinical practice from neuro-oncology centers in Asian countries, such as China, Taiwan, and India. There are QOL studies from both clinical trials and routine clinical practice from developed countries.[57–60]

A QOL study from Brazil ($n = 30$) with FACT Br and SF36 questionnaires showed the feasibility of QOL studies in routine clinical practice.[18] Tsay et al. from Taiwan evaluated the impact of pre-surgery distress and anxiety in benign primary brain tumors ($n = 58$) in routine clinical practice and its impact on QOL.[58] There was impairment of QOL scores with severe distress and anxiety. A QOL evaluation from China using the EORTC- QLQ C30 questionnaire showed emotional impairment in 84.8%, social and cognitive impairment in 75%, physical impairment in 70.7% and role impairment in 50% of patients with gliomas ($n = 92$).[57] Factors, such as age, KPS, WHO grade, and tumor recurrence, significantly affected QOL scores. Ruge et al. ($n = 33$) performed a short-term (median follow-up, 18 months) QOL evaluation with SF-36 in LGGs treated in routine clinical practice.[61] Chaichana et al. showed that, in HGGs ($n = 544$), preoperative KPS score ≥90, preoperative seizures, gross-total resection, TMZ, new postoperative motor deficit, older age, and tumor recurrence influences functional status and QOL in routine clinical practice.[62] A Canadian study ($n = 130$) suggested that older age has a detrimental effect on QOL scores.[63] Computer-based QOL monitoring (EORTC C30 and BN20) has also been shown to be feasible in routine clinical practice.[64] Patients with GBM ($n = 50$) in routine practice with poor distress and anxiety scores had poorer QOL questionnaire compliance.[60] Patients with HGG ($n = 648$) with better seizure control had better preservation of QOL scores.[60] A retrospective series of 91 patients with meningioma treated in Germany confirmed the negative impact of age on cognitive function.[59]

Our earlier published study showed that patients with brain tumors treated in routine clinical practice in developing countries have a different patient demographic profile, compared with patients from developed countries.[65] In developing countries, HGGs occur 1 decade earlier than in developed countries, and the proportion of patients with benign tumors was relatively lower in developing country data. It seems that these variations

in patient demographic profile may be related to differential life expectancy in different countries. QOL in routine clinical practice ($n = 243$) described the difference in baseline future uncertainty scores in patients from developed countries with that in patients from developing countries.[11] Tumor type (HGG and LGG) and neurological function status (KPS and NPS) influenced baseline QOL domain scores. On the other hand, economic and literacy status did not have a significant influence on QOL scores. In the same cohort of patients, follow-up evaluation showed >20-point improvements in scores in seizure control, motor dysfunction (34%), pain (30%), insomnia (28%), headaches (26%), and communication deficit (22%). In LGGs, significant (>20 point) improvement was seen in seizure (33%), social function (30%), and headache (30%) domains, whereas there was some deterioration was in appetite loss (39%) and fatigue (24%) domains. During post-treatment follow-up, patients from high economic strata had more preserved global QOL function than did those form middle or low economic strata. Patients with complete or near-total excision of tumor had preserved QOL scores and patients who underwent only biopsy had poor pretreatment QOL scores. This suggests that site of the disease (surgically unapproachable region or deep-seated tumor) and type of tumor adversely influences the QOL score rather than surgical intervention itself. On the contrary, this may be a result of reduction of effect of tumor (mass effect/hydrocephalus) after radical surgery. Although there were differences in few QOL domains, in overall review, there was no significant difference between QOL data obtained from developing countries and those from developed countries.

QOL Evaluation Concerns and Issues

Evaluation, interpretation, and collection of QOL data are the most contentious issues and are now seriously evaluated.[66–68] A major problem of the questionnaire method of QOL measurement is the internal consistency.[66] There are debates regarding the change in QOL domain scores, which may have a clinically meaningful impact of follow-up evaluation. A small change in QOL scores from baseline may have statistical significance; however, if the change in score is small, there may not be any clinically meaningful change in patient perception. It seems that clinically relevant QOL domain score change depends on different domains and may also be influenced by socio-economic and cultural factors.[66] Recent studies suggest that minimum clinically important difference (MCID) in BN 20 domain scores for improvement or deterioration in physical domain is 9, role function 12, cognitive functioning 8, global health status 4, fatigue 9, and motor dysfunction 5. In mini-mental state examination, MCID ranges from 5 to 14.[66]

