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Life after surgical resection of a meningioma: a prospective cross-sectional study evaluating health-related quality of life

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Abstract

Background. Few studies have evaluated the health-related quality of life (HRQoL) of patients with meningiomas. Here, we report the largest prospective, longitudinal cross-sectional cohort study of HRQoL in meningiomas to date, in order to identify possible actionable determinants of global HRQoL.

Methods. Adults who had undergone resection of a grade I intracranial meningioma and were in routine follow-up at a single large tertiary center underwent HRQoL assessment using the QLQ-C30 questionnaire administered opportunistically at follow-up visits. Averaged transformed QLQ-C30 scores at 12-month intervals were compared with scores from a normative reference population, with reference to known minimal clinically meaningful difference (CMD) in scores. To evaluate for possible determinants of changes in global HRQoL, global HRQoL scores were correlated (Spearman's Rho) with subdomain and symptom scores and with interval time from surgical resection.

Results. A total of 291 postoperative patients with histologically confirmed and surgically treated grade I meningiomas consented to participation and a total of 455 questionnaires were included for analysis. Patients with meningiomas reported reduced global HRQoL at nearly every 12-month interval with clinically and statistically significant impairments at 12, 48, 108, and 120 months postoperative compared with the normative population ($P < 0.05$). Meningioma patients at the 12-month interval also reported a reduction of each subdomain of HRQoL assessment ($P < 0.05$); however, a CMD was only seen in cognitive functioning. Physical, emotional, cognitive, and social subdomains, as well as fatigue and sleep/insomnia, 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.

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Conclusions. Meningioma patients report considerable limitations in HRQoL for more than 120 months after surgery, particularly in cognitive, emotional, and social function, as well as suffering significant fatigue and sleep impairment compared with a normative reference population. The majority of these reported functional impairments and symptoms are strongly associated with global HRQoL and thus can be considered determinants of global HRQoL that if treated, have the potential to improve HRQoL for our meningioma patients. This hypothesis requires future study of targeted interventions to determine their efficacy.

Keywords

cognition | fatigue | health-related quality of life | insomnia | meningioma | surgery

Importance of the study

This is the largest prospective longitudinal study of HRQoL in postoperative meningioma patients yet reported and the study is ongoing. It identifies a number of determinants of impaired HRQoL for which management options and interventions are available that have the potential to significantly improve HRQoL in these patients.

With advances in surgical techniques and adjuncts, and increasing adjuvant therapy options, there have been dramatic improvements in the care of brain tumor patients over the past two decades. Consequently, with extended survival and reduction of gross neurological morbidity, measures of treatment success have appropriately shifted to more patient-centered metrics, including health-related quality of life (HRQoL). Health-related quality of life is a complex, self-assessed, multidimensional concept that encompasses the physical, emotional, role, social, and cognitive components of quality of life (QoL) associated with illness and its treatment.

Meningiomas are the most common primary intracranial tumor, with rising incidence in adults aged 65 years and older.[1] The majority of meningiomas are benign and patients are typically considered surgically cured once tumor resection is complete. Postoperatively, patients enjoy long survival, with 5-year survival exceeding 80%, and 10- and 15-year survival both exceeding 70%.[2] However, despite the historically benign perception, the literature would suggest that these tumors and their treatment can have long-lasting effects, but comprehensive studies assessing HRQoL or the long-term functional, cognitive, social, or emotional outcomes following resection of meningiomas are lacking. Furthermore, up to 35% of meningioma patients harbor a biologically aggressive or surgically inaccessible tumor, with significant risk of recurrence, resulting in a clinical course of repetitive debilitating treatments, long-term impairment of function and HRQoL, together with an unmitigated uncertainty about the future.[3] This, combined with the increasing incidence of meningiomas in our aging population, results in challenges not previously encountered.

Depending on the tumor location, patients with meningiomas may experience a range of cognitive, psychiatric, somatic, and other symptoms, including neurological deficit and epilepsy.[4] Moreover, patients often also suffer from more nonspecific symptoms, including headaches, fatigue, anxiety, and sleep disturbance.[5–8] Most symptomatic patients are treated with surgical resection, and a smaller subset with radiation therapy, both of which can have long-lasting effects on function and HRQoL. Therefore, both the tumor and its treatment may affect HRQoL. Even in those patients considered surgically cured and without significant or discernible physical or cognitive deficits, long-term reduction in HRQoL is now recognized and gaining attention.[5,8] In fact, it is increasingly understood that meningioma is a disease that may portend chronic HRQoL impairments.[9] Despite this, the long-term HRQoL of meningioma patients, particularly after surgical resection, has been understudied and at large remains an underrecognized challenge for this patient population. Here, we report on a single-center prospective longitudinal evaluation of HRQoL in a cross-sectional cohort of postoperative meningioma 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 known or unknown, but nonmodifiable, predictors of HRQoL, such as tumor size, site, and extent of resection, or patient age, sex, and comorbidities, which, although prognostic and able to predict risk, do not lend themselves to interventions to improve HRQoL. Thus, attention was turned to factors for which interventions may be available, such as fatigue, sleep disturbance, social function, emotional disturbance, and cognitive dysfunction.

