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Health Related Quality of Life (HRQOL) in Long-Term Survivors of Pediatric Low Grade Gliomas (LGGs)

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Abstract

BACKGROUND—The purpose of this study was to assess the health-related quality of life (HRQOL) and the impact of treatment on HRQOL in long-term survivors of pediatric low-grade gliomas (LGGs) using an adult instrument.

METHODS—QOL of 121 patients with a diagnosis of LGG from the Mayo Clinic were assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30 for cancer in general) and (EORTC QLQ-BN20 specific for brain tumors).

RESULTS—Median follow-up was 21.9 years for the participants. Median age at diagnosis was 11.8 years and at assessment was 33 years. Mean (standard deviation) global QOL score for the study was 78 (18) and 76.4 (22.8) in a reference population of healthy adults. Using QLQ-C30, radiation treated patients compared to non-radiation patients reported lower physical functioning ($p=0.002$), role functioning ($p=0.004$), and more constipation problems ($p<0.001$). Patients with tumor recurrence reported lower role functioning ($p=0.016$), social functioning ($p=0.040$), and

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more financial problems (p=0.029) compared to their counterparts. Using QLQ-BN20, patients with deep tumors compared to cortical tumors reported more bladder control problems (p=0.016). Radiation treated patients also reported more bladder control problems (p<0.001) compared to their counterparts. In the multivariable analysis, radiation therapy remained an independent predictor of physical and role functioning as well as symptoms related to brain tumors like visual disorders and motor dysfunction.

CONCLUSION—Global QOL of long-term survivors of pediatric LGGs is similar to that of a reference population of healthy adults. The following tumor and treatment related factors were most consistently associated with poorer QOL: CNS tumor location, post-operative radiation, and tumor recurrence. Future studies are necessary to identify strategies to improve QOL in this subgroup of patients.

Keywords

Pediatrics; Low-grade gliomas; Health-related quality of life; Radiation therapy; EORTC-QLQ-C30; EORTC-QLQ-BN20

INTRODUCTION

Health-related quality of life (HRQOL) is an important outcome measure in the treatment of patients with all types of cancers and QOL in childhood cancers in particular has become the focus of recent studies [1, 2]. Pediatric Low-Grade Gliomas (LGGs) consist of a heterogeneous set of tumors with histologic subtypes that differ in their degree of infiltration, relative aggressiveness and prognosis. In contrast to adult LGGs which are much more aggressive with a poorer prognosis [3], the majority of pediatric LGGs do not undergo malignant transformation. Furthermore, advances in imaging technologies and multimodality therapy using surgery, chemotherapy, and radiation therapy (RT) have achieved greater than 90% survival rates at 10 years [4-7]. The excellent prognosis of pediatric LGGs warrants the understanding of long-term effects of various treatment modalities. While studies assessing QOL in pediatric patients with varying subtypes of CNS tumors have used different tools [8-10], the most appropriate tool to measure HRQOL in this population remains to be determined. Nevertheless, most providers agree that HRQOL of these patients may become significantly compromised; therefore, identifying contributing factors affecting HRQOL and potentially intervening at an early stage in this population is necessary. To date, the literature on HRQOL for long-term survivors of pediatric LGGs is limited. The purpose of this study was to evaluate HRQOL in survivors of pediatric LGGs, diagnosed at Mayo Clinic between 1970 and 2009 using adult HRQOL instruments and to assess the relative contributions of patient symptoms, tumor characteristics, and various treatment modalities on HRQOL.

MATERIALS AND METHODS

Patient Identification

This study retrospectively analyzed 351 consecutive pediatric patients with pathology-proven LGG from the Mayo Clinic Tumor Registry database. Eligible patients were diagnosed with either the World Health Organization (WHO) grade 1 or 2 tumor between

1970 and 2009 and were 21 years or younger at the time of diagnosis [11]. Patients included in this study had a minimum of 3-year follow-up at the time of data collection. Of the 351 identified patients, 37 patients had passed away at time of survey distribution. Surveys were mailed to 314 eligible patients whose vital statuses were confirmed using the cancer registry database as well as the social security death Index (SSDI). An additional 5 patients had passed away at the time of the assessment and one patient was lost to follow-up. At the time of assessment, it was noted that 2 of the participants were within 5 year of the initial diagnosis, 5 participants were within 10 years of the initial diagnosis and the remainder of the participants were greater than 10 years post initial diagnosis, with the majority between 15 and 30 years. The study participants were subsequently referred to as long-term survivor. Patients either signed the consent form or a surrogate signature was accepted if the patient was unable to sign at the time of survey distribution. Patient-related and treatment-related data were extracted from the medical record. The Mayo Clinic Institutional Review Board approved this study.

