



Clinical study

Life after surgical resection of a low-grade glioma: A prospective cross-sectional study evaluating health-related quality of life



Ken X. Teng^{a,c}, Benjamin Price^{a,c}, Shubhum Joshi^{a,c}, Lobna Alukaidey^{a,c}, Ameer Shehab^{a,c}, Kristy Mansour^{a,c}, Gurvinder S. Toor^{a,c}, Rosemary Angliss^{a,c}, Katharine Drummond^{a,b,c,*}

^a Department of Neurosurgery, The Royal Melbourne Hospital, Parkville, VIC, 3050, Australia

^b The Melbourne Brain Centre, The Royal Melbourne Hospital, Parkville, VIC, 3050, Australia

^c Department of Surgery, University of Melbourne, Parkville, VIC, 3052, Australia

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ABSTRACT

Health related quality of life (HRQoL) has become an important consideration in LGG patients. We report the largest prospective, longitudinal, cross-sectional cohort study of HRQoL in LGG patients, aiming to identify actionable determinants of HRQoL. Post-operative LGG adults at a large tertiary center underwent HRQoL assessment using the EORTC QLQ-C30 questionnaire administered at follow-up visits and by mail. Scores at 12 month intervals were compared with those from a normative reference population. Spearman's Rho was used to evaluate correlation of subdomain and symptom scores with global HRQoL and change over time. There were 167 participants and 366 questionnaires analysed. Patients reported reduced global HRQoL at nearly every 12 month interval with significant impairments at 12, 72, 108, and 120+ months postoperative. They also reported a significant impairment in each functional subdomain at 12 months, which persisted to varying degrees over 120 months, as did significant fatigue and insomnia. Role, emotional, and social subdomains, as well as fatigue, were significantly associated with global HRQoL at the first 12 month interval. Overall, there was no significant correlation between time from surgery and global HRQoL or the subdomain functional or symptom sections of the QLQ-C30. LGG patients report considerable, sustained impairments in HRQoL after surgery, particularly in cognitive, emotional, and social function, as well as suffering significant fatigue and insomnia. These are strongly associated with global HRQoL and thus can be considered determinants of global HRQoL that with intervention, may improve HRQoL for our LGG patients.

This is the largest prospective longitudinal study of HRQoL in postoperative LGG patients yet reported and is ongoing. It identifies several determinants of impaired HRQoL with available management options and interventions that have the potential to significantly improve HRQoL in these patients.

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1. Introduction

Advances in surgical techniques and adjuvant therapy options, have led to dramatic improvements in brain tumor patient care over the past two decades. Consequently, with extended survival and reduction of gross neurological morbidity, measures of treatment success have shifted to more patient-centred metrics, including health-related quality of life (HRQoL).^{1,2} HRQoL is a complex, self-assessed, multidimensional concept encompassing the physical, emotional, role, social and cognitive components of quality of life associated with illness and its treatment.

Low-grade gliomas (LGG) are a heterogeneous group of almost universally fatal primary central nervous system neoplasms classified by the World Health Organisation (WHO) as tumour grades I or II.³ They are uncommon, with an incidence of 1/100,000 people per year⁴, but due to young age at diagnosis (median 37 years)⁵ and association with neurological deficit, LGG cause disproportionate levels of morbidity.⁵

Maximal safe surgical resection is the mainstay of initial treatment.^{6–9} Aggressive surgical resection and adjuvant radiation and chemotherapy have modestly improved survival of this fatal disease, resulting in challenges not previously encountered.^{10–13} Improvements in quantity of survival must be accompanied by improvements in quality of survival. HRQoL is thus a key quality metric for care of patients with LGG.

* Corresponding author.

E-mail address: kate.drummond@mh.org.au (K. Drummond).

Depending on tumor location, patients with LGG may experience cognitive, psychiatric, somatic, and other symptoms, including neurological deficit and epilepsy.^{14–16} Patients also suffer from nonspecific symptoms, including headaches, fatigue, anxiety, and sleep disturbance.^{17,18} Additionally, surgical resection and subsequent radio- and chemotherapy may also have effects on HRQoL. Therefore, both tumor and treatment may affect HRQoL. Despite this, the long-term HRQoL of LGG patients is an understudied, and at times an under-recognized, challenge for this population.

Previous studies are limited by small populations, use of a range of non-comparable HRQoL instruments, inadequate evaluation of longitudinal change and lack of comparison with a normative population or consideration of clinically meaningful difference (CMD).^{7,19,20} Our recent study that specifically investigated these parameters in meningioma patients demonstrated significantly impaired HRQoL for years postoperative relative to a normative population.²¹ A LGG population study investigating longitudinal HRQoL changes at multiple time points with reference to a normative population represents a knowledge gap.

Here, we report a single-center prospective longitudinal evaluation of HRQoL in a cross-sectional cohort of postoperative LGG patients. The main aim of the study was to identify factors contributing to impaired HRQoL that could be modified to improve HRQoL for our patients. Therefore, less attention was given to non-modifiable predictors that do not lend themselves to interventions to improve HRQoL. Thus, attention was given to factors for which interventions may be available, such as fatigue, sleep disturbance, social function, emotional disturbance, and cognitive dysfunction.