Patients and Methods

The Melbourne Health Human Research Ethics Committee approved this study in 2013 (study number 2013.246). The study is prospective and longitudinal, with a cross-sectional cohort design. The design was chosen to represent a "real-world" outpatient population in which measures to improve HRQoL are desperately needed. The study included adults (age >18 y) who had undergone resection of an intracranial meningioma and were in routine follow-up at the Royal Melbourne Hospital Neuro-Oncology and Neurosurgery Outpatient and Private clinics between February 2014 and June 2018. This includes patients treated at 2 large tertiary institutions that service remote, rural, and urban populations and both public (government insurance) and private (insured) patients by 16 neurosurgeons. Patients with other brain or spine lesions and those with grade II or III meningiomas 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 while in the waiting room of the clinic, and written informed consent was obtained. Participants completed the study questionnaires before or after their scheduled appointment. 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 postoperatively and then complete the questionnaire at every subsequent visit. Postoperative follow-up is standardized to a 6-week postoperative appointment with no imaging, then follow-up with a baseline MRI scan at 3 months and yearly follow-up with an MRI scan for 5 years and once at 7 years postoperative. Patients are then discharged unless there is residual disease, in which case 2 yearly follow-ups are undertaken. No data were collected preoperatively or on patients with presumed meningioma but with no histological confirmation.

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. 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 either 4-point (1 = not at all, 2 = a little, 3 = quite a bit, 4 = very much) or 7-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 (with 100 representing no impairment in HRQoL) 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 postoperative intervals for longitudinal assessment.

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

Statistical Analysis

To determine whether HRQoL in postoperative meningioma patients was impaired relative to the normal population, averaged transformed QLQ-C30 scores at 12-month intervals were compared with a European normative population of 16 151 healthy people.[10] Although it is to be expected that patients with a meningioma would have reduced HRQoL compared with the normal population, it is often not appreciated that even a "normal" population will not report "perfect" HRQoL. This is important to consider when analyzing HRQoL measures from any disease-specific population, so as to not over-interpret the effect of the disease. The minimal clinically meaningful difference (CMD) in meningioma patient scores compared with the normative population was set as per previous publications.[11,12] We performed 2-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.[12] 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 Pearson's correlation coefficient. This aimed to determine which subdomains and symptoms were most likely to be determinants of global HRQoL. All analyses were performed in accordance with the EORTC SC Manual for the QLQ-C30 (https://www.eortc.be/qol/files/SCManualQLQ-C30.pdf). All statistical analyses were performed using SPSS v23.0 (IBM). 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 Center of the University of Melbourne.

Results

A total of 291 postoperative patients with histologically confirmed and surgically treated meningiomas consented to participate and a total of 455 questionnaires were included for analysis. There were 181 patients who completed the questionnaires once, 71 patients who completed the questionnaires twice, 28 patients who completed the questionnaires 3 times, and 11 patients who completed the questionnaires 4 times, generally at yearly intervals. The median time from surgery to completion of the first questionnaire for the 291 patients was 37 months and the median time from surgery to completion for all 455 questionnaires was 47.5 months. Demographic characteristics and clinical and tumor factors are summarized in Supplementary Table 1 and Supplementary Table 2. In 71% of patients, a gross macroscopic resection of the tumor was achieved. A further 21% had undergone a subtotal resection with observation of a stable residual, in general treated with radiotherapy or radiosurgery at progression. Thus, only a small fraction of patients were not "cured" or stable. Overall, at study entry, meningioma patients reported a statistically significant reduction in global HRQoL, and in each of the subdomains. However, a CMD was only seen in cognitive function, with emotional and

Table 1 Demographic characteristics of the meningioma patient participants ($n = 291$) who completed 455 questionnaires and comparing patients who completed 1, 2, 3, and 4 survey(s), respectively