Outcome measures

Patients (n=314) who met the above criteria were mailed the QOL Questionnaire version 3 (EORTC-QLQ-C30), supplemented by the EORTC QLQ-BN20, which was specifically developed and validated for patients with brain tumors [12, 13]. EORTC-QLQ-C30 is a self-reported 30-item questionnaire organized into a global QOL score, 5 functional subscales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, nausea/vomiting, and pain), and six single item symptoms (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial burden). EORTC-QLQ-BN20 is a 20-item questionnaire assessing symptoms related to brain tumors including visual disorder, motor dysfunction, disease symptoms (such as headaches and seizures), treatment toxicities (such as hair loss), and future uncertainty. Each item has four response alternatives except for the global health-status/QOL scale, which has response options ranging from (1) “very poor” to (7) “excellent”. The reported scores were transformed to a linear scale (1-100) based on the recommended EORTC protocol [14, 15].

Statistical analysis

Comparison of baseline demographic and clinical characteristics between participants and non-participants were conducted using t-tests and the ANOVA test. Log-rank tests were used to compare overall and progression free survival between participants and non-participants. Univariable analysis was used to determine the association between all potential patient, tumor, or treatment related factors and QLQ-C30 and BN20 scores. Continuous and categorical variables were tested using linear regression and ANOVA tests, respectively. All pairwise comparisons were made using the Tukey-Kramer HSD for multiple comparison adjustments to control type 1-error rates. Statistical significance was set at $P< 0.05$. Clinical significant differences were defined by differences in scores >10 points, while changes >20 points were classified as large effects [13]. Factors that showed a clinically relevant association with quality of life, and were statistically significant in the univariable analyses, were entered into a multivariable generalized linear model analysis. Analyses were performed using the JMP statistical software (JMP.LNK)

RESULTS

Patient Characteristics

The baseline characteristics of the entire patient cohort are presented in Table 1. Of 314 LGG patients, 38.5% (n=121) returned the survey and were included in the data analysis, nine surveys were signed and filled out by a guardian. The median follow-up was 21.9 years for the participants compared to 7.4 years in the non-participants. More male than female participants declined to participate in the survey. There were no statistically significant differences between the participants and the non-participants with regards to the median age at diagnosis, tumor histology, grade, primary CNS tumor location, tumor laterality, and presenting symptoms such as seizures, headaches, motor weakness, or sensory abnormalities. Seventy-seven percent of the survey participants had a gross total resection (GTR) compared to 62% in the non-participants (p=0.005). Nineteen percent of study participants had a subtotal resection (STR) and 4% had a biopsy only. There was no difference between the two groups based on post-operative treatment. Absence of tumor recurrence was higher in the survey participants compared to non-participants (75% vs. 63%, p=0.003). A trend toward longer median overall-survival in the participants, but no difference in progression-free survival, was observed (Table 1).

Baseline QLQ-C30 and BN20 scores

In both EORTC modules, a higher scaled score represents a higher response level (highest scaled score is 100). Therefore, a high score for global health status represents a high QOL. A high score for a functional subscale represents a healthy level of functioning, while a high score for a symptom subscale or item represents higher level of symptomatology [15]. Over half of the patients had global QOL scaled scores of 83 or greater. The end point of the global health status was “very poor” or an un-scaled score of 0 and no patient reported their quality of life to be “very poor”. Based on the QLQ-C30 functional scale, the mean scores for self-reported cognitive (84), emotional (80), and social functioning (87) were lower than reported for role (91) and physical functioning (92). These values are similar to the mean scores reported for a reference population of healthy adults [16] (Table 2). Self-reported symptoms of fatigue, pain and insomnia were the highest mean scores reported on the QLQ-C30 symptom subscale or item. Nevertheless, the mean scores remained were very similar between the study participants and the reference population except for higher financial burden reported in the study participants (16 vs. 4.4). The highest mean scores using the BN20 subscales were for self-reported symptoms of motor dysfunction, communication difficulties, headache, and drowsiness (Table 2).

QLQ-C30 scores and tumor related factors

Table 3 presents all variables listed in Table 1 that were tested for associations with patient reported QOL. Multiple variables were found to have both a clinically and statistically significant association with the QLQ-C30 subscales. Patients who presented with motor weakness compared to no motor weakness reported more difficulty with role functioning (mean 84 vs. 94, p=0.020), while those who presented with sensory loss compared to no sensory loss reported more insomnia (25 vs. 13, p=0.016). Patients with bilateral/midline tumors reported increased fatigue compared to those with right-sided tumors (26 vs. 13,

p=0.025). Patients with deep tumors also reported increased fatigue compared to those with cortical tumors (26 vs. 10, p=0.003). Additionally, patients with deep tumors reported lower cognitive functioning compared to patients with cortical or cerebellar tumors (71 vs. 87 vs. 86, p=0.042). While QLQ-C30 scores were not significantly associated with the extent of resection, post-operative radiation therapy (PORT) had a substantial effect on self-reported QOL subscales. Patients who received PORT reported more difficulty with physical (80 vs. 95, p=0.002) and role (79 vs. 94, p=0.004) functioning as wee as increased symptoms of constipation (20 vs. 4, p= 0.001) compared to those who did not receive PORT. Finally, patients who experienced a tumor recurrence reported increased difficulty with role (83 vs. 94, p=0.016) and social functioning (80 vs. 90, p=0.040), as well as increased financial burden (25 vs. 13, p=0.029) (Table 3).