2. Patients and methods

The Melbourne Health Human Research Ethics Committee approved this study in 2013 (study number 2013.246). The study is a prospective longitudinal study, with a cross-sectional cohort design. The study included adults (age > 18 years) who had undergone biopsy or resection of an intracranial LGG and were in routine follow-up at the Royal Melbourne Hospital Neuro-Oncology and Neurosurgery Outpatient and Private clinics over 5 years. This includes patients treated at two large tertiary institutions that service remote, rural and urban populations and both public (government insurance) and private (insured) patients by 16 neurosurgeons and seven medical and radiation oncologists. Patients with other brain or spine lesions, previous malignancy, Grade III or IV gliomas or neurofibromatosis type 1 or 2 were excluded. Patients needed to be able to complete the questionnaires independently in English. Patients were approached opportunistically for participation, and written informed consent was obtained. In a subset of consenting patients, follow-up questionnaires were completed by mail to obtain longitudinal assessment. Patients could enter the study at any point post-operatively and then completed the questionnaire at every subsequent visit. Post-operative follow-up is standardised to a 6-week post-operative appointment with no imaging, then a baseline MRI scan at 3 months and then 3 to 6 monthly follow up until death, depending on clinical and radiological stability. Monthly appointments without imaging occurred if the patient was under treatment with chemotherapy (generally temozolomide). No data was collected pre-operatively or on patients with presumed LGG without histological confirmation.

2.1. Data collection

HRQoL was measured using the widely validated questionnaire developed by the European Organisation for the Research and Treatment of Cancer (EORTC): the QLQ-C30.²² The EORTC QLQ-C30 is a 30-item questionnaire that assesses global HRQoL, as well

as its physical, role, emotional, social, and cognitive domains in patients with any cancer. The responses are provided on four-point (1 - not at all, 2 - a little, 3 - quite a bit, 4 - very much) or seven-point (1 - poor, 7 - excellent) Likert scales. Completed HRQoL surveys were de-identified, collated into a spreadsheet and transformed into total scores out of 100 for each HRQoL domain as per EORTC guidelines. For the symptom scales higher scores represent a higher symptom burden and therefore lower HRQoL. Responses were stratified for time-from-surgery by grouping into 12-month post-operative intervals for longitudinal assessment.

Demographic details, as well as tumor and clinical management details were recorded for each participant from their medical record or the Royal Melbourne Hospital Central Nervous System Tumour Database (part of the Australian Comprehensive Cancer Outcomes and Research Database [ACCORD]) but are not the primary subject of this report.

2.2. Statistical analysis

Average transformed QLQ-C30 scores, stratified by time since surgery and divided into 12-month intervals, were compared to a European normative population of 16,151 healthy people.²³ The CMD in LGG patient scores compared to the normative population was set as per previous publications.^{24,25} We performed two-tailed t-tests to determine whether global HRQoL scores or domain-specific scores were statistically or clinically meaningfully different from the normative population and were correlated with time from surgery. To determine which HRQoL domains were most correlated with overall changes in HRQoL, domain-specific and symptom HRQoL scores were correlated with global HRQoL scores using Spearman's Correlation Coefficient. All analyses were performed in accordance with the EORTC Manual for the QLQ-C30.²² All statistical analyses were performed using SPSS Version 23.0 (IBM, Armonk, NY, USA). A p -value < 0.05 was considered statistically significant unless otherwise stated. Counts (and proportions) are reported for categorical variables and means (and standard deviations) for continuous variables, unless otherwise stated. Statistical advice was obtained from the Statistical Consulting Centre of the University of Melbourne.

3. Results

We consented 167 post-operative patients for participation and a total of 366 questionnaires were included for analysis. There were 64 patients who completed the questionnaires once, 51 patients who completed them twice, 25 patients who completed them three times and 27 patients who completed them four or more times, generally at 6 monthly intervals. The median time from surgery to completion of each questionnaire for the 167 patients was 25, 38, 50 and 60 months for the first, second, third, and fourth and beyond questionnaire, respectively. The median time from surgery to completion for all 366 questionnaires was 38 months. Patient demographics are summarised in supplementary Table 5, and clinical and tumor characteristics of the study population are summarized in Table 1.

Overall, at study entry, LGG patients reported a statistically significant reduction in global HRQoL, and in each of the subdomains ($p < 0.05$). Additionally, a CMD was seen in all domains except physical function and role function (Fig. 1). Correlations between global HRQoL scores and the five functional domains found that role, social and physical function were the domains most strongly correlated with reduced global HRQoL (Spearman's Rho 0.558, 0.534 and 0.522 respectively). Furthermore, fatigue was the symptom most strongly correlated with global HRQoL (Spearman's Rho -0.609).

Table 1

Clinical and tumor characteristics of 167 LGG patients who completed 366 questionnaires and comparing patients who completed 1, 2, 3 and 4 + survey(s), respectively. Diffuse gliomas were not further subclassified as many patients were diagnosed pre-molecular diagnosis.