	Demographic Factors							
	1 Survey (175)		2 Surveys (78)		3 Surveys (27)		4 Surveys (11)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	60.08	11.95	59.49	12.50	58.89	11.64	55.18	8.96
	Number (n)	**Percent (%)**	**Number (n)**	**Percent (%)**	**Number (n)**	**Percent (%)**	**Number (n)**	**Percent (%)**
Study Site								
Private	72	41.14	26	33.33	8	29.63	0	0.00
Public	72	41.14	35	44.87	10	37.04	10	90.91
Unknown	31	17.71	17	21.79	9	33.33	1	9.09
Sex								
Male	41	23.43	12	15.38	7	25.93	1	9.09
Female	134	76.57	66	84.62	20	74.07	10	90.91
Unknown	0	0.00	0	0.00	0	0.00	0	0.00
Relationship								
Married	102	58.29	47	60.26	21	77.78	9	81.82
De facto	13	7.43	5	6.41	1	3.70	0	0.00
Other	1	0.57	0	0.00	0	0.00	0	0.00
Single	23	13.14	11	14.10	3	11.11	0	0.00
Divorced	20	11.43	7	8.97	2	7.41	2	18.18
Widowed	14	8.00	8	10.26	0	0.00	0	0.00
Unknown	2	1.14	0	0.00	0	0.00	0	0.00
Employment								
Full-time	28	16.00	12	15.38	3	11.11	1	9.09
Part-time	28	16.00	8	10.26	4	14.81	1	9.09
Casual	9	5.14	4	5.13	1	3.70	2	18.18
Unemployed	30	17.14	8	10.26	1	3.70	0	0.00
Retired	49	28.00	25	32.05	5	18.52	1	9.09
Other	0	0.00	0	0.00	0	0.00	0	0.00
Unknown	31	17.71	21	26.92	13	48.15	5	45.45
Driving								
Able	114	65.14	52	66.67	16	59.26	9	81.82
Unable	59	33.71	26	33.33	11	40.74	2	18.18
Unknown	2	1.14	0	0.00	0	0.00	0	0.00

social function almost reaching the threshold for a CMD (Fig. 1). Correlations between global HRQoL scores and the five functional domains found that emotional function was the domain most strongly correlated with reduced global HRQoL (Spearman's Rho 0.556). Furthermore, on the symptom scores, fatigue was found to be the most strongly correlated with global HRQoL (Spearman's Rho –0.615).

Longitudinal HRQoL data are summarized in Table 2. Overall, there was no significant correlation between time from surgery and global HRQoL or the subdomain functional or symptom sections of the QLQ-C30. 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. Only 26 of the 291 patients described clinically meaningful impairments in HRQoL for any given domain at all time points studied, thus the relationship with time and other variables such as life events and other illnesses is not clear and is likely to be complex. Table 3 shows the number and percentage of patients at each 12-month time point who had a clinically meaningful impairment of global HRQoL, its subdomains, and selected important symptoms.

The lack of a strong correlation of the various components of HRQoL with time, with most meningioma patients fluctuating, but with no clear trend to improvement or significant deterioration, suggests that changes in HRQoL may be long-lasting, and makes the planning of interventions to improve HRQoL challenging. We therefore considered the determinants of HRQoL in the first 12 months postoperative, a time when it would be most feasible and presumably

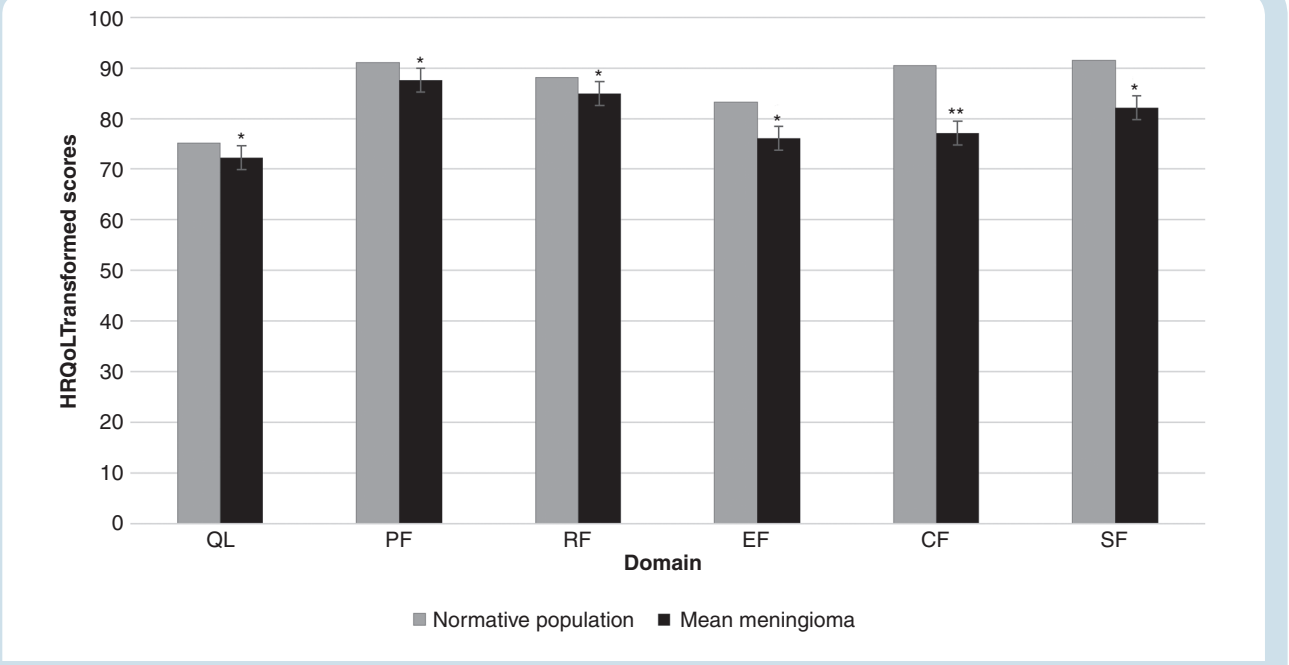

Fig. 1 Comparison of global HRQoL and subdomains, using the EORTC QLQ-C30 validated questionnaire, between postoperative meningioma patients and a normative European population. QL = global HRQoL; PF = physical function; RF = role function; EF = emotional function; CF = cognitive function; SF = social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

Table 2 Correlation between time from surgery and global HRQoL, subdomains, and selected symptoms using the EORTC QLQ-C30.