Brain-specific scores and tumor related factors

Similar to QLQ-C30 scores, multiple variables were found to have both a clinically and statistically significant effect on QLQ-BN20 scales. The median age of the patients at the time of assessment was 33 years. Older patients reported more visual disorders complaints, similar to patients with follow-up times greater than the median of 21.9 years. Notably, this was not related to the age at diagnosis. Male patients reported more headaches than female patients (mean 21 vs. 11, p=0.008). More reports of motor dysfunction were associated with patients who initially presented with motor weakness compared to patients without initial symptoms of motor weakness (25 vs. 12, p=0.006). Patients with deep tumors reported more bladder control problems than patients with tumors in the cortical location (24 vs. 4, p=0.016). Interestingly, patients managed with either an STR or biopsy also reported more bladder control problems (23 vs. 5, p< 0.001) compared to those treated with GTR. Patients who received radiation reported more symptoms of visual disturbances (19 vs. 6, p=0.002), motor dysfunction (28 vs. 12, p=0.006), leg weakness (22 vs. 5, p=0.001), and bladder control (30 vs. 4, p<0.001) compared to those not treated with PORT. Finally, patients who experienced a tumor recurrence reported more problems with leg weakness (15 vs. 5, p=0.038) (Table 4).

Multivariable Analysis

Patient or tumor related factors, that showed a clinically and statistically significant association with QOL subscales, were entered into a multivariable model (Table 5). Motor weakness (p=0.039), RT (p=0.005), and tumor recurrence (p=0.015) were all significantly associated with decreased role functioning. Only CNS tumor location (p=0.016) was associated with more reports of fatigue. Visual disorders were significantly associated with RT (p=0.010) and follow-up greater than 21 years (p=0.039), but not with older age at survey completion. Tumor location (p=0.026) and RT (p=0.018) were associated with more motor dysfunction. Leg weakness was significantly affected by RT (p=0.001) and tumor recurrence (p=0.033). Finally, RT alone maintained an association with bladder control problem (p=0.001) (Table 5).

DISCUSSION

Pediatric LGGs account for the majority of brain tumors in children [17]. These patients have an excellent prognosis with 10 year overall survival rates greater than 90%; however, QOL data in long-term survivors is scarce. In this study, the majority of participants (95%) had survived for greater than 10 years since the initial diagnosis. Based on EORTC-QLQ-C30, overall excellent QOL in both functional and symptom subscales were observed. The factors that consistently affected QOL subscales included tumor location, presence of recurrence and PORT.

Comparison of the study results to a reference population of independently functioning healthy adults, showed no significant difference in baseline QOL scores in QLQ-C30 domains except for increased financial burdens [16], which is likely due to expenses related to cancer care. Reports assessing QOL in pediatric patients have demonstrated lower overall QOL in children with CNS tumors compared to their healthy counterparts [9, 18]; however, those patients were either undergoing or within one year of treatment completion, while the majority of the participants in this study were several years post treatment. In comparison to previously published reports of adult patients with LGGs, the current study of adult survivors of pediatric LGGs appear to have better overall QOL scores. The role, cognitive, and emotional functioning scores were all 10 points greater compared to the adult LGG studies. Symptom scores were also comparatively lower [19, 20]. These differences may be attributed to the length of time since treatment completion and assessment, as long-term survivors tend to document a better quality of life [21]. In addition, variable tumor histology may also be a contributing factor as pediatric patients are diagnosed with a higher frequency of indolent low grade gliomas in contrast to the low grade diffuse astrocytomas reported in adults [6]. Thus, the tumor histology may favor a better prognosis, and a better overall QOL in pediatric LGG patients. Studies have reported that pediatric patients with CNS tumors have overall lower QOL than pediatric patients undergoing leukemia treatment [8, 9]. In contrast, the current study population reports higher QOL functional scores in comparison to adult long-term survivors of acute myeloid leukemia (AML). The role, emotional, and social functioning scores were all 10 points greater. Symptom scores were also comparatively lower [22]. These differences may be attributed to time of assessment since initial diagnosis as the median follow-up in this study was 21.9 years and the median follow up in the AML study was 8 years.