Subjective questionnaire-based QOL evaluation has few other concerns, such as questionnaire filling and missing data. Caregivers commonly fill out questionnaires on behalf of patients with HGGs and severe neurological deficits.[67] There are differences in concordance between the patient and caregiver scores, and these factors dilute subjective assessment scales. Prospective study regarding concordance suggested that, in >50% of questions, there was some degree of disagreement between the patients and their caregivers. The most common disagreements were in the domains of emotions and household needs.[68]

Concerns regarding the effects of missing pattern of patient in subsequent follow-up have been the topic of discussion for the past 2 decades.[69] Initially, the missing pattern was thought to be a random phenomenon and, thus, may not influence the QOL scores in subsequent follow-up. Of interest, patients who had missed baseline QOL evaluation because of some administrative error also had lower QOL scores. Quality of QOL data may be improved by minimizing administrative error, collection of consecutive patient data, and reducing dropout rates in subsequent follow-up.[69] Implications of QOL domain score may be different in patients from developed or developing countries with vast contrast in social support system and cultural influence. Questionnaire in regional language is critical for appropriate QOL evaluation.

In summary, QOL is an important end point in modern day clinical practice. In neuro-oncology, there are several patient-related, treatment-related, and socio-cultural factors that influence the QOL scores and their interpretation. There are no apparent differences in QOL domain score interpretation in clinical trial or routine clinical practice. There are differences in few QOL domains in patients from developing and developed countries, particularly in future uncertainty related domains. There is a need to incorporate QOL study in most clinical trials with modern aggressive treatment modalities.

Search Parameters

Our PubMed search was done with ("brain tumour"[All Fields] OR "brain neoplasms"[MeSH Terms] OR ("brain"[All Fields] AND "neoplasms"[All Fields]) OR "brain neoplasms"[All Fields] OR ("brain"[All Fields] AND "tumor"[All Fields]) OR "brain tumor"[All Fields]) AND ("quality of life"[MeSH Terms] OR ("quality"[All Fields] AND "life"[All Fields]) OR "quality of life"[All Fields]) AND ("adult"[MeSH Terms] OR "adult"[All Fields]).

Conflict of interest statement. None declared.