	Time Since Surgery	
	Spearman's Rho	*P*-value
Global HRQoL	0.046	0.335
Physical Function	0.076	0.106
Role Function	0.231**	<0.001
Emotional Function	0.0500	0.291
Cognitive Function	0.066	0.166
Social Function	0.171**	<0.001
Fatigue	–0.162**	0.001
Pain	–0.179**	<0.001
Sleep/Insomnia	–0.061	0.201

Note. Spearman's Rho >0.5 was considered a strong correlation.
**$P < 0.001$.

most effective to implement interventions to improve HRQoL. In the subset of 81 patients who completed a questionnaire in the first 12 months postoperatively, significant associations (Spearman's Rho >0.5) with global HRQoL were found for physical, emotional, cognitive, and social subdomains, as well as fatigue, pain, and sleep/insomnia. Therefore, these could be considered "actionable" determinants of HRQoL. For all time groups combined, emotional function, social function, pain, and fatigue were consistently highly correlated with global HRQoL (Table 4).

Longitudinally, using the QLQ-C30, patients with meningiomas reported reduced global HRQoL (range 57.29 [SD = 16.35] to 81.08 [SD = 20.38]) at nearly every 12-month interval with clinically and statistically significant impairments at 12, 48, 108, and 120 months postoperative compared with the normative population ($P < 0.05$) (Fig. 2). Although patients reported a degree of impaired physical function (range 78.33 [SD = 20.00] to 96.34 [SD = 6.81]), these values did not reach meaningful clinical significance except at 120 months after surgery, and in fact at 60 months, postoperative values were significantly better compared with the normative population ($P < 0.0001$). Whether this represent a genuine improvement or a resetting of the benchmark to "the new normal" is not clear. Patients also reported impairment of role function (range 72.86 [SD = 28.11] to 94.74 [SD = 15.98]) 12 months after surgery ($P < 0.0001$), with return to near normal levels thereafter, with better role function scores at 60 and 120+ months ($P < 0.05$) compared with the normative population. Patients reported sustained impairments in emotional function (range 61.11 [SD = 25.13] to 87.16 [SD = 18.27]) compared with the normative population ($P < 0.05$), and these reached clinical significance at 48 and 120 months after surgery (Fig. 2). Patients reported statistically significant impairments in social function (range 71.19 [SD = 28.20] to 95.95 [SD = 13.27]) at 12, 48, 84, 108, and 120 months postoperatively ($P < 0.05$) and these reached clinical significance at 12, 84, 108, and 120 postoperatively. Scores at 60 months postoperative were significantly better than the normal population ($P < 0.05$) (Fig. 2). We observed sustained clinically meaningful and statistically significant impairment in cognitive function

Table 3 Summary table of the number and percentage of patients at each 12-month interval for each domain who reported scores that reached the clinically meaningful difference (CMD)

		Interval (mo)										
		12	24	36	48	60	72	84	96	108	120	120+
Global QoL	(n) CMD	37	20	22	20	11	9	9	8	8	14	32
	(%) CMD	45.68	36.36	44.00	52.63	29.73	34.62	34.62	28.57	57.14	87.50	41.03
Physical	(n) CMD	30	16	15	13	2	10	5	8	5	9	12
	(%) CMD	37.97	28.57	30.00	34.21	5.41	38.46	19.23	28.57	35.71	56.25	15.38
Role	(n) CMD	40	11	15	8	3	6	8	4	5	6	12
	(%) CMD	50.00	19.64	30.00	21.05	8.11	23.08	30.77	14.29	35.71	37.50	15.38
Emotional	(n) CMD	34	19	19	19	7	5	8	10	5	9	21
	(%) CMD	41.98	34.55	38.00	50.00	18.92	19.23	30.77	35.71	35.71	60.00	26.92
Cognitive	(n) CMD	39	25	17	18	6	8	11	8	3	11	21
	(%) CMD	48.15	45.45	34.00	47.37	16.67	30.77	42.31	28.57	21.43	68.75	26.92
Social	(n) CMD	37	15	13	11	3	5	11	7	4	7	15
	(%) CMD	45.68	27.27	26.00	28.95	8.11	19.23	42.31	25.00	28.57	43.75	19.23
Fatigue	(n) CMD	47	20	21	20	5	6	11	5	6	7	22
	(%) CMD	58.75	37.04	42.00	52.63	13.51	23.08	42.31	17.86	42.86	43.75	28.21
Sleep	(n) CMD	50	32	32	20	16	15	12	16	10	11	41
	(%) CMD	62.50	57.14	64.00	52.63	43.24	57.69	46.15	57.14	71.43	68.75	52.56