In general, fatigue is a common complaint among long-term survivors of LGGs and brain tumor patients [19, 23, 24]. Insomnia or some sort of sleep disorder has been reported as a common phenomenon among new diagnosed or recently treated cancer patients at rates significantly higher than in non-cancer patients [25, 26]. Although the study participants reported high mean scores for fatigue and insomnia, these scores were not different from the scores reported by the reference population. The lack of an observed difference may be because patients can often adjust to a new way of life with symptoms like fatigue and in subjective questionnaires may not be report it as burdensome, whereas other symptoms like pain may be more difficult to ignore. Furthermore, only a small percentage of participants reported high scores (scaled score great than 50) for fatigue (7%) and insomnia (9%). Hence, the numbers might be too small to tease out real differences. Even so, identification

of the subset of patient who are prone to fatigue and sleep disturbances, given that they are are particularly worrisome factors that affect QOL, can be met with early intervention and education from providers.

Overall, the study participants reported excellent QOL with regard to physical and role functioning; however, RT was a predictor of lower physical and role functioning. Role functioning assesses limitations in work or in leisure activities, whereas physical functioning assesses daily activities including self-care. Patients who received RT likely harbored tumors not initially amenable to a GTR and required more intensive treatments. Similarly, it has been reported that long term adult survivors of pediatric tumors who were treated with intense multimodality treatment, tend to report excess physical morbidity [29]. This group of patients and their family may benefit from early interventions to assist with activities of daily living.

The lack of cognitive decline in patients' receiving RT has been previously documented [30]. Similarly, RT was not associated with lower self-reported cognitive function in this study. Deep tumor location was the only factor associated with lower self-reported cognitive functioning; however, the long-term effects of RT are well known. For example, cognitive decline has been reported in long-term survivors of adult LGGs who received RT [31]. It is possible that patients' subjective perception of their cognitive status may not reflect their true cognitive capabilities, as incongruences have been reported between self-reported cognitive function and formal neurocognitive tests [32, 33], with patients over-estimating their neurocognitive abilities. Additionally, tumor location may also be an important determinant of cognitive function since lower self-reported cognitive functioning was seen in patients with deep tumors who would not have been candidates for surgical resection.

Radiation therapy was the only independent predictor of bladder control problem. This was an unexpected finding and review of the literature revealed that worse bladder control problems were reported in patients with poor karnofsky performance or progressive disease [36, 37]. One possibility is that patients' who received RT are likely patients with progressive disease. It is also possible that RT could lead to disruption of afferent or efferent innervations important in controlling micturition as studies have shown deactivated micturition in brain control areas of patients with incontinence problems [38, 39]. Further studies are needed to follow-up this observation. RT was also an independent predictor of motor dysfunction in the multivariable analysis and because the tumor location determines the extent of surgery and by extension the post-operative course, tumor location may represent a more important factor in influencing QOL.

Our study has some limitations. Although our sample size is one of the largest reported in a QOL study for long-term survivors of pediatric LGGs, the number of patients receiving adjuvant chemotherapy or RT is limited. Since pediatric LGGs have an overall excellent prognosis, a multicenter study may be needed to validate the results in an attempt to understand the effects of these adjuvant treatments. Also, we only had a 38% participation rate. It is possible that non-participants had significantly different QOL than the participants and the analysis may have been biased towards those with an overall better QOL and may limit the generalizability of these results. Another limitation is the lack of objective means to

perform neurocognitive testing in our patient cohort. It is possible that the questionnaire does not adequately address neurocognitive functioning and formal objective testing of cognitive function in the future is warranted. In the absence of any prospective data, with a longer follow-up, this study provides some insight into functioning of long-term survivors of childhood LGGs.