	Tumour Factors		1 Survey (n = 64)		2 Surveys (n = 51)		3 Surveys (n = 25)		4 + Surveys (n = 27)		Total (n = 167)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Time Since Surgery	67.20	83.04	65.20	190.73	39.20	38.17	32.26	32.20	60.66	110.48		
	n	%	n	%	n	%	n	%	n	%	n	%
Lateralisation												
Right	26	40.63	26	50.98	13	52.00	14	51.85	79	47.31		
Left	26	40.63	21	41.18	11	44.00	10	37.04	68	40.72		
Midline	9	14.06	2	3.92	1	4.00	1	3.70	13	7.78		
Unknown	3	4.69	2	3.92	0	0.00	2	7.41	7	4.19		
Diagnosis												
Grade II Diffuse Glioma	44	68.75	50	98.04	23	92.00	27	100.00	144	86.23		
Grade I Pilocytic Astrocytoma	13	20.31	1	1.96	2	8.00	0	0.00	16	9.58		
Other	7	10.94	0	0.00	0	0.00	0	0.00	7	4.19		
Grade												
I	17	26.56	1	1.96	2	8.00	0	0.00	20	11.98		
II	47	73.44	50	98.04	23	92.00	27	100.00	147	88.02		
Extent of Resection												
Biopsy	8	12.50	13	25.49	7	28.00	4	14.81	32	19.16		
Partial	3	4.69	6	11.76	2	8.00	1	3.70	12	7.19		
Sub-total	28	43.75	15	29.41	7	28.00	11	40.74	61	36.53		
Gross-macroscopic	19	29.69	12	23.53	9	36.00	9	33.33	49	29.34		
Unknown	6	9.38	5	9.80	0	0.00	2	7.41	13	7.78		
Radiotherapy												
Yes	24	37.50	20	39.22	5	20.00	3	11.11	52	31.14		
No	38	59.38	29	56.86	20	80.00	24	88.89	111	66.47		
Unknown	2	3.13	2	3.92	0	0.00	0	0.00	4	2.40		
Chemotherapy												
Yes	13	20.31	6	11.76	2	8.00	1	3.70	22	13.17		
No	49	76.56	43	84.31	21	84.00	26	96.30	139	83.23		
Unknown	2	3.13	2	3.92	2	8.00	0	0.00	6	3.59		
Anti-epileptic Medications												
Yes	33	51.56	36	70.59	13	52.00	21	77.78	103	61.68		
No	28	43.75	13	25.49	12	48.00	6	22.22	59	35.33		
Unknown	3	4.69	2	3.92	0	0.00	0	0.00	5	2.99		
Seizure History												
Yes	27	42.19	28	54.90	13	52.00	19	70.37	87	52.10		
No	29	45.31	14	27.45	10	40.00	6	22.22	59	35.33		
Unknown	8	12.50	9	17.65	2	8.00	2	7.41	21	12.57		

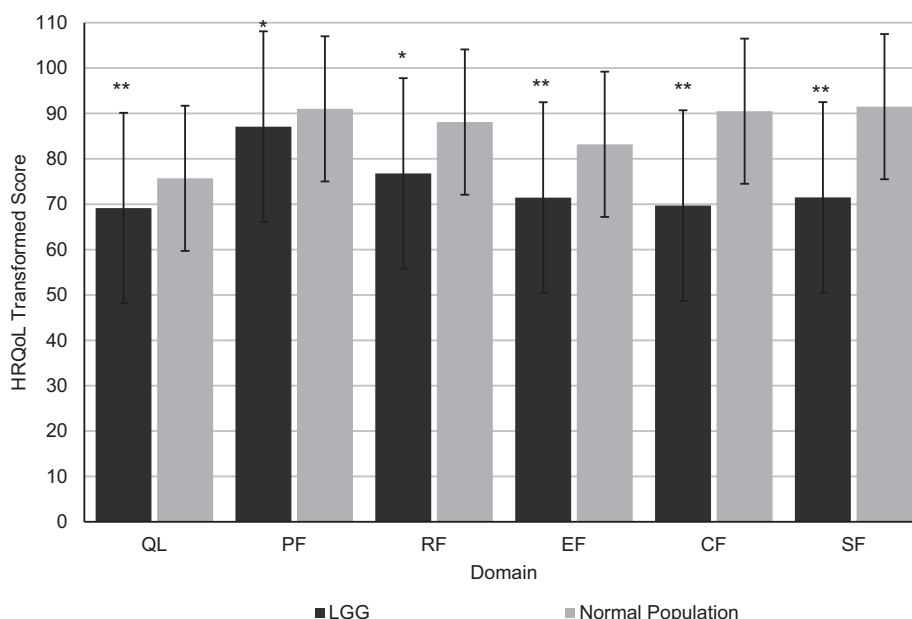


Fig. 1. Comparison of global HRQoL and subdomains, using the EORTC QLQ-C30 validated questionnaire, between postoperative LGG patients and a normative European population. QL = global HRQoL; RF = role function; EF = emotional function; CF = cognitive function; SF = social function; PF = physical function. Bars are standard error of the mean. *Statistically significant difference (p < 0.0001), **statistically and clinically meaningful difference.

Longitudinal HRQoL data are summarized in Table 2. Overall, there was no significant correlation between time from surgery and global HRQoL or for the functional or symptom domains. Thus, despite fluctuations for individual patients and individual domains, there was no clear pattern for the group as a whole of deterioration or improvement with time. Overall, 181 of the 366 questionnaires completed by participants demonstrated clinically meaningful impairments in global HRQoL at any time point studied, and only 68 of the 167 patients described clinically meaningful impairments in global HRQoL at all timepoints studied. Thus, the relationship with time and variables such as life events and other illnesses is not clear and likely to be complex. Table 3 shows the number and percentage of patients at each 12-month time point who reached the CMD of global HRQoL, its subdomains and selected important symptoms.

The lack of a strong correlation of HRQoL with time suggests that changes in HRQoL may be long-lasting, and makes the planning of interventions to improve HRQoL challenging. We therefore considered the HRQoL determinants in the first 12 months post-operative; a time when it would be most feasible and presumably most effective to implement interventions to improve HRQoL over the course of the disease, particularly while in periods of relative stability and before clinical deterioration. In the subset of 83 patients who completed a questionnaire in the first 12 months post-operatively, significant associations (Spearman’s Rho > 0.5) with global HRQoL were found for role, emotional and social function subdomains, as well as fatigue. Therefore, these could be considered “actionable” determinants of HRQoL. For all the time intervals combined, physical function, role function, social function, and fatigue were consistently highly correlated with global HRQoL (Table 4).