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

	Physical	Role	Emotional	Cognitive	Social	Fatigue	Pain	Sleep
	First 12 Months (n = 81)							
Spearman's Rho	.613**	.494**	.661**	.547**	.561**	−.721**	−.626**	−.570**
Sig. (2-tailed)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	All Intervals (n = 455)							
Spearman's Rho	.487**	.467**	.556**	.466**	.520**	−.619**	−.515**	−.334**
Sig. (2-tailed)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Note. Strong correlations between parameters are denoted by a Spearman's Rho >0.5, ***$P < 0.001$.

(range 58.33 [SD = 29.81] to 88.73 [SD = 16.35] at nearly every time period postoperatively ($P < 0.01$) (Fig. 2).

From the symptom scales of the QLQ-C30, a number of significant associations were found with time from surgery. Meningioma patients reported greater fatigue than the normative population (range 12.21 [SD = 15.61] to 29.37 [SD = 25.26)] at 12 and 48 months postoperative; however, a clinically meaningful difference was seen at 12, 48, 108 months after surgery ($P < 0.05$). Fatigue scores at 60 months postoperative were significantly better than the normative population, but again whether this represents a true improvement or fluctuation to the "new normal" is unknown ($P < 0.01$) (Fig. 3). Patients reported statistically significant impairments in insomnia/sleep compared with the normative population (range 42.85 [SD = 37.96] to 20.51 [SD = 28.40]) at every postoperative interval except 60 and 84 months ($P < 0.05$). Clinically meaningful impairments were seen at 12, 24, 36, 48, 72, 96, 108, 120, and 120+ months postoperatively (Fig. 3).

Discussion

Treating practitioners are adept at predicting and explaining the medical risks and benefits of meningioma treatment. However, patients are rarely informed about the expected changes in HRQoL and in the majority of cases health care providers are not educated to have awareness of this critical component of patient care. Despite, or perhaps because of, the overall favorable survival of the majority of patients with meningiomas, few studies have investigated HRQoL in large cohorts of these patients. In particular, longitudinal change in HRQoL after time from diagnosis