CONCLUSION

This study to analyze the health related QOL in long term survivors of pediatric LGGs. Adult survivors of pediatric LGGs have QOL scores similar to a reference population of healthy adults. RT is significantly associated with a decreased QOL in the domains of physical and role functioning but not in cognitive functioning. Radiation treatment remained an independent predictor of visual disorder, motor dysfunction, weak legs, and bladder control- all parameters specifically associated with brain tumors. Deep tumors are associated with lower self-reported cognitive functioning. Further studies are necessary to determine whether supportive therapy or early interventions can improve or ameliorate the observed symptoms and improve HRQOL in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Speechley KN, Barrera M, Shaw AK, Morrison HI, Maunsell E. Health-related quality of life among child and adolescent survivors of childhood cancer. J Clin Oncol. 2006; 24(16):2536–2543. [PubMed: 16735706]
2. Zareifar S, Farahmandfar MR, Cohan N, Modarresnia F, Haghpanah S. Evaluation of health related quality of life in 6-18 years old patients with acute leukemia during chemotherapy. Indian journal of pediatrics. 2012; 79(2):177–182. [PubMed: 21638073]
3. Louis, D.; Ohgaki, H.; Wiestler, OD.; Cavenee, WK. WHO classification of tumours of the central nervous system. 4. World Health Organization; 2007.
4. Qaddoumi I, Sultan I, Gajjar A. Outcome and prognostic features in pediatric gliomas: a review of 6212 cases from the Surveillance, Epidemiology, and End Results database. Cancer. 2009; 115(24): 5761–5770. [PubMed: 19813274]
5. Fisher PG, Tihan T, Goldthwaite PT, Wharam MD, Carson BS, Weingart JD, Repka MX, Cohen KJ, Burger PC. Outcome analysis of childhood low-grade astrocytomas. Pediatric blood & cancer. 2008; 51(2):245–250. [PubMed: 18386785]
6. Sievert AJ, Fisher MJ. Pediatric low-grade gliomas. Journal of child neurology. 2009; 24(11):1397–1408. [PubMed: 19841428]
7. Pollack IF. Multidisciplinary management of childhood brain tumors: a review of outcomes, recent advances, and challenges. J Neurosurg Pediatr. 2011; 8(2):135–148. [PubMed: 21806354]
8. Meeske K, Katz ER, Palmer SN, Burwinkle T, Varni JW. Parent proxy-reported health-related quality of life and fatigue in pediatric patients diagnosed with brain tumors and acute lymphoblastic leukemia. Cancer. 2004; 101(9):2116–2125. [PubMed: 15389475]
9. Pogorzala M, Styczynski J, Kurylak A, Debski R, Wojtkiewicz M, Wysocki M. Health-related quality of life among paediatric survivors of primary brain tumours and acute leukaemia. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2010; 19(2):191–198.
10. Kulkarni AV, Piscione J, Shams I, Bouffet E. Long-term quality of life in children treated for posterior fossa brain tumors. J Neurosurg Pediatr. 2013

11. Youland RS, Schomas DA, Brown PD, Nwachukwu C, Buckner JC, Giannini C, Parney IF, Laack NN. Changes in presentation, treatment, and outcomes of adult low-grade gliomas over the past fifty years. Neuro Oncol. 2013; 15(8):1102–1110. [PubMed: 23814262]
12. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. Journal of the National Cancer Institute. 1993; 85(5):365–376. [PubMed: 8433390]
13. Taphoorn MJ, Sizoo EM, Bottomley A. Review on quality of life issues in patients with primary brain tumors. Oncologist. 2010; 15(6):618–626. [PubMed: 20507891]
14. Taphoorn MJ, Claassens L, Aaronson NK, Coens C, Mauer M, Osoba D, Stupp R, Mirimanoff RO, van den Bent MJ, Bottomley A. 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. [PubMed: 20181476]
15. Fayers, PM.; A, N.; Bjordal, K.; Groenvold, M.; Curran, D.; Bottomley, A. on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual. 3. EORTC; 2001.
16. Derogar M, van der Schaaf M, Lagergren P. Reference values for the EORTC QLQ-C30 quality of life questionnaire in a random sample of the Swedish population. Acta oncologica. 2012; 51(1): 10–16. [PubMed: 21961499]
17. Blaney, SM.; K, LE.; Hunter, J., et al. Tumors of Central Nervous System. 5. Philadelphia: Lippincott Williams & Wilkins; 2006.
18. Bhat SR, Goodwin TL, Burwinkle TM, Lansdale MF, Dahl GV, Huhn SL, Gibbs IC, Donaldson SS, Rosenblum RK, Varni JW, et al. Profile of daily life in children with brain tumors: an assessment of health-related quality of life. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005; 23(24):5493–5500. [PubMed: 16110009]
19. Gustafsson M, Edvardsson T, Ahlstrom G. The relationship between function, quality of life and coping in patients with low-grade gliomas. Support Care Cancer. 2006; 14(12):1205–1212. [PubMed: 16710652]
20. Budrukkar A, Jalali R, Dutta D, Sarin R, Devlekar R, Parab S, Kakde A. Prospective assessment of quality of life in adult patients with primary brain tumors in routine neurooncology practice. J Neurooncol. 2009; 95(3):413–419. [PubMed: 19548070]
21. Bosma I, Reijneveld JC, Douw L, Vos MJ, Postma TJ, Aaronson NK, Muller M, Vandertop WP, Slotman BJ, Taphoorn MJ, et al. Health-related quality of life of long-term high-grade glioma survivors. Neuro Oncol. 2009; 11(1):51–58. [PubMed: 18617599]
22. Messerer D, Engel J, Hasford J, Schaich M, Ehninger G, Sauerland C, Buchner T, Schumacher A, Krahl R, Niederwieser D, et al. Impact of different post-remission strategies on quality of life in patients with acute myeloid leukemia. Haematologica. 2008; 93(6):826–833. [PubMed: 18469349]
23. Struik K, Klein M, Heimans JJ, Gielissen MF, Bleijenberg G, Taphoorn MJ, Reijneveld JC, Postma TJ. Fatigue in low-grade glioma. Journal of neuro-oncology. 2009; 92(1):73–78. [PubMed: 19066729]
24. Taillibert S, Laigle-Donadey F, Sanson M. Palliative care in patients with primary brain tumors. Current opinion in oncology. 2004; 16(6):587–592. [PubMed: 15627022]
25. Fiorentino L, Ancoli-Israel S. Sleep dysfunction in patients with cancer. Current treatment options in neurology. 2007; 9(5):337–346. [PubMed: 17716597]
26. Davidson JR, MacLean AW, Brundage MD, Schulze K. Sleep disturbance in cancer patients. Social science & medicine. 2002; 54(9):1309–1321. [PubMed: 12058848]
27. Cheng KK, Lee DT. Effects of pain, fatigue, insomnia, and mood disturbance on functional status and quality of life of elderly patients with cancer. Critical reviews in oncology/hematology. 2011; 78(2):127–137. [PubMed: 20403706]
28. Shankar S, Robison L, Jenney ME, Rockwood TH, Wu E, Feusner J, Friedman D, Kane RL, Bhatia S. Health-related quality of life in young survivors of childhood cancer using the Minneapolis-Manchester Quality of Life-Youth Form. Pediatrics. 2005; 115(2):435–442. [PubMed: 15687453]