References

1. Jemal A, Siegel R, Ward E, et al. *CA Cancer J Clin*. 2006;56:106–130.
2. Wen PY, Kesari S. Malignant gliomas in adults. *N Engl J Med*. 2008;359:492–507.
3. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352:987–996.
4. van den Bent MJ, Afra D, de Witte O, et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. *Lancet*. 2005;366(9490):985–990.
5. Meyers CA, Brown PD. Role and relevance of neurocognitive assessment in clinical trials of patients with CNS tumors. *J Clin Oncol*. 2006;24:1305–1309.
6. Mauer M, Stupp R, Taphoorn MJ, Coens C, Osoba D, Marosi C. 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*. 2007;97(3):302–307.
7. Tan A, Novotny P, Kaur J. A patient-level meta-analytic investigation of the prognostic significance of baseline quality of life (QOL) for overall survival (OS) among 3,704 patients participating in 24 North Central Cancer Treatment Group (NCCTG) and Mayo Clinic Cancer Center (MC) oncology clinical trials. *J Clin Oncol*. 2008;26(15S): 9515.
8. Quinten C, Coens C, Mauer M, Comte S, Sprangers MAG, Cleeland C. Baseline quality of life as a prognostic indicator of survival:a meta-analysis of individual patient data from EORTC clinical trials. *Lancet Oncol*. 2009;10:865–871.
9. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA. Early palliative care for patients with metastatic non–small-cell lung cancer. *N Engl J Med*. 2010;363:733–742.
10. Efficace F, Bottomley A, Smit EF. Is a patient's self-reported health-related quality of life a prognostic factor for survival in non-small-cell lung cancer patients? A multivariate analysis of prognostic factors of EORTC study 08975. *Ann Oncol*. 2006;17:1698–1704.
11. Budrrukar A, Jalali R, Dutta D. Prospective Quality of Life assessment using EORTC QLQ 30 and brain cancer module (BN 20) in 257 consecutive adult patients with primary brain tumours in a typical Neuro-Oncology clinic in India. *J Neurooncol*. 2010;95(3): 413–419.
12. Brazil L, Thomas R, Laing R, et al. Verbally administered Barthel Index as functional assessment in brain tumour patients. *J Neurooncol*. 1997;34(2):187–192.
13. Wade DT. Measurement in neurological rehabilitation. *Curr Opin Neurol Neurosurg*. 1992;(5):682–6.
14. Dutta D, Vanere P, Gupta T, Munshi A, Jalali R. Factors influencing activities of daily living using FIM-FAM scoring system before starting adjuvant treatment in patients with brain tumors: results from a prospective study. *J Neurooncol*. 2009;94(1):103–110.
15. Armstrong TS, Mendoza T, Gring I. Validation of the M.D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT). *J Neurooncol*. 2006;80:27–35.
16. Hahn CA, Dunn RH, Logue PE, King JH, Edwards CL, Halperin EC. Prospective study of neuropsychologic testing and quality-of-life assessment of adults with primary malignant brain tumors. *Int J Radiat Oncol Biol Phys*. 2003;55(4):992–999.
17. Jalali R, Dutta D, Kamble R, Gupta T, Munshi A, Sarin R. Prospective assessment of activities of daily living using Modified Barthel's scoring system in children with low-grade gliomas treated with stereotactic conformal radiotherapy. *J Neurooncol*. 2008;90(3): 321–328.
18. Gazzotti MR, Malheiros SM, Batan Alith M, et al. Quality of life and physical limitations in primary brain tumor patients. *Qual Life Res*. 2011;20(10):1639–1643.
19. Weitzner MA, Meyers CA, Gelke CK. 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*. 1995;75:1151–1161.
20. Armstrong T, Wefel JS, Wang M, et al. Clinical utility of neurocognitive function, quality of life, and symptom assessment as prognostic factors for survival and measures of treatment effects on RTOG 0525. *J Clin Oncol*. 2011;(suppl):29;abstr 2016.
21. Taphoorn MJ, Stupp R, Coens C, Osoba D, Kortmann R, van den Bent MJ. Health-related quality of life in patients with glioblastoma: a randomised controlled trial. *Lancet Oncol*. 2005;6(12):937–944.
22. Kiebert GM, Curran D, Aaronson NK, Bolla M, Menten J, Rutten EH. Quality of life after radiation therapy of cerebral low-grade gliomas of the adult: results of a randomised phase III trial on dose response (EORTC trial 22844). EORTC Radiotherapy Co-operative Group. *Eur J Cancer*. 1998;34(12):1902–1909.
23. van Nieuwenhuizen D, Klein M, Stalpers LJ, Leenstra S, Heimans JJ, Reijneveld JC. Differential effect of surgery and radiotherapy on neurocognitive functioning and health-related quality of life in WHO grade I meningioma patients. *J Neurooncol*. 2007;84(3): 271–278.
24. Talacchi A, Santini B, Savazzi S, Gerosa M. Cognitive effects of tumour and surgical treatment in glioma patients. *J Neurooncol*. 2011;103(3):541–549.
25. Murray RD, Skillicorn CJ, Howell SJ, et al. Influences on quality of life in GH deficient adults and their effect on response to treatment. *ClinEndocrinol (Oxf)*. 1999;51(5):565–573.
26. Chaichana KL, Parker SL, Olivi A, Quiñones-Hinojosa A. Long-term seizure outcomes in adult patients undergoing primary resection of malignant brain astrocytomas. *Clinical article. J Neurosurg*. 2011;114(3): 604–612.
27. Chaichana KL, Halthore AN, Parker SL. Factors involved in maintaining prolonged functional independence following supratentorial glioblastoma resection. *Clinical article. J Neurosurg*. 2011;114(3): 604–612.
28. Ushio Y, Kochi M, Hamada J, Kai Y, Nakamura H. Effect of surgical removal on survival and quality of life in patients with supratentorial glioblastoma. *Neurol Med Chir (Tokyo)*. 2005;45(9):454–460.
29. Mitchell T, Turton P. 'Chemobrain': concentration and memory effects in people receiving chemotherapy - a descriptive phenomenological study. *Eur J Cancer Care (Engl)*. 2011;20(4):539–548.
30. Mauer ME, Taphoorn MJ, Bottomley A, Coens C, Efficace F, Sanson M. EORTC Brain Cancer Group. Prognostic value of health-related quality-of-life data in predicting survival in patients with anaplastic oligodendrogliomas, from a phase III EORTC brain cancer group study. *J ClinOncol*. 2007;25(36):5731–5737.
31. Liu R, Solheim K, Polley MY, Lamborn KR, Page M, Fedoroff A. Quality of life in low-grade glioma patients receiving temozolomide. *NeuroOncol*. 2009;11(1):59–68.