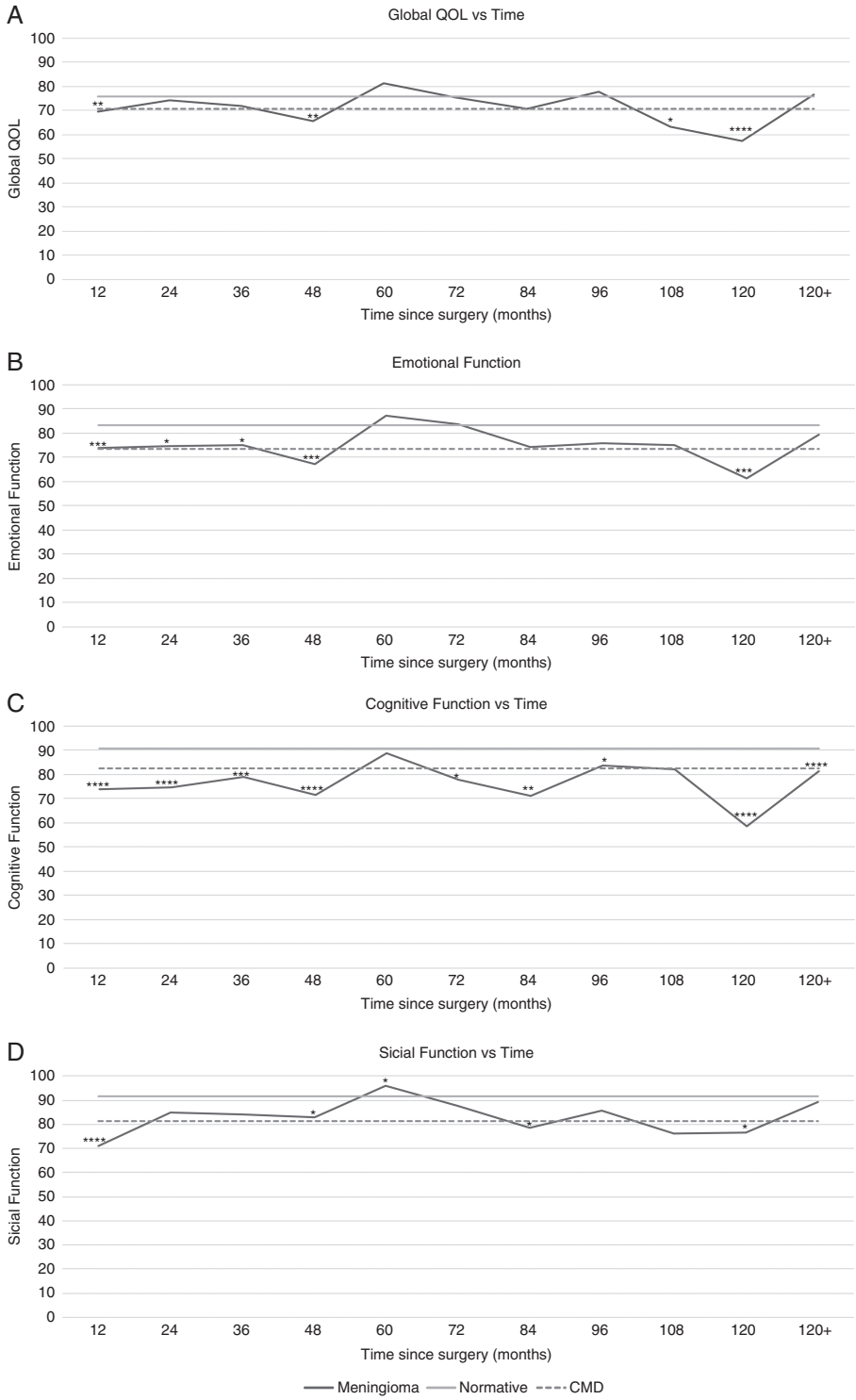

Fig. 2 Longitudinal global HRQoL (A) and subdomain scores (B-D) from the EORTC QLQ-C30. Scores for meningioma patients (black line) are depicted longitudinally in 12-month intervals and compared with a normative European population mean (gray line) with the clinically meaningful difference (CMD) threshold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

or treatment is understudied. Another deficient area is of studies seeking to identify determinants of reduced HRQoL for which an effective treatment or intervention might be available. In general, studies have compared treatment modalities or concentrated on patient-specific or surgical factors predicting poor HRQoL, such as large tumor size,

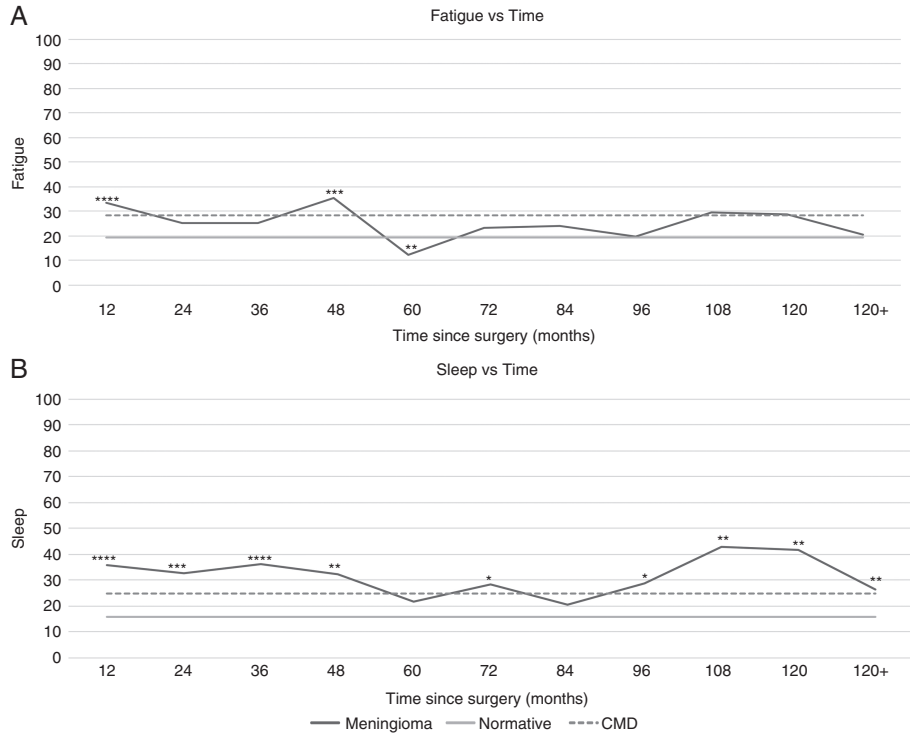

Fig. 3 Longitudinal fatigue (A) and sleep (B) symptom scores from the EORTC QLQ-C30. Scores for meningioma patients (black line) are depicted longitudinally in 12-month intervals and compared with a normative European population mean (gray line) with the clinically meaningful difference (CMD) also shown (dotted line). Statistically significant differences are shown as $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, and $^{****}P < 0.0001$.

location in the dominant hemisphere or frontal lobes, tumors causing seizures and requiring anti-epileptic medications, incomplete resection, or higher histological grade.[4,13–18] While these studies are valuable for prognostication, risk assessment, patient counseling, and treatment choice, they do not necessarily provide options for the vast majority of patients to improve their HRQoL after treatment of a meningioma. Supplementary Table 1 shows a summary of studies of HRQoL in meningioma patients, which outlines the deficiencies in the literature, including but not limited to small patient cohorts, variability in use of instruments, and population addressed. The lack of a validated, specific, and universally employed instrument for HRQoL in meningiomas precludes pooling of the limited existing data; however, reviewing the work that has been completed identifies gaps to be addressed in the future.