29. Crom DB, Chathaway DK, Tolley EA, Mulhern RK, Hudson MM. Health status and health-related quality of life in long-term adult survivors of pediatric solid tumors. Int J Cancer Suppl. 1999; 12:25–31. [PubMed: 10679867]

30. Taphoorn MJ, Schiphorst AK, Snoek FJ, Lindeboom J, Wolbers JG, Karim AB, Huijgens PC, Heimans JJ. Cognitive functions and quality of life in patients with low-grade gliomas: the impact of radiotherapy. Ann Neurol. 1994; 36(1):48–54. [PubMed: 8024261]

31. Douw L, Klein M, Fagel SS, van den Heuvel J, Taphoorn MJ, Aaronson NK, Postma TJ, Vandertop WP, Mooij JJ, Boerman RH, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. Lancet Neurol. 2009; 8(9):810–818. [PubMed: 19665931]

32. Li J, Bentzen SM, Renschler M, Mehta MP. Relationship between neurocognitive function and quality of life after whole-brain radiotherapy in patients with brain metastasis. Int J Radiat Oncol Biol Phys. 2008; 71(1):64–70. [PubMed: 18406884]

33. Maddrey AM, Bergeron JA, Lombardo ER, McDonald NK, Mulne AF, Barenberg PD, Bowers DC. Neuropsychological performance and quality of life of 10 year survivors of childhood medulloblastoma. J Neurooncol. 2005; 72(3):245–253. [PubMed: 15937648]

34. Laack NN, Brown PD, Ivnik RJ, Furth AF, Ballman KV, Hammack JE, Arusell RM, Shaw EG, Buckner JC. Cognitive function after radiotherapy for supratentorial low-grade glioma: a North Central Cancer Treatment Group prospective study. Int J Radiat Oncol Biol Phys. 2005; 63(4): 1175–1183. [PubMed: 15964709]

35. Brown PD, Buckner JC, Uhm JH, Shaw EG. The neurocognitive effects of radiation in adult low-grade glioma patients. Neuro Oncol. 2003; 5(3):161–167. [PubMed: 12816722]

36. Heimans JJ, Taphoorn MJ. Impact of brain tumour treatment on quality of life. J Neurol. 2002; 249(8):955–960. [PubMed: 12195437]

37. Yavas C, Zorlu F, Ozyigit G, Gurkaynak M, Yavas G, Yuce D, Cengiz M, Yildiz F, Akyol F. Health-related quality of life in high-grade glioma patients: a prospective single-center study. Support Care Cancer. 2012; 20(10):2315–2325. [PubMed: 22160582]

38. Fowler CJ, Griffiths DJ. A decade of functional brain imaging applied to bladder control. Neurourol Urodyn. 2010; 29(1):49–55. [PubMed: 19412958]

39. Tadic SD, Griffiths D, Schaefer W, Cheng CI, Resnick NM. Brain activity measured by functional magnetic resonance imaging is related to patient reported urgency urinary incontinence severity. J Urol. 2010; 183(1):221–228. [PubMed: 19913803]