Longitudinally, patients with LGG reported reduced global HRQoL (range 63.02 [SD = 23.76] to 76.61 [SD = 21.28]) at the first 12-month interval and subsequently at 72, 108 and 120 + months after surgery compared to the normative population (P < 0.05) (Fig. 2). Patients also reported a similar pattern of impairment of role function (range 65.51 [SD = 33.67] to 91.67 [SD = 14.91]) (Fig. 2). Physical function impairments were evident 12 months after surgery (range 77.92 [SD = 28.46] to 92.92 [SD = 9.86]) (P < 0.05), but with return to near normal levels thereafter until 120 + months. Whether these fluctuations and return to normal represent a genuine improvement or a resetting of the benchmark to “the new normal” up to this timepoint is not clear (Fig. 2).

Patients reported sustained impairments in emotional function (range 65.94 [SD = 28.91] to 78.94 [SD = 22.35]) compared to the normative population, (P < 0.05), and these reached clinical significance at 12, 36, 48, 72, 96 and 120 + months after surgery. We observed sustained clinically meaningful and statistically significant impairment in cognitive function (range 62.28 [SD = 29.94] to 74.09 [SD = 13.98]) at every interval post-operatively (P < 0.01). Similarly, patients reported clinically meaningful and

statistically significant impairments in social function (range 63.06 [SD = 34.05] to 79.08 [SD = 25.69]) at all timepoints post-operative (p < 0.05) (Fig. 2).

Regarding the QLQ-C30 symptom scales, several significant associations were found with time from surgery. LGG patients reported greater fatigue than the normative population (range 26.44 [SD = 22.92] to 41.67 [SD = 35.47]) at most timepoints post-operatively up to 120+ months (P < 0.05), and a CMD was seen at all timepoints except at months 24, 36 and 48 (Fig. 2). Patients reported statistically significant impairments in insomnia/sleep compared to the normative population (range 26.19 [SD = 26.73] to 33.33 [SD = 36.15]) at every post-operative interval from 12 to 72 months, and at 120+ (p < 0.05). Importantly, CMDs were seen at all timepoints post-operatively (Fig. 2).

4. Discussion

Treating clinicians are well versed in the risks and benefits of LGG management, however, discussions around expected HRQoL changes after surgery are difficult and seldom occur between practitioner and patient. Despite the relatively prolonged survival of many LGG patients, few studies have investigated HRQoL in large cohorts. In particular, longitudinal change in HRQoL after time from diagnosis is understudied with many studies only comparing two arbitrary timepoints in different patient groups. These studies, for several brain tumour types, including LGG, may report improved HRQoL over time.^{19,26–29} However, the study design may have significant selection bias, as patient dropout due to clinical deterioration may lead to over-estimation of long-term HRQoL. Our findings show no significant correlation with time since surgery, despite LGG natural history. This may too result from selection bias, but may also illustrate a failure to recognise and act on the sustained HRQoL impairment post-resection.

Another deficient area is of studies seeking to identify determinants of reduced HRQoL for which an effective intervention exists. In general, studies have compared treatment modalities or concentrated on largely “fixed” patient-specific or surgical factors predicting poor HRQoL, such as large tumor size, location in the dominant hemisphere or frontal lobes, tumour-associated epilepsy requiring anti-epileptic medications, extent of resection, or higher histological grade.^{7,30,31} While these studies are valuable for prognostication, risk assessment, and treatment choice, they fail to provide options for the vast majority of patients to improve their HRQoL after treatment.

Despite these limitations, published studies using cancer specific HRQoL questionnaires have demonstrated poorer HRQoL relative to a normal population up to 5 years postoperatively in LLG.^{19,27} The absence of studies using common instruments validated specifically in LGGs prohibits data pooling or meta-analysis.

This is the largest reported study of longitudinal HRQoL in post-operative LGG patients. Our results are in concordance with the literature^{29,31–33} and additionally demonstrate that most LGG patients report considerable limitations in HRQoL for >120 months postoperatively, although the relationship with time is complex and fluctuating for individual patients. They report clinically significant impairment in all the HRQoL domains on the QLQ-C30, as well as suffering significant fatigue and insomnia compared with a normative reference population at the majority of postoperative intervals assessed, and often lasting for many years. In many cases reported functional impairments and symptoms strongly correlate with global HRQoL and for some domains and symptoms, such as cognitive function and insomnia, there are clinically meaningful sustained deficits, although not overall correlation with global HRQoL. These domain and symptoms can be considered determinants of HRQoL that if treated, may improve HRQoL for our LGG

Table 2

Correlation between time from surgery for LGG and global HRQoL, subdomains, and selected symptoms using the EORTC QLQ-C30. Spearman’s Rho > 0.5 or < -0.5 was considered a strong correlation. *p < 0.05.

	Time Since Surgery Spearman’s Rho	P Value
Global HRQoL	−0.025	0.635
Physical Function	−0.055	0.301
Role Function	0.131*	0.013
Emotional Function	0.053	0.313
Cognitive Function	−0.071	0.174
Social Function	0.013	0.809
Fatigue	−0.029	0.577
Sleep/Insomnia	−0.05	0.34

Table 3

Summary table of the number (n) and percentage (%) of LGG patients at each 12-month interval for each domain who reported scores that reached the clinically meaningful difference (CMD).