32. Bampoe J, Laperriere N, Pintilie M, Glen J, Micallef J, Bernstein M. Quality of life in patients with glioblastoma multiforme participating in a randomized study of brachytherapy as a boost treatment. *J Neurosurg*. 2000;93(6):917–926.
33. Osoba D, Brada M, Prados M, Yung W. Effect of disease burden on health-related quality of life in patients with malignant gliomas. *Neuro-Oncology*. 2000;2(4)221–228.
34. Taphoorn MJ, van den Bent MJ, Mauer ME, Coens C, Delattre JY, Brandes AA. 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*. 2007;25(36):5723–5730.
35. Smith JS, Chang EF, Lamborn KR, Chang SM, Prados MD, Cha S. Role of Extent of Resection in the Long-Term Outcome of Low-Grade Hemispheric Gliomas. *J Clin Oncol*. 2008;26:1338–1345.
36. Stupp R, Hegi ME, Mason WP. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet*. 2009;10:459–466.
37. Taphoorn MJ, Claassens L, Aaronson NK, et al. An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients. *Eur J Cancer*. 2010;46(6):1033–1040.
38. Curran WJ, Jr, Diaz A, Mehta M, Movsas B. Health related quality of life and cognitive status in patients with glioblastoma multiforme receiving escalating doses of conformal three dimensional radiation on RTOG 98–03. *J Neurooncol*. 2009;95(2):247–257.
39. Osoba D, Brada M, Yung W. Health-related quality of life in patients with anaplastic astrocytoma during treatment with temozolomide. *Eur J Cancer*. 2000;36:1788–1795.
40. Gehring K, Sitskoorn MM, Gundy CM, et al. Cognitive rehabilitation in patients with gliomas: a randomized, controlled trial. *J Clin Oncol*. 2009;27(22):3712–3722.
41. Wang M, Cairncross G, Shaw E, Jenkins R, Scheithauer B, Brachman D. Cognition and quality of life after chemotherapy plus radiotherapy (RT) vs. RT for pure and mixed anaplastic oligodendrogliomas: radiation therapy oncology group trial 9402. *Int J Radiat Oncol Biol Phys*. 2010;77(3):662–669.
42. Trojanowski T, Peszyn'ski J, Turowski K, et al. Quality of survival of patients with brain gliomas treated with postoperative CCNU and radiation therapy. *J Neurosurg*. 1989;70:18–22.
43. Hart MG, Grant R, Garside R, et al. Chemotherapeutic wafers for high grade glioma. *Cochrane Database Syst Rev*. 2008;3:CD007294.
44. Henriksson R, Asklund T, Poulsen HS. Impact of therapy on quality of life, neurocognitive function and their correlates in glioblastoma multiforme: a review. *J Neurooncol*. 2011;104:639–646.
45. Guiu S, Taillibert S, Chinot O, et al. Bevacizumab/irino- tecan. An active treatment for recurrent high grade gliomas: preliminary results of an ANOCEF Multicenter Study. *Rev Neurol (Paris)*. 2008;164:588–594.
46. Nieder C, Astner ST, Mehta MP, Grosu AL, Molls M. Improvement, clinical course, and quality of life after palliative radiotherapy for recurrent glioblastoma. *Am J ClinOncol*. 2008;31(3):300–305.
47. Jakola AS, Unsgård G, Solheim O. Quality of life in patients with intracranial gliomas: the impact of modern image-guided surgery. *J Neurosurg*. 2011;114(6):1622–1630.
48. Taphoorn MJ, Schiphorst AK, Snoek FJ. Cognitive functions and quatity of life in patients with low-grade gliomas: The impact of radiotherapy. *Ann Neurol*. 1994;36:48–54.
49. Pignatti F, van den Bent M, Curran D, et al. Prognostic factors for survival in adult patients with cerebral low-grade glioma. *J Clin Oncol*. 2002;20(8):2076–2084.
50. Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. *Lancet Neurol*. 2004;3:159–168.
51. Klein M, Heimans J, Aaronson N. Mid- to long-term cognitive sequelae in low-grade gliomas: the impact of radiotherapy and other treatment-related factors. *Lancet*. 2002;360:1361–1368.