Table 1

Demographic and Clinical characteristics of Pediatric LGG Patients

Baseline Characteristics	Non-participants No. of patients (%) n=230	Participants No. of patients (%) n=121	P-value
Age at Diagnosis, (yrs.)			
Mean	10.43	11.2	
Median	10.5	11.8	0.201
Range	0.05-19.0	0.9-19.6	
Age at Survey completion, (yrs.)			
Mean	32	33.5	0.243
Median	31	33	
Range	0.005-35.6	18--60	
Follow-up, (yrs.)			
Mean	9.2	11	0.052
Median	7.4	21.9	
Range	0.005-36.1	2.5-41.4	
Gender			
Female	95(41.3)	64 (53)	0.038*
Male	135(58.7)	57 (47)	
Seizures [a]			
Yes	93(40)	45(37)	0.475
No	135(59)	76(63)	
Unknown	2(1)	0(0)	
Headaches [a]			
Yes	108(47)	67(55)	0.155
No	120(52)	54(45)	
Unknown	2(1)	0(0)	
Motor Weakness [a]			
Yes	55(24)	35(29)	0.365
No	173(75)	86(71)	
Unknown	2(1)	0(0)	
Sensory Symptoms [a]			
Yes	60(26)	27(22)	0.420
No	168(73)	94(78)	
Unknown	2(1)	0(0)	
Histology			
Glioma [b]	104(45)	51(42)	0.594
Pilocytic Astrocytoma	106(46)	62 (51)	
Subependymal Giant Cell Astrocytoma/other	20(9)	8 (7)	
Grade			
I	133(57)	77(64)	0.291
II	97(42)	44(36)	

Baseline Characteristics	Non-participants No. of patients (%) n=230	Participants No. of patients (%) n=121	P-value
Primary CNS location			
Brain Stem	7(3)	2 (2)	0.108
Cerebellum	52(23)	41 (34)	
Cortical	86(37)	46 (38)	
Deep Structure	66(29)	22 (18)	
Multiple	17(7)	10 (8)	
Spinal Cord	2(1)	0(0)	
Laterality			
Bilateral/ Midline/ other	61(27)	29 (24)	0.844
Left	78(34)	44 (36)	
Right	91(39)	48 (40)	
Extent of Resection			
Biopsy (BX)	32(14)	5 (4)	*0.005
Gross Total resection (GTR)	143(62)	93 (77)	
Subtotal (STR)	55(24)	23 (19)	
Post-operative Treatment			
Observation	164(71)	97 (80)	0.286
Radiotherapy	55(24)	21 (17)	
Radiotherapy +Chemotherapy	5(2)	2 (2)	
Chemotherapy	6(3)	1(1)	
Tumor Recurrence			
Yes	66(29)	30(25)	*0.003
No	146(63)	91(75)	
Unknown	18(8)	0(0)	
Survival			
PFS Survival	7.6	8.7	0.183
Overall Survival	9.22	11	0.052

[a] Represents patient presenting symptoms.

[b] Include WHO grade II tumors: astrocytoma NOS, mixed oligoastrocytoma, oligodendrioma, tectal glioma, and angiocentric astrocytoma. PFS, Progression Free survival.

* represents statistically significance variable (P<0.05)

Table 2

Comparison of QOL baseline score with published data [17] EORTC QLQ-C30 and BN20 scales and items. Presented with mean score, standard deviation and median scores

Variable	Nwachukwu et. al Mean (SD)	Median (IQR)	Deroger et al [17] Mean (SD)
QLQ-C30 domain[a]			
Global	78 (18)	83 (67-92)	76.4 (22.8)
Functional Scales			
Physical	92(21)	100(93-100)	88.0 (18.3)
Role	91(23)	100(100-100)	88.2 (23.9)
Emotional	80(23)	83(67-100)	85.8 (18.7)
Cognitive	84(21)	83(83-100)	88.1 (16.9)
Social	87(25)	100(83-100)	91.2 (19.0)
Symptoms Scales			
Fatigue	17(20)	11(0-22)	19.1 (21.7)
Nausea/Vomiting	2(7)	0(0-0)	2.6 (9.3)
Pain	10(21)	17(0-17)	18.9 (25.7)
Dyspnea	7(16)	0(0-0)	16.3 (24.3)
Insomnia	15(23)	0(0-33)	17.5 (25.9)
Appetite Loss	6(18)	0(0-0)	3.3 (12.8)
Constipation	8(20)	0(0-0)	5.4 (6.1)
Diarrhea	7(18)	0(0-0)	5.6 (15.9)
Financial	16(29)	0(0-33)	4.4 (16.2)
QLQ-BN20 domain [b]			
Overall	12(14)	7(2-15)	
Future Uncertainty	0(0.17)	0(0-0.17)	
Visual Disorders	9(18)	0(0-11)	
Motor Dysfunction	15(25)	0(0-22)	
Communication Difficulty	15(23)	0(0-22)	
Headaches	17(22)	0(0-33)	
Seizures	5(16)	0(0-0)	
Drowsiness	20(25)	0(0-0)	
Itchy Skin	8(19)	0(0-0)	
Hair Loss	9(21)	0(0-0)	
Weak Legs	8(23)	0(0-0)	
Bladder Control	9(25)	0(0-0)	

[a] For QLQ-C30 functional subscales -higher values reflect higher functioning or better quality of life; symptom subscales- lower scores reflect less symptomatology.