		Interval											
		12	24	36	48	60	72	84	96	108	120	120+	All
Global QOL	(n) CMD	43	20	16	15	11	15	10	9	11	6	22	181
	(%) CMD	51.81	40.82	43.24	46.88	39.29	48.39	55.56	56.25	68.75	37.50	57.89	49.73
Physical	(n) CMD	28	12	6	5	7	10	6	3	7	5	18	107
	(%) CMD	34.15	24.49	16.22	15.63	25.00	32.26	33.33	18.75	43.75	35.71	48.65	29.72
Role	(n) CMD	46	16	11	12	10	7	10	4	9	5	18	148
	(%) CMD	55.42	32.65	29.73	37.50	35.71	22.58	55.56	25.00	56.25	33.33	48.65	40.88
Emotional	(n) CMD	40	21	19	16	10	12	4	8	5	7	17	159
	(%) CMD	48.19	42.86	51.35	50.00	35.71	38.71	22.22	50.00	33.33	46.67	44.74	43.92
Cognitive	(n) CMD	40	23	23	19	15	19	9	6	9	7	24	194
	(%) CMD	48.19	46.94	62.16	59.38	53.57	61.29	50.00	37.50	56.25	43.75	63.16	53.30
Social	(n) CMD	44	18	17	16	10	18	8	7	8	7	24	177
	(%) CMD	53.01	36.73	45.95	50.00	35.71	58.06	44.44	43.75	50.00	43.75	64.86	48.76
Fatigue	(n) CMD	49	19	15	12	15	15	10	8	10	7	22	182
	(%) CMD	59.04	39.58	40.54	37.50	53.57	48.39	55.56	50.00	62.50	46.67	59.46	50.42
Sleep	(n) CMD	50	29	21	19	20	17	10	9	7	8	18	208
	(%) CMD	60.24	59.18	56.76	59.38	71.43	54.84	55.56	56.25	46.67	57.14	50.00	57.94

Table 4

HRQoL at 12 months postoperative compared with all intervals postoperative. Spearman's correlations between global HRQoL and HRQoL domains and important symptom scales at the first 12 months postoperative, and at all intervals postoperative. Spearman's Rho > 0.5 or < -0.5 was considered a strong correlation. ** p < 0.01.

Domain	Global QOL All Time Points Spearman's Rho	P Value	Global QOL First 12 Months Spearman's Rho	P Value
Physical	0.522**	<0.001	0.471**	<0.001
Role	0.568**	<0.001	0.578**	<0.001
Emotional	0.484**	<0.001	0.514**	<0.001
Cognitive	0.493**	<0.001	0.481**	<0.001
Social	0.534**	<0.001	0.625**	<0.001
Fatigue	-0.609**	<0.001	-0.608**	<0.001
Sleep	-0.439**	<0.001	-0.391**	<0.001

patients, although this hypothesis remains untested. There is evidence that LGG patients report improved HRQoL after surgical resection.³⁴ However, although therapy (either by surgery alone or combined with radiation therapy and chemotherapy) may confer a HRQoL and neurocognitive benefit for some, residual neurocognitive deficits may persist for many years after completing treatment. Adjuvant therapies, most commonly radiotherapy, may add to HRQoL impairments,⁷ as do seizures^{14,35} and their treatment^{36,37}. Our findings, in combination with the previous literature, clearly highlight that care aimed specifically at improving HRQoL must continue throughout the treatment trajectory of LGG patients. Additionally, as the disease ultimately progresses,³⁷ treatment and supportive care should dynamically adapt to the evolving needs of the patient.

The psychological impact of a brain tumor diagnosis is often less acknowledged by clinicians in patients with low grade tumors compared their high-grade counterparts. Patients fear tumor progression or recurrence, as well as impairments in physical, cognitive and functional well-being, fatigue and sleep disturbance.^{38,39} This varying symptomatology is unlikely to solely be explained by physiological factors and highlights the dramatic psychosocial and emotional impact of a LGG diagnosis.

We have reported on HRQoL outcomes of LGG patients with a focus on identifying possible actionable determinants of global HRQoL. We found that fatigue and emotional, role and social function impairment were consistently highly correlated with global HRQoL in LGG patients, particularly at 12 months, but for some extending well beyond 5 years. Patients also reported considerable sustained insomnia and cognitive impairments. This perceived cognitive deficit is an interesting finding, as it even occurred in stable patients with small tumors, which would not normally be considered to confer a risk of cognitive dysfunction. The biological

substrate of cognitive dysfunction (and other reported symptoms including fatigue and sleep disturbance) is unknown. Although our study did not objectively assess cognitive function, it suggests that perceived cognitive dysfunction is a major contributor to poor HRQoL, which may not be reflected by objective testing, as demonstrated in other conditions, including epilepsy.⁴⁰

Our findings suggest that interventions targeting fatigue, sleep disturbance, cognitive function, or the perception of cognitive deficits, as well as assistance for patients to fulfill their social and role responsibilities, may aid maximizing HRQoL for LGG patients. These interventions should be targeted to the relevant patients by early screening and begin with simple behavioral modification and proceed in a graded fashion to more complex interventions. For example, with the very prevalent problem of fatigue (a well-documented adverse outcome associated with neurosurgical procedures and cancer, and which may contribute to perceived cognitive deficit, and social and role dysfunction), a graded management program, starting with simple education in fatigue management, moving to physical activity and psychosocial interventions and advancing to pharmacological interventions in selected patients, may be transformational for affected patients.⁴¹