In this study, we report the HRQoL outcomes of 291 meningioma patients treated with surgical resection. This is the largest reported study of HRQoL in meningioma patients. Our results demonstrate that patients with meningiomas report considerable limitations in HRQoL for more than 120 months after surgery. They report clinically significant impairment in cognitive, emotional, and social function, as well as suffering significant fatigue and sleep impairment compared with a normative reference population at the majority of postoperative intervals assessed, and often lasting for many years. These reported functional impairments and symptoms are strongly correlated with global HRQoL and thus can be considered determinants of global HRQoL that if treated, may improve HRQoL for our meningioma patients, although this hypothesis remains untested. Our findings are based on the largest postoperative population studied to date and are supported by the current literature.[15,19,20]

The majority of meningioma patients report improved HRQoL after surgical resection of tumors.[15,21,22] However, although therapy (either by surgery alone or combined with radiation therapy) appears to confer an HRQoL and neurocognitive benefit for some, residual neurocognitive deficits may persist for many years after completing treatment.[19,22,23] Adjuvant therapies, most commonly radiotherapy, may add to impairments in HRQoL.[20,24] Our study, like others,[9] demonstrates that patients with meningiomas exhibit considerable sustained impairments in global HRQoL compared with a reference normative population, although the relationship with time is complex and fluctuating for individual patients. In the literature, the rate of reported posttreatment HRQoL impairment is variable,[4,16,25] with up to 80% of patients continuing to experience HRQoL impairments long after treatment.[16] Thus, neither surgery nor radiotherapy have been proven to confer long-lasting improvements in HRQoL,[9] with the limitation that existing studies have largely lacked preoperative assessment for comparison. Our findings, in combination with the previous literature, clearly highlight that for many patients, care must continue beyond treatment of the meningioma.

Knowing the determinants of impaired HRQoL in meningioma patients may guide interventions to preserve HRQoL. The psychological impact of a brain tumor diagnosis is often overlooked in patients with "benign" brain tumors. Previous studies have suggested that a subset

of treated meningioma patients report continued fear of tumor progression or recurrence, as well as impairments in physical and functional well-being and fatigue.[23] This varying symptomatology is not currently explained by physiological factors alone and highlights the dramatic psychosocial and cognitive impact that the diagnosis of a meningioma can have.

In our study, we have reported on HRQoL outcomes of patients with meningiomas with a focus on identifying possible actionable determinants of global HRQoL. We have found that fatigue, sleep impairment, and emotional and social function impairment were consistently highly correlated with global HRQoL in patients with meningiomas, particularly at 12 months, but for some patients extending well beyond 5 years. Patients also reported considerable sustained cognitive impairments. This perceived cognitive deficit is an interesting finding, as many patients had small extra-axial tumors, which would not normally be considered to confer a risk of cognitive dysfunction. The biological substrate of cognitive dysfunction (and indeed other reported symptoms such as fatigue and sleep disturbance) is not known. Although our study did not objectively assess cognitive functioning, it does suggest that perceived cognitive dysfunction is a major determinant of HRQoL, which may not always be reflected by objective testing, as has been shown in other conditions, including epilepsy.[26]

Our findings suggest that interventions targeting fatigue, sleep disturbance, cognitive function, or the perception of cognitive deficits, anxiety, and depression may aid maximizing HRQoL for patients with meningiomas. 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 which may be a contributing factor to perceived cognitive deficit and role dysfunction), a graded management program, starting with simple education in fatigue management, moving to physical activity and psychosocial interventions and advancing to stimulants in selected patients, may have a transformational effect for affected patients.[27–29]

The available studies evaluating HRQoL in meningiomas have used a variety of different tools, none of which have been specifically designed for, or validated in, patients with meningiomas (Supplementary Table 1). A recent systematic review evaluated the relevance and comprehensiveness of these questionnaires used in meningioma research and found that the existing questionnaires, which include the SF-36[30–33] and the Functional Assessment of Cancer Therapy (FACT) general and brain tumor modules FACT-G and FACT-Br,[34–36] did not cover the full spectrum of relevant issues important to patients with meningiomas.[9,37]

In this study, we used the EORTC QLQ-C30 to assess HRQoL in patients with meningiomas. The advantage of the QLQ-C30 is that it has been validated in many languages and takes a short time to complete (~10 minutes) with an available repository of reference values for over 16000 European patients.[10] One of the major limitations 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 on the order of months.[38] 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 about the mean, and may also be attributed to incidental factors including life events and intercurrent illness episodes. The brain tumor–specific offshoot of the QLQ-C30, the QLQ-BN20, has also been reliably validated, but again not for meningioma.[39] Ultimately, there is a critical need for the development and validation of a meningioma-specific HRQoL tool that can be used in future studies.