[b] For BN-20 domain, higher scores reflect greater degree of dysfunction

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Table 3

Association between patient, tumor and treatment related factors and EORTC QLQ-C30

	QOL MEAN SCORES					p-value
Presenting Symptom: motor weakness	No	Yes				
Role	94	84				0.020*
Presenting Symptom: Sensory loss	No	Yes				
Insomnia	13	25				0.016*
Radiation Therapy	No	Yes				
Physical	95	80				0.002*
Role	94	79				0.004*
Constipation	4	20				0.001*
Tumor Recurrence	No	Yes				
Role	94	83				0.016*
Social	90	80				0.040*
Financial	13	25				0.029*
Tumor Laterality	Bilateral/Midline/Other	Left	Right			
Fatigue	26	16	13			0.025*
Post-operative Treatment [a]	Observation	Radiation	Radiation + Chemotherapy			
Physical	95	83	65			0.004*
Role	94	84	50			0.001*
Pain	9	13	39			0.034*
Diarrhea	6	8	44			0.001*
CNS location [b]	Brainstem	Cerebellum	Cortical	Deep Structures	Multiple	
Cognitive	83	86	87	71	87	0.042*
Fatigue	50	19	10	26	14	0.003*
Pain	50	10	5	16	12	0.018*

Table represents only clinically and statistically significant factors affecting QOL parameters, full results in the appendix.

[a] Only 2 patients received radiation + chemotherapy

[b] Only 2 patients with brainstem tumors

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Table 4

Association between patient, tumor and treatment related factors and EORTC QLQ-BN20.

	MEAN SCORES					P-value
Age at survey completion > 33	No	Yes				
Visual Disorders	4	15				0.001*
Follow up greater than 21	No	Yes				
Visual Disorders	3	15				< 0.001*
Gender	Male	Female				
Headaches	21	11				0.008*
Presenting Symptom: motor weakness	No	Yes				
Motor Dysfunction	12	25				0.006*
Tumor Recurrence	No	Yes				
Weak Legs	5	15				0.038*
Extent resection	GTR	STR/bx				
Bladder Control	5	23				<0.001*
Radiation Therapy	No	Yes				
Visual Disorders	6	19				0.002*
Motor Dysfunction	12	28				0.006*
Weak Legs	5	22				0.001*
Bladder Control	4	30				<0.001*
Histology	Astrocytoma	Pilocytic Astrocytoma	Subependymal Giant Cell Astrocytoma			
Seizures	5	3	21			0.009*
Post-Operative Treatment [a]	Observation	Radiation	Radiation + Chemotherapy			
Visual Disorders	6	20	11			0.008*
Motor Dysfunction	13	26	30			0.037*
weak legs	5	17	44			0.001*
Bladder Control	4	24	67			<.0.001*
CNS location [b]	Brainstem	Cerebellum	Cortical	Deep Structures	Multiple	
Motor Dysfunction	72	15	11	23	8	0.003*
Bladder Control	0	6	4	24	20	0.016*

Table represents only clinically and statistically significant factors affecting QOL parameters, full results in the appendix.

[a] Only 2 patients received radiation + chemotherapy

[b] Only 2 patients with brainstem tumors

Table 5

Results of multivariable analysis of QLQ-C30 and QLQ-BN20 parameters

	QLQ-C30 Subscales	
	Role functioning	**Fatigue (Symptom)**
Independent variables		_
Motor weakness	0.039*	_
CNS tumor location	_	0.016*
Radiation therapy	0.005*	_
Tumor Laterality	_	0.191
Tumor Recurrence	0.015*	

	QLQ-BN20 Subscales			
	Visual Disorder	**Motor Dysfunction**	**Weak Legs**	**Bladder control**
Independent variables				
Follow-up > 21.9 years [a]	0.039*	_	_	_
Age at Survey completion >33years[b]	0.201	_	_	_
Motor weakness	_	0.102	_	_
CNS Tumor location	_	0.026*	_	0.084
Radiation Therapy	0.010*	0.018*	0.001*	0.001*
Extent Resection	_	_	_	0.119
Tumor Recurrence	_	_	0.033*	_

* represents statistically significance variable (P<0.05)

[a] 21.9 is the median at follow-up time.

[b] 33 years is the median age at survey completion.

_ represents factors not used in the multivariate model.