In this study, we used the EORTC QLQ-C30 to assess HRQoL in patients with LGG. The advantage of the QLQ-C30 is that it has been validated in many languages and takes a short time to complete (~10 min) with an available repository of reference values for over 16 000 European patients.²³ One key limitation is that participants are surveyed about their experiences in the past week only, limiting sensitivity in capturing episodic events, such as seizures or pain, or when administered at follow-up intervals that are in the order of months. This may partly explain the episodic fluctuations of statistical and clinical significance at interval time points in our study. These fluctuations are presumed to be natural oscillations

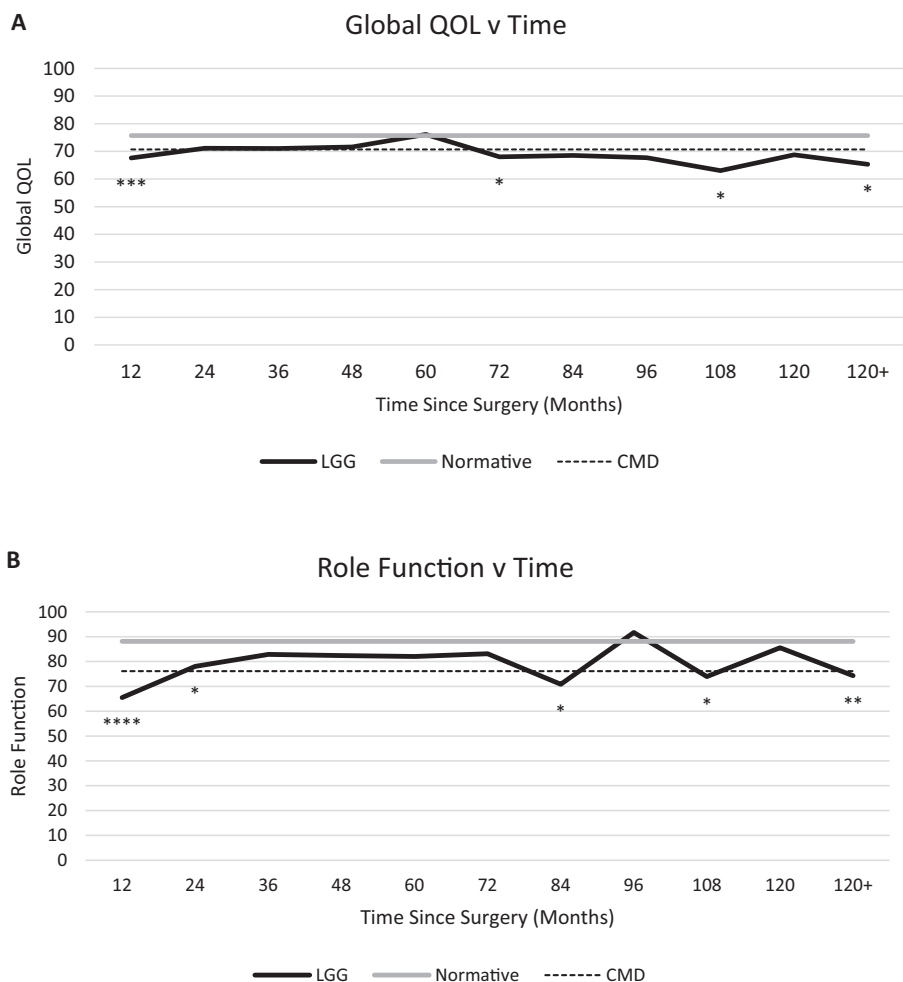


Fig. 2. Longitudinal global HRQoL (A) and subdomain scores (B-H) from the EORTC QLQ-C30. Scores for LGG patients (black solid line) are depicted longitudinally in 12-month intervals and compared with a normative European population mean (grey solid line) with the clinically meaningful difference (CMD) threshold also shown (black dotted line). Statistically significant differences are shown as * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, and **** $P < 0.0001$.

tions about the mean and may also be attributed to incidental factors including life events and intercurrent illness. They are likely to be affected by anxiety about an upcoming appointment or the results of a recent clinical discussion.

Based on the findings of this and previous studies, how can we preserve and improve the HRQoL of our LGG patients? The first step would be greater attention to the clear risk of long-term HRQoL compromise, despite excellent surgical and radiological outcomes. Education of clinicians and patients on the short- and long-term considerations for management of multiple domains of function is essential and should be as comprehensive as the informed consent process detailing the specific risks and benefits of treatment. Furthermore, at the time of diagnosis, in addition to standard neurological and radiological investigations, an assessment of baseline HRQoL should be performed with a validated tool, as well as cognitive and neuropsychological assessment, if feasible. Identifying existing impairments allows neurosurgeons to better counsel patients and provides a baseline for comparison throughout follow-up.

Subsequent to treatment, resources to manage the less visible effects of LGG require development. Focal neurologic deficits including visual loss or hemiparesis are usually well catered to, but services for fatigue management, cognitive rehabilitation, psychological support and sleep management are usually lacking or not offered but should be part of a comprehensive rehabilitation

multidisciplinary program.^{35,36} Novel interventions are desperately needed and should be rigorously tested as part of ongoing research. It should also be understood that patients may report poor cognition, but on objective neuropsychological testing have scores within the normal range. Thus, formal neuropsychological assessment, at both baseline and follow-up, is important in this population, followed by either appropriate neurocognitive rehabilitation or interventions aimed at the factors underlying perceived poor cognition, which may include hypervigilance, fatigue, sleep disturbance, anxiety, or depression.