52. Dekkers OM, Biermasz NR, Smit JW, et al. Quality of life in treated adult craniopharyngioma patients. *Eur J Endocrinol*. 2006;154(3):483–489.
53. van der Klaauw AA, Kars M, Biermasz NR, Roelfsema F, Dekkers OM, Corssmit EP. Disease-specific impairments in quality of life during long-term follow-up of patients with different pituitary adenomas. *Clin Endocrinol (Oxf)*. 2008;69(5):775–784.
54. Matta MP, Couture E, Cazals L, Vezzosi D, Bennet A, Caron P. Impaired quality of life of patients with acromegaly: control of GH/IGF-I excess improves psychological subscale appearance. *Eur J Endocrinol*. 2008;158(3):305–310.
55. Trepp R, Everts R, Stettler C, et al. Assessment of quality of life in patients with uncontrolled vs. controlled acromegaly using the Acromegaly Quality of Life Questionnaire (AcroQoL). *Clin Endocrinol (Oxf)*. 2005;63(1):103–110.
56. Okamoto Y, Okamoto F, Yamada S, Honda M, Hiraoka T, Oshika T. Vision-related quality of life after transsphenoidal surgery for pituitary adenoma. *Invest Ophthalmol Vis Sci*. 2010;51(7):3405–3410.
57. Cheng JX, Liu BL, Zhang X, et al. Health-related quality of life in glioma patients in China. *BMC Cancer*. 2010;10:305.
58. Tsay SL, Chang JY, Yates P, Lin KC, Liang SY. Factors influencing quality of life in patients with benign primary brain tumors: prior to and following surgery. *Support Care Cancer*. 2012;20(1):57–64.
59. Krupp W, Klein C, Koschny R, Holland H, Seifert V, Meixensberger J. Assessment of neuropsychological parameters and quality of life to evaluate outcome in patients with surgically treated supratentorial meningiomas. *Neurosurgery*. 2009;64(1):40–47.
60. Fluchel M, Horsman JR, Furlong W, Castillo L, Alfonz Y, Barr RD. Self and proxy-reported health status and health-related quality of life in survivors of childhood cancer in Uruguay. *Pediatr Blood Cancer*. 2008;50(4):838–843.
61. Ruge MI, Ilmberger J, Tonn JC, Kreth FW. Health-related quality of life and cognitive functioning in adult patients with supratentorial WHO grade II glioma: status prior to therapy. *J Neurooncol*. 2011;103(1):129–136.
62. McGirt MJ, Mukherjee D, Chaichana KL, Than KD, Weingart JD, Quinones-Hinojosa A. Association of surgically acquired motor and language deficits on overall survival after resection of glioblastoma multiforme. *Neurosurgery*. 2009;65(3):463–469.
63. Ownsworth T, Henderson L, Chambers SK. Social support buffers the impact of functional impairments on caregiver psychological well-being in the context of brain tumor and other cancers. *Psychooncology*. 2010;19(10):1116–1122.
64. Erharter A, Giesinger J, Kemmler G, Schauer-Maurer G, Stockhammer G. Implementation of computer-based quality-of-life monitoring in brain tumor outpatients in routine clinical practice. *J Pain Symptom Manage*. 2010;39(2):219–229.
65. Jalali R, Datta D. Prospective analysis of incidence of central nervous system tumours presenting in a tertiary cancer hospital from India. *J Neurooncol*. 2008;87:111–114.

66. Maringwa J, Quinten C, King M, et al. Minimal clinically meaningful differences for the EORTC QLQ-C30 and EORTC QLQ-BN20 scales in brain cancer patients. *Ann Oncol*. 2011;22(9):2107–2112.
67. Sadura A, Pater J, Osoba D. Quality-of-life assessment: patient compliance with questionnaire completion. *J Natl Cancer Inst*. 1992;84:1023–1026.
68. Giesinger JM, Golser M, Erharter A, Kemmler G, Schauer-Maurer G. Do neurooncological patients and their significant others agree on quality of life ratings? *Health Qual Life Outcomes*. 2009;7:87.
69. Parvataneni R, Polley MY, Freeman T, et al. Identifying the needs of brain tumor patients and their caregivers. *J Neurooncol*. 2011;104(3): 737–744.