Based on the findings of this and previous studies, how can we preserve and improve the HRQoL of our meningioma patients? The first step would seem to be the recognition that these patients are at high risk of long-term HRQoL compromise, despite excellent surgical and radiological outcomes. Education of health care providers and patients and their families on this chronic condition with 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 physicians to better counsel patients and provides a baseline for comparison after treatment and through follow-up.

Subsequent to treatment, resources to manage the less visible effects of the meningioma need to be developed. Focal neurologic deficits such as 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. 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, anti-epileptic medications, anxiety, or depression. In some patients, impairments of HRQoL improve with time, and simple education, reassurance, and self-management may suffice.

Along with assessing the MRI scan, follow-up protocols should incorporate assessment of neurologic and cognitive function and HRQoL, both in the early posttreatment period and the long term, as patients' perception of HRQoL will change over time. The need for anti-epileptic therapy[13,40] and all medications should be reevaluated regularly.

A large prospective database, which will likely require multi-institutional efforts, is required to gather a comprehensive dataset to allow for detection of significant symptoms, influencing factors, and novel interventions

for symptoms and disabilities that are important determinants of HRQoL, but currently underaddressed. Many determinants of poor HRQoL are not, or are only partially, under the control of the treating 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 patients.

Limitations of the Study

In addition to questionnaire-related limitations, our study is susceptible to selection and reporting bias inherent in the design, as for other survey-based HRQoL studies. Firstly, despite significant effort to obtain longitudinal data on each patient, there is an expected drop-off of participation at later time points. Thus determination of the true longitudinal impact of meningioma on HRQoL is difficult. Table 1 and Supplementary Table 2 suggest that patients completing multiple questionnaires are similar to those completing only a single questionnaire; nonetheless, longest follow-up is likely to be achieved in patients with complex, residual, or recurrent meningiomas, which may create a bias toward poorer reported HRQoL at later time points. However, this remains the largest and most comprehensive such cohort, and data collection continues. Therefore, reports in future years may overcome this limitation.

Secondly, patients were allowed to enter the study at any time point postoperatively as they presented for follow-up. This introduces a significant spread of initial responses in terms of time from surgery and potential data heterogeneity. However, it also allows inclusion of all patients followed in the service for a large "real-world" cohort in which interventions to improve HRQoL could reasonably be instituted on the basis of our results, which was the aim of the study. As data collection continues, this limitation will be overcome.

Thirdly, there are no preoperative baseline data. These would, of course, be interesting data but were not included for a number of reasons. The primary reason was that the study did not aim to assess the effect of treatment on HRQoL, which is in some respects "nonmodifiable," but rather to determine factors influencing HRQoL in a large group of postoperative patients, and identify interventions for improvement. In addition, the difficulty of interpreting HRQoL measures in preoperative patients recently confronted with the diagnosis of a brain tumor brings its own complexities, and changes after surgical treatment are probably not related to the effects of treatment alone. Including only patients for whom preoperative assessment was available would greatly reduce the speed of data collection and patient inclusion but could be obtained for a subset of patients as data continues.

Fourthly, 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. This bias may imply that the results are more significant than can be reported from the current study population. However, the nature of neurosurgical care in Victoria, Australia, is such that neurosurgery is concentrated in a small number of central hospitals. Patients are almost exclusively followed up through these services and the lost-to-follow-up rate is low. Therefore, apart from catastrophically disabled or palliative patients (who are uncommon among grade I meningioma patients), we expect the majority of patients to be captured. In cases where it was identified that a patient had not been captured at a follow-up visit (largely due to administrative error), questionnaire mail-outs were used.

Lastly, this is a single center study, which introduces a number of biases, and future multicenter studies are needed. However, the population is diverse and includes remote, rural, and urban patients, with both government and private insurance and treatment by a large number of neurosurgeons, all of which may mitigate some of these biases.

Conclusions

We present the largest prospective longitudinal series of long-term HRQoL outcomes following surgical resection of a meningioma. We found that meningioma patients report sustained and clinically significant impairments in global HRQoL, with particular impairments in cognition and sleep/insomnia. Emotional 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 point in treatment should be rigorously tested as they may offer the best approach for maximizing HRQoL in patients with meningiomas.

Recommendations

To facilitate maximizing HRQoL in patients with meningiomas and advancing HRQoL research, the International Consortium on Meningiomas recommends:

- Cooperative efforts be aimed at developing and validating disease-specific, and possibly location-specific, HRQoL assessment tools.
- Incorporating HRQoL into a core outcome set that also includes intervention complication rates, epilepsy, and cognitive function.
- Core outcome sets be evaluated at baseline and serially at follow-up to track trends in HRQoL changes.
- Strategies targeting fatigue/sleep, cognitive functioning, social functioning, and emotional functioning from an early stage in treatment may offer the best approach at maximizing HRQoL for patients with meningiomas and should be developed and rigorously evaluated.
- Resource allocation for the development of facilities that provide multidisciplinary services (such as physiotherapy, occupational therapy, speech therapy, cognitive therapy, and medical therapy) aiming to preserve and improve HRQoL of patients in a longitudinal fashion.

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