Follow-up protocols should incorporate assessment of neurological and cognitive function and HRQoL, both in the early post-treatment period and the long term, as HRQoL will change over time. The need for anti-epileptic therapy and all medications should be re-evaluated regularly.

A large prospective database, likely requiring multi-institutional efforts, is necessary to gather a comprehensive dataset allowing detection of significant symptoms, influencing factors, and novel interventions for symptoms and disabilities that are important HRQoL determinants, but currently under-addressed. Many determinants of poor HRQoL are not, or are only partially, under the control of the physician, such as tumor size, location, and grade. However, “actionable” but often neglected symptoms and disabilities may be addressed to make a significant difference for our patients.

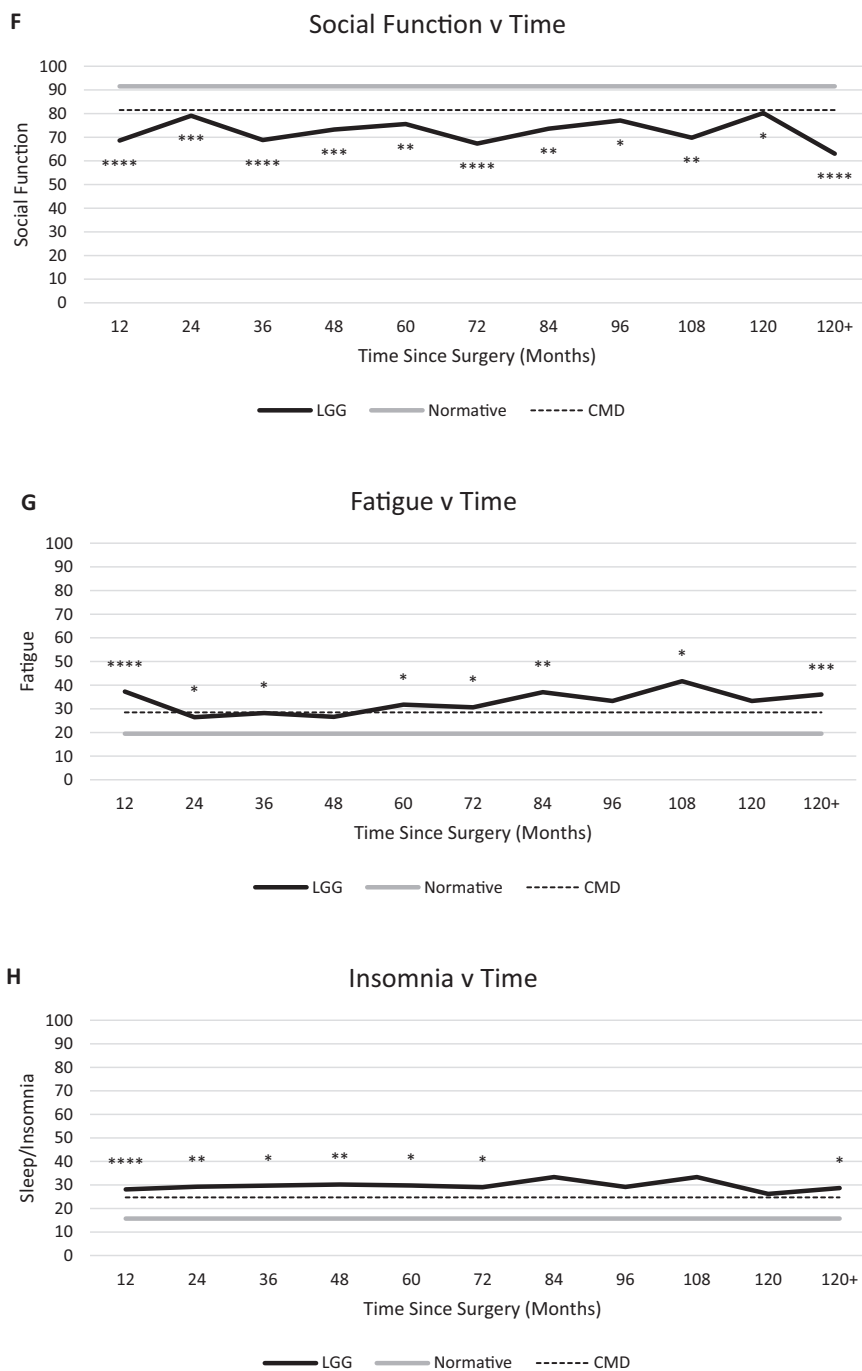


Fig. 2 (continued)

5. Limitations

In addition to the questionnaire limitations, our study is susceptible to selection and reporting bias inherent in the design, as for other survey based HRQoL studies. The study included only patients attending the clinic for follow up, thus potentially selecting against those with severe impairments, and underestimating the magnitude of HRQoL impairment. In cases where a patient had not been captured (largely due to administrative error), questionnaire mail-outs were used. The study design may also not account for post-traumatic growth, a poorly acknowledged factor

contributing to improved HRQoL over time. This phenomenon refers to psychological mechanisms that enable patients to cope with trauma that lead to positive mental change to accept the “new normal”.^{37,42} This may explain the more modest impairment in global HRQoL longitudinally despite more striking impairments in individual domains and symptoms.

Secondly, patients were recruited at any time point at postoperative follow-up. This introduces a significant spread of initial responses regarding time from surgery and potential data heterogeneity. As data collection continues, this limitation will be overcome.

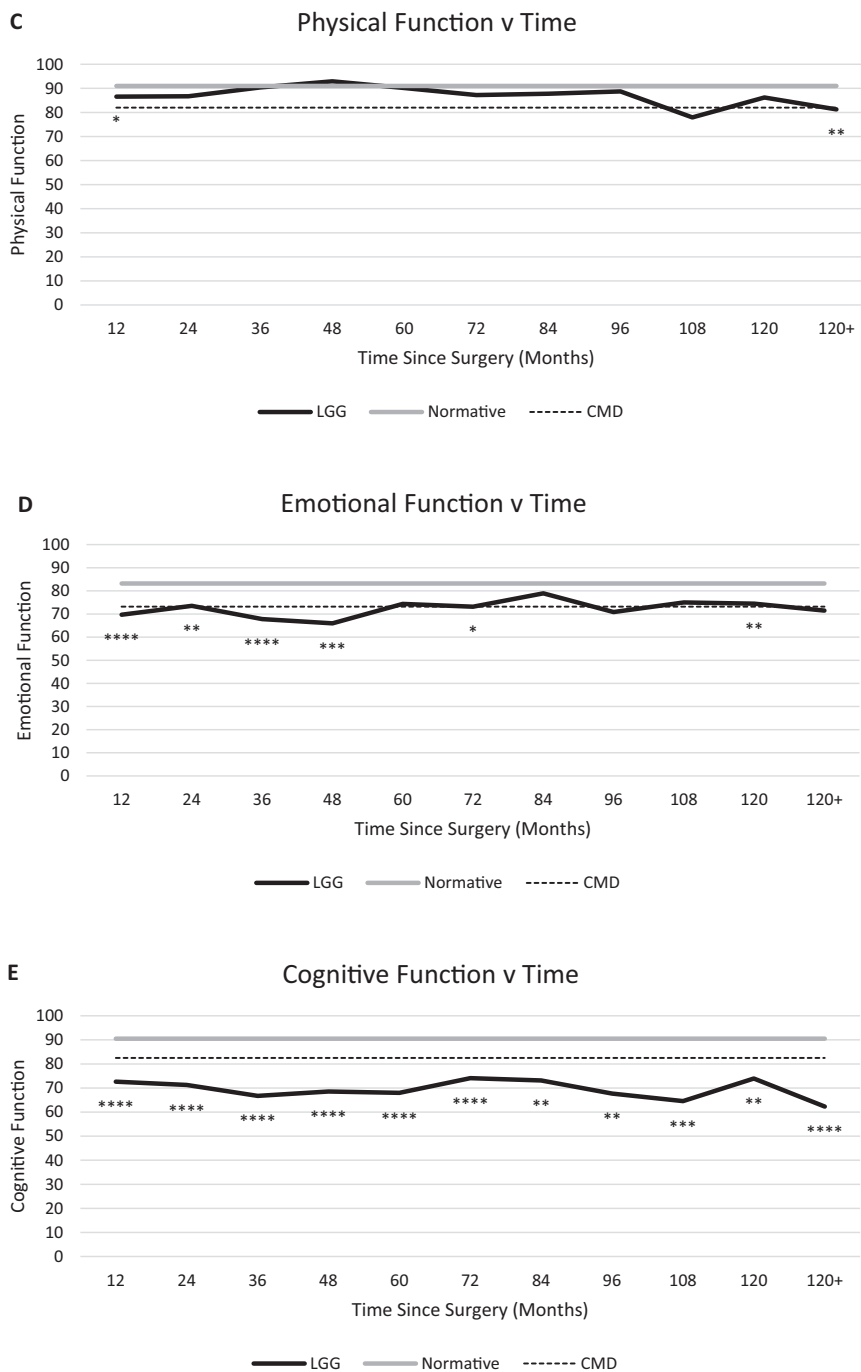


Fig. 2 (continued)

Thirdly, there are no preoperative baseline data. These would, of course, be interesting data but were not included for several reasons. The primary reason was that assessing the effect of treatment on HRQoL is not a study aim but rather to determine factors influencing HRQoL in a large postoperative patient cohort and identify interventions for improvement. Additionally, the difficulty of interpreting HRQoL measures in preoperative patients recently confronted with the diagnosis of a brain tumor brings its own complexities.

Although this is a single center study, this remains the largest and most comprehensive cohort, and data collection continues. Therefore, reports in future years may overcome these limitations.

6. Conclusion

We present the largest prospective longitudinal series of long-term HRQoL outcomes following surgical resection of a LGG. We found that LGG patients report sustained clinically significant impairments in global HRQoL, particularly in perceived cognitive, emotional, role and social functioning, and fatigue and insomnia. Role functioning, social functioning, and fatigue were highly correlated with global HRQoL outcomes at 12 month interval assessments, and strategies targeting these domains from an early phase in treatment should be rigorously tested as they may offer the best approach for maximizing HRQoL in LGG patients.

To facilitate maximizing HRQoL in LGG patients we would recommend development and validation of a disease specific LGG HRQoL assessment tool and incorporation of HRQoL into core outcomes, along with treatment complication rates, epilepsy, and cognitive function, evaluated at baseline and serially during follow-up to track trends in HRQoL. Additionally, strategies targeting fatigue, insomnia and cognitive, role, social and emotional functioning from an early stage in treatment may offer the best approach at maximizing HRQoL for LGG patients and should be developed, adequately resourced and rigorously evaluated.

Authorship: KD conceived and designed the analysis; KT, BP, SJ, LA, AS, GT, KM, RA collected the data; BP, KT and SJ contributed data analysis tools; BP performed the analysis; KT, BP, SJ, KD wrote the paper; all authors revised and approved the final manuscript